No. 23-12155

UNITED STATES COURT OF APPEALS
FOR THE ELEVENTH CIRCUIT

August Dekker et al.,
Plaintiffs-Appellees,

v.

Secretary, Florida Agency for Health Care Administration et al.,
Defendants-Appellants.

U.S. District Court for the Northern District of Florida, No. 4:22-cv-325
(Hinkle, J.)

APPELLANTS' APPENDIX – VOLUME XVIII OF XXI

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Dated: October 13, 2023

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Q. What is it?
A. This is the invoice -- the after the fact request invoice for Quentin Van Meter.
Q. And what was Mr. Van Meter being retained to do for the Agency?
A. The same, consultant for developing the GAPMS report.
Q. And you signed these after the fact request forms for both Mr. Van Meter and Mr. Van Mol?
A. Yes.
Q. You approved payment for these individuals?
A. Yes.
Q. And if you can just look at the dates of service on the request for Mr. Van Meter, what were the dates of service for his services?
A. 4/15/22 through 6/30/22.
Q. So that would indicate that he had started working for the Agency in a consultant capacity on April 15, 2022?
A. That's what the invoice says, yes.
Q. We're now pulling up what has been marked as Plaintiffs' Exhibit 292A. Do you recognize this invoice at all?
A. No.
Q. Do you recognize the person named in the invoice?
A. Can you point out where the name is?
Q. At the very top, it's italicized. I'm sorry.
A. No.

Q. So Ms. Brignardello-Petersen completed one of the attachments to the 2022 GAPMS for gender dysphoria. Have you reviewed those attachments?
A. I did a year ago.
Q. And so this appears to be an invoice for services that she provided to the Agency. Would you have been required to approve this invoice if she was paid?
A. It depends on who was ordering the invoice or who had filled out the form. If I was in the chain of revision or supervision or signing, then, yes.
Q. And when we looked at Mr. Van Meter and Mr. Van Mol's requests, those were done by Ms. Pickle, who was part of the team working on the 2022 GAPMS for gender dysphoria, were they the same individuals who would have been retaining the other authors of the GAPMS reports -- attachments?
A. I don't know.
Q. Do you recall signing an invoice for Ms. Brignardello-Petersen's services?
A. I don't remember.
Q. Do you recall signing an invoice for the services of the other consultants who provided attachments to the GAPMS memo?
A. I don't remember specifically. You just showed me the two. But I don't remember specifically all of the invoices that I signed, no.
Q. We'll pull up Plaintiffs' Exhibit 294. This document is

entitled, "Projected Rulemaking Timeline," and it makes reference to the GAPMS specifically.

Have you ever seen this document?

A. I don't recall if I have or not.

Q. Just from your knowledge as an Agency employee, do you know what some of these acronyms mean, for example, do you know what NORD refers to?

A. Yes.

Q. What does that?

A. Notice of Rule Development.

Q. And what does FAR refer to?

A. Florida Administrative Register.

Q. And are these activities that the Agency undertakes, the Notice of the Rule Development, for example?

A. Yes. Those are required steps in the promulgation process per Chapter 124 of the statutes.

Q. And in the third box, June 17th, there's an acronym NOPR. What does that refer to?

A. Notice of Proposed Rule.

Q. And that's also published in the Florida Administrative Register?

A. Yes.

Q. Under July 12th, there is an acronym JAPC. Do you know what that acronym stands for?

A. Joint Administrative Procedures Committee, I think.

Q. And when it says "Adoption package submitted to JAPC," does the Agency submit rule adoption packages to JAPC?
A. We have to file the rule with the Department of State, but I believe that we submit them for review to JAPC.
Q. And July 19th, where it says, "File for adoption with DoS," that would be Department of State as you just mentioned?
A. Yes.
Q. And on the second row under June 16th, it says, "Send NOPR to OFARR and FAR," I think FAR is Florida Administrative Register, we said. Do you know what OFARR is?
A. I don't know if I can remember off the top of my head. They are an entity.
Q. A state agency entity in the rulemaking process; is that accurate?
A. Yes.
Q. And we are now going to pull up what's been marked Plaintiffs' 295 on the screen.
This is a flowchart entitled, "Gender Dysphoria/Transgender Health Care Non-Legislative Pathway."
Have you ever seen this particular document?
A. I don't remember seeing this before.
Q. Does this document seem to reflect the process by which AHCA completed the GAPMS process for gender dysphoria and promulgated the rule that's being challenged today?

A. Yes.
Q. And one more document that we'll pull up, Plaintiffs' Exhibit 296. This document is another flowchart this is entitled, "Gender Dysphoria/Transgender Health Care Policy Pathway."
Do you recognize this document?
A. No.
MS. DUNN: Just one second. This might just take a minute. I'm sorry.
BY MS. DUNN:
Q. We are pulling up what has been marked as 297. Do you recognize this document?
A. Yes.
Q. What is this document? Oh, I'm sorry. This is not the version of the document that I intended.
This is what has been marked as 297A. Do you recognize this document?
A. Yes.
Q. And what is it?
A. This is an internal form that we use to track routing and approval of documents through the Agency.
Q. And what is this particular routing and tracking form referencing?
A. The GAPMS report assignment.
Q. And this would have been what was completed when

Mr. Brackett, Ms. Pickle, and Mr. Chen had finished the GAPMS for gender dysphoria and submitted it to the management team?

A. Yes.

Q. And they completed or they submitted that form for review on June 1st, 2022; is that right?

A. Yes.

Q. So Ms. Pickle signed it on June 1st, 2022?

A. Looks like Matt Brackett for D.D.

Q. Oh, that's what the "MB for DVP," means, Matt Brackett signed it for her?

A. Yes.

Q. And you signed it on that same date, June 1st, 2022?

A. Yes.

Q. Mr. Weida, your direct supervisor, also signed it on June 1st, 2022?

A. Yes.

Q. And then it was sent to Tom Wallace, who is the Deputy Secretary for Medicaid, and he signed it the next day, June 2nd, 2022?

A. Yes.

MS. DUNN: I have no further questions. Thank you.

THE COURT: Redirect?

MR. BEATO: No, Your Honor.

THE COURT: Ms. Dalton, I want to make sure I understood this, and I have a follow-up question, too.

Let me start by saying, I get it, when you give special attention to a request that came from the boss as opposed to something that was routine or came some other way. So I take it this process was a request essentially that came from the boss, and I think you said Tom Wallace, as you understood it, at the very beginning of the GAPMS process.

THE WITNESS: Yes. It was a request from the Secretary essentially directing the Medicaid Director, Tom Wallace, to assign it to his team; and, because of the assignment, that would come to my Bureau.

THE COURT: So it came actually from the Secretary.

THE WITNESS: Yes.

THE COURT: Did you understand at that point that the Executive Office of the Governor had some involvement with this, too?

THE WITNESS: I don't -- I wasn't really involved in any of that. I was taking direction from my supervisor.

THE COURT: You're keeping your head down and doing your job.

THE WITNESS: Yes.

THE COURT: So, as you understood it, this is a request from the Secretary. And so it's a request from the Secretary so you want it done well, and you know the Canadian team has time on its hands, and you have confidence in them, and you give it to them.

THE WITNESS: Yes.

THE COURT: I understood all of that.

I think I understood you to say that you didn't remember those flowcharts that they were showing you on cross a minute ago.

THE WITNESS: Yes. I don't recall ever seeing them.

THE COURT: Nobody quite asked you what they really care about, and so I'm going to ask you about it.

Over on the right side at the very end of that flowchart, it said, "Care Effectively Banned."

Now, I have to tell you that it seems to me that, if somebody was starting out at the beginning and wanted to describe the process that we're going to use to evaluate some kind of medical care, we would set out all of those steps, and then at the end it might say, "Rule adopted or result reached"; but, if you're really trying to figure out what the policy ought to be, and you adopted this flowchart in the beginning to show where you were going, the last thing it said wouldn't already have the results.

When you got this assignment, did you know what the result was supposed to be?

THE WITNESS: No. I mean, I was aware of the Department of Health and what had been going on there. I wasn't intimately aware of it, but being part of a government worker, I was aware. But my direction from my supervisor was

always, approach this following the standard process, thoroughly review of the research, and this is a GAPMS report following the rules.

THE COURT: So you knew what was going on, which is to say trans individuals were in the crosshairs. Is that -- that's probably a colloquial way to say it, but, look, I live in this town, too, and read the papers. Trans individuals were targeted. Is that a fair description?

THE WITNESS: As a person living in the town, I agree that I was aware of the political -- I mean, the things that were going on politically or some of the other -- with some of the other agencies.

THE COURT: Nobody ever gave you a wink and a nod and said, "Where this is supposed to come out is that care is supposed to be effectively banned"?

THE WITNESS: No.

THE COURT: And when you picked the Canadian team, it wasn't because you thought these people will understand what they are supposed to do, you picked them because they had time and you thought they would do a good product.

THE WITNESS: Correct. It was not -- yes, it was because I thought that they had time and would do a good product and could accomplish the task.

THE COURT: We saw while you were being cross-examined three invoices, I suppose, one was for $6100,

and I didn't make a note of what the second one was for. The third one was for $34,800. This is money out the door to people that don't work for the State. And I understand that's not a whole lot of money in a state budget. Can you think of other things where your Bureau approved that kind of money to outside consultants?

THE WITNESS: I believe there had been a consultant for the Canadian Importation Drug Program when the legislation first passed. I don't know the amounts associated with that. So I personally have not had much experience with outside consultants.

THE COURT: Fair enough. Thank you.

Questions just to follow up on mine?

MR. BEATO: No, Your Honor.

MS. DUNN: Yes, Your Honor, just one or two.

RECROSS-EXAMINATION

BY MS. DUNN:

Q. Ms. Dalton, did you select the Canadian Drug Importation Program team on your own?

A. I initially recommended it, but I believe it was a discussion with my supervisor at the time, and I think he agreed that that was like, okay, let's move forward that way.

Q. And do you know why the particular consultants that were used in this process were chosen?

A. I don't.

Q. Do you know how the particular consultants used in this process were contacted or selected?
A. No.
Q. To your knowledge, has the Agency ever used seven outside consultants on a GAPMS process prior to this?
A. My personal experience with GAPMS is limited, and I have not had any experience prior with consultants on a GAPMS.
MS. DUNN: Thank you. No further questions.
THE COURT: I think the record already shows this. When you said you may have talked about it with your supervisor, that was Mr. Weida?
THE WITNESS: Yes, Jason Weida.
THE COURT: Thank you. You may step down.
Please call your next witness.
MR. JAZIL: Your Honor, Mr. Brackett is the next witness.
May I ask for five minutes to use the restroom?
THE COURT: Let's take five minutes. We'll start back at 11:20.
(*A recess was taken at 11:16 a.m.*)
(*The proceedings resumed at 11:20 a.m.; plaintiffs counsel not present.*)
THE COURT: Please be seated. We'll be at ease for a minute.
You're welcome to have a seat. We'll make you stand

up in just a minute, but you can sit down right now.

MS. DUNN: We can start.

THE COURT: Good to go?

MS. DUNN: Yes.

THE COURT: Please call your next witness.

MR. JAZIL: Thank you, Your Honor. Matt Brackett is our next witness.

DEPUTY CLERK: Please raise your right hand.

JOHN MATTHEW BRACKETT, DEFENSE WITNESS, DULY SWORN

DEPUTY CLERK: Be seated.

Please, state your full name and spell your last name for the record.

THE WITNESS: My full name is John Matthew Brackett; my last name is spelled B-r-a-c-k-e-t-t.

DIRECT EXAMINATION

BY MR. JAZIL:

Q. Good morning, Mr. Brackett.

Where do you work?

A. I work for the Florida Agency for Health Care Administration.

Q. And if I refer to it as AHCA, will you know what I mean?

A. Yes, I will.

Q. When did you start working at AHCA, sir?

A. I started working at AHCA in October 2015.

Q. Where did you work before October 2015?

A. I worked for the Florida Department of Health as a medical disability adjudicator.
Q. How long did you have that job?
A. I had that job for 15 months, from July 2014 to October 2015.
Q. And what did you do in that job?
A. So that job was responsible for handling the medical aspect of social security disability claims, reviewing medical records, and determining whether or not those records and the medical evidence, determine whether or not somebody met the criteria for social security disability.
Q. What did you do before that?
A. I was a school teacher.
Q. How long were you a school teacher for?
A. I was a school teacher for six years.
Q. So you joined AHCA in October 2015, what was your first job?
A. So my first job at AHCA was a medical health care program analyst under the deputy secretary for health quality assurance.
Q. How long did you have that job?
A. I had that job for 15 months.
Q. And what did you do in those 15 months?
A. So that job, I worked on coordinating the completion of bill analyses; tracking legislation; completing monthly,

quarterly and annual reports; and I also worked on the Agency's online licensing program.

Q. What was your next job at the Agency?

A. My next job with the Agency was a Government Analyst II. That was in the Bureau of Medicaid Policy.

Q. And what did you do as a Government Analyst II?

A. That role, was responsible for completion of Generally Accepted Professional Medical Standards reports.

Q. What was your next job?

A. My next job was a program administrator over the specialized and behavioral health services coverage policy section.

Q. And how long did you have that job for?

A. I held that job for three and a half years.

Q. Next job at the Agency, sir?

A. My next and current position is a program consultant for the State's Canadian Prescription Drug Importation program.

Q. Were you a political appointee in any of those jobs at the two agencies you've mentioned?

A. No, I was not.

Q. Now, you mentioned Generally Accepted Medical Standards, GAPMS. Is it okay if I refer to it as that, would you know what I mean?

A. Absolutely.

Q. I'm pretty sure I just butchered the acronym, so I

apologize.

You talked about GAPMS, and you told us what it stands for. Do you know that a GAPMS report is?

A. Yes.

Q. What is it, sir?

A. So a GAPMS report is a document that is prepared in accordance with Rule 59G-1.035, Florida Administrative Code. So that report takes a comprehensive look at evidence as required by that rule to determine whether or not a medical service conforms to Generally Accepted Professional Medical Standards.

Q. Are there different kinds of GAPMS reports?

A. We have a couple.

Q. And what are they?

A. So we have a traditional GAPMS and then we have an expedited GAPMS.

Q. What's the difference between the two?

A. So an expedited GAPMS, this is a GAPMS that is usually done by request from one of our managed care plans. It is usually specific to one recipient. And because it's one recipient who is awaiting a service or a determination needs to be done quickly, that GAPMS has to be done kind of individualized, looking at that recipient's condition and whether or not that service will benefit that recipient.

Q. And the other kind of GAPMS, the traditional GAPMS, can

you tell us what that is?
A. A traditional GAPMS is much more comprehensive. So because there's not an urgent request for it, it provides a comprehensive report looking at like multiple medical conditions if they are applicable, and looking it through the guise of recipients who might benefit from that particular service that's being evaluated.
Q. Mr. Brackett, you testified earlier that you held a Government Analyst II job, and as part of that you wrote GAPMS reports. Can you remind us how long you held that job for?
A. I held that position for ten months.
Q. And how many traditional GAPMS reports did you write in those ten months?
A. During that role, I drafted nine.
Q. Mr. Brackett, you mentioned Rule 59G-1.035.
MR. JAZIL: Can we bring up Plaintiffs' Exhibit 23, please.
Your Honor, may I approach the witness with a copy as well?
THE COURT: You may.
BY MR. JAZIL:
Q. Mr. Brackett, as I understood your testimony just now, you said that this rule guides your work. What specific provision in this rule do you look to when you're working on

your GAPMS reports?
A. In particular, subsection (4).
Q. I would like to work through the subsections so we get an understanding of what these factors mean to you.
What's your understanding of what subsection (4)(a) requires of you as you're working through a GAPMS report?
A. So subsection (a) applies to evidence-based clinical practice guidelines. That does require us to look at what's available, evidence-based clinical practice guidelines are available pertaining to the medical service under consideration.
Q. Okay. And what about the subsection (b)?
A. Subsection (b) is referring published reports and articles in authoritative medical, research journals -- peer-reviewed articles to be short. So that's going to require an exhaustive search for what peer-reviewed literature is available on the subject.
Q. And subsection (c)?
A. Subsection (c) is requires the evaluation of the effectiveness of the health service in improving the individual's health conditions.
Q. What about (d), sir?
A. That is in reference to utilization trends.
Q. What does that mean to you?
A. How is the service being used at the time of its

evaluation.
Q. What about subsection (e), sir?
A. (E) is looking at coverage by other credible insurance payors.
Q. And what would those other credible insurance payors be?
A. Those could be first and foremost other states' Medicaid programs, Medicare, other payors, such as TriCare, Veterans Administration. It can also include private insurers.
Q. And what's your understanding of subsection (f), sir?
A. Recommendations or assessments by clinical or technical experts on the subject or field. This is to take a look at what the authorities out there are saying about this particular service under consideration.
Q. And based on your experience, sir, which of the factors in subsection (4) dictates the results of your GAPMS decisions?
A. There isn't really one in particular. It's all taken as a whole.
Q. So, sir, you mentioned that you wrote GAPMS reports. What happens after you finish your draft of your GAPMS report? What's the next step?
A. So after I've prepared a finalized version of that draft, and it's ready to go, I give that draft to my immediate supervisor.
Q. What happens after that?

A. Either my immediate supervisor signs off and gives it to their immediate supervisor, or it comes back to me with questions or edits.

Q. If it moves up the chain from your immediate supervisor to their supervisor, what happens after that?

A. It eventually makes its way up to the Deputy Secretary of Florida Medicaid.

Q. And do you know what the Deputy Secretary's role is in this process?

A. The Deputy Secretary of Medicaid gets the final say in agreeing or disagreeing with the conclusions and findings of the report.

Q. And where in Rule 59G-1.035 does it say that?

A. That is in subsection (5).

MR. JAZIL: We can take that down.

BY MR. JAZIL:

Q. Mr. Brackett, I would like to move on to the June 2022 GAPMS report on gender dysphoria, which is Defendants' Exhibit 6.

MR. JAZIL: Your Honor, may I approach with a copy?

THE COURT: You may.

BY MR. JAZIL:

Q. Mr. Brackett, please take a look at the report and let me know when you're done, and you can look back at me.

Are you familiar with this document, sir?

A. Yes, I am.
Q. How so?
A. It's -- well, it's our complete GAPMS report from June 2022, on treatment for gender dysphoria. It contains my report as well as all of our attachments.
Q. And when you say "your report," what are you referring to, sir?
A. I'm referring to the first part, the General Accepted Professional Medical Standards Determination. That's the part that I wrote.
Q. And who asked you to write this GAPMS report, sir?
A. I was asked to write this report by our Bureau Chief, Ann Dalton.
Q. What's your understanding of why you were asked to write this report?
A. My understanding of why I was asked to write this report was that I had extensive experience not only just working on GAPMS reports, but also executing special projects for the Bureau of Policy over my time there. And also the time because our proposal had been submitted to the Food and Drug Administration related to the drug importation program, we were still awaiting feedback, that we had the bandwidth -- I had the bandwidth to do this project.
Q. When were you asked to work on the report, stir?
A. Around mid April 2022.

Q. So mid April 2022, you get asked to work on the report, what's your first step?
A. My first stop was to start combing the literature, to start finding articles, anything that pertained to the subject, anything in a peer-reviewed journal, and to start gathering the materials and start reading them, and kind of letting the research -- letting the research guide me.
Q. And where did you go to gather these materials?
A. Primarily went to PubMed. That's the National Institutes of Health's database for peer-reviewed medical literature.
Q. What was your next step?
A. My next step, of course, as I gathered more and more materials, reading the articles, kind of understanding what the literature was saying, kind of trying to get a complete picture of -- kind of cumulatively what the literature said about these services. And then kind of began kind of making a mental outline of how to structure the report.
Q. So you've done your mental outline. What comes next?
A. Once the mental outline is done, that's when I began drafting.
Q. Okay. And how long did it take you to draft your first draft of the report?
A. My first draft, which was a polished first draft, took me about three weeks.
Q. I'm bad with math so remind me, approximately when in

2022 would that put us?
A. That would put us in early May 2022.
Q. Did anyone at the Agency help you with your draft of the report?
A. As far as the actual writing goes, no. But when it came down to gathering information on other insurance payors, I did have some support with that.
Q. Who helped you with gathering information on other insurance payors?
A. D.D. Pickle and Nai Chen.
Q. Can you tell me what specifically D.D. Pickle did for this report?
A. So D.D. Pickle's role in this was to go out there and find what other State Medicaid programs were doing in terms of coverage of these treatments.
Q. Anyone else help you with this report?
A. Nai Chen.
Q. What was Nai Chen's role?
A. His role was to take a look at Western European countries and to take a look at what they were also doing regarding these treatments.
Q. Now, you said Ms. Pickle went and looked at other Medicaid agencies around the country and what they were doing. Why didn't Ms. Pickle work with you, look at private insurance companies and what they were doing?

A. So, since Florida Medicaid, since we are a public payor, when we do the section of the GAPMS, we are primarily interested in other Medicaid programs first and foremost. And since she was taking an exhaustive search, far more exhaustive than we have done for other reports, and we got a nice breakdown of what the 50 states said, considering that we had a very complete picture of Medicaid and other public payors, and we just for this one we did not emphasize -- we did not emphasize private insurers, but also this is not a unique situation with that GAPMS. We have done other GAPMS where we did not look at private payors.

Q. I think you mentioned this earlier, but I just want to make sure this is clear.

Did Mr. Chen or Ms. Pickle write any portion of the report?

A. No.

Q. And in the report on pages 31 and 32, if you wouldn't mind turning to them, it discusses the coverage policies. What did y'all conclude?

A. So, for Medicaid, we concluded that there was disagreement among the states regarding coverage. Some states covered it, other states said they would not cover it. A lot of states said they didn't have a policy one way or the other.

Q. It does say that other Medicaid perspectives were

considered. How exactly did you and your team go about checking to see what other states were doing?

A. So as part of the research we do in the Bureau of Policy is scouring other state Medicaid programs for research, D.D. took the same approach, scoured the 50 state Medicaid program published policies, their handbooks, their coverage statements, and, of course, recorded the findings.

Q. Y'all also looked at what Western European countries. Why did you do that?

A. Because Western European countries, since they are generally almost all utilize some kind of universal health care system, we also considered them to be public payors, and we also were curious to see what their input was.

Q. What did you find when y'all started looking at the Western European countries?

A. We found that they had put in place prohibitions regarding these services.

Q. Mr. Brackett, you testified earlier that the rule for GAPMS requires you to look at utilization trends. Did y'all do that here?

A. Yes, we did.

Q. What did you find?

A. So we found that the utilization of these services had been increasing; that it had been increasing in almost a reverse manner. We had a lot more young women transitioning

to males as opposed to the other way around where you had more young men who wanted to transition into females. And we found that the number of cases, of course, had been rising steadily in recent years.

Q. Mr. Brackett, the rule says that you should look at evidence-based clinical practice guidelines. Did you look at evidence-based clinical practice guidelines?

A. I did.

Q. Which ones, sir?

A. I looked at the guidelines from the World Professional Association for Transgender Health, more colloquial known as WPATH; and the Endocrine Society, as well as guidelines from the University of California at San Francisco.

Q. Let's take those one at a time, sir.

Based on your review of WPATH's guidelines, what did you conclude for purposes of your GAPMS report?

A. For the purpose of the GAPMS report, after having read all of the literature, I kind of concluded that the WPATH guidelines were founded on low to very low quality evidence.

Q. What about the Endocrine Society guidelines, sir?

A. The Endocrine Society guidelines, while they were more transparent in sayings that these recommendations were based on low to very low quality evidence, their recommendations didn't really mesh with what their evidence was saying, in addition, to the grade that their evidence had been given.

Q. And what about the University of California, San Francisco, guidelines, sir?
A. So I found their guidelines to be more -- a little bit more I guess basic, but also found they conflicted with some of what WPATH and what Endocrine Society said.
Q. Understood. The rule requires a review of published reports, articles, authoritative medical literature. You said you looked at those. Where in your report do you provide a list of the articles that you reviewed?
A. Starting on page 39 through page, I think, 46.
Q. Is this an exhaustive list of the papers that you reviewed?
A. This is an exhaustive list, yes.
Q. And which of these articles did you review in their entirety, sir?
A. I reviewed all of the articles in their entirety.
Q. Did you review papers that contradicted the findings ultimately reached in your GAPMS report?
A. Yes. I reviewed numerous articles in peer-reviewed literature that asserted that these treatments were beneficial to mental health.
Q. Sir, can you take a minute to just take a look at your works cited and point me to one or two articles that ultimately disagreed with the findings that you reached?
A. Sure. On page 43.

Q. Okay. Can you read off the author?
A. Sure. One was by Tordoff and a group of other scholars, talked about mental health outcomes in transgender and nonbinary youths.
Another one was by I think Olson-Kennedy, and I think it was about gender identity five years after social transition.
Q. Sir, after your report there are attachments. Are you familiar with those attachments to the GAPMS report?
A. Yes, I am.
Q. How, if at all, do they influence the report itself?
A. Considering that we didn't receive those reports until after I had already drafted mine, they didn't.
Q. Mr. Brackett, do you know Andre Van Mol?
A. Yes.
Q. How do you know him, sir?
A. I do know him through collaborations with this project.
Q. What role did he play in this project?
A. He served in an advisory capacity. We had a few conference calls with him.
Q. What did you discuss on those conference calls?
A. Resources, articles.
Q. Anything else?
A. He did give us -- I think in one of the calls he gave us some suggestions for edits when we were polishing the draft.
Q. I would like to show you what has been admitted into

evidence as PX329.

MR. JAZIL: Your Honor, may I approach?

THE COURT: You may.

BY MR. JAZIL:

Q. Mr. Brackett, just look up at me when you are done taking a look at it.

Do you recognize this document, sir?

A. Yes, I do.

Q. What is it?

A. So, Dr. Van Mol had supplied us with a bibliography to help guide our research.

Q. How did this document guide your work specifically?

A. It was a resource to take a look to see if there are articles out there. By the time we had already received this, I had already pulled numerous studies. This helped make sure that, if there was anything else that was valid or current or could contribute to our own analysis, this helped served as a resource for that.

Q. And based on this document and based on the conversations that you had with Mr. Van Mol, the charge has been made that Mr. Van Mol was the one who actually wrote this GAPMS report. What is your response to that, sir?

A. Well, to that one, I am actually personally offended to that allegation.

Q. Why?

A. Because this was my work product. I am an experienced researcher. I have written a lot of reports. I have peer-reviewed publications. I did the research for this report. I also structured it. I determined how best to approach writing it, and I also -- that was my analysis on the literature; that they didn't conform to GAPMS. That was my assessment.

Q. Mr. Brackett, do you know Miriam Grossman?

A. Yes, I do.

Q. How do you know her?

A. Through collaboration on this project.

Q. Again, tell me what that means, sir.

A. So, we had, like with Dr. Van Mol, we did have some conference calls with Dr. Grossman. She provided the -- gave us some historical background on gender dysphoria treatments, talked to us a little bit about Dr. John Money. She also provided us some background on studies and some background information in general.

Q. I want to make sure the record is clear on this.

Did either Dr. Van Mol or Dr. Grossman write any part of the GAPMS report?

A. Neither one of them wrote any part of it.

MR. JAZIL: I would like to bring up Plaintiffs' Exhibit 297A, please.

BY MR. JAZIL:

Q. Do you recognize this document, sir?
A. Yes, I do recognize this.
Q. What is it?
A. This is our signed routing form for the June 2022 GAPMS.
Q. Looking at this form, it looks like everyone on the review list signed off on the GAPMS report within a day.
A. Uh-huh, yes.
Q. How did that happen?
A. So, during the drafting process, and especially after we had our initial drafts complete, there were numerous briefings held with leadership. In the week before that this was signed, there was a large briefing with everybody on there, including Secretary Marstiller. They had all been provided copies and drafts of the report. They all had a chance to look through it, and they also had a chance to ask questions while I was briefing them on how the report was done, how I reached the conclusions, what research I used.

So by the time we printed up the routing sheet, every person who had signed off on it had already had an opportunity to review, ask questions, had been briefed on it. So they were well aware what they were signing and approving.
Q. In these briefings did anyone tell you to arrive at a particular result?
A. No.
Q. Now, you mentioned there were briefings, the Secretary

was there, et cetera.

What is your understanding of why it was that this project was being pursued on such an expedited basis?

A. My understanding behind the urgency for this project was that the Department of Health and Human Services of the United States, on the federal level, had released guidance citing that these -- that the treatments for gender dysphoria, that these were evidence-based, should be, you know, should be utilized in treating gender dysphoria, and also there had been a Department of Justice document that had been sent out, I think, advising people that they can contact DOJ if they felt they had been discriminated against.

Q. I would like to show you some of those documents.

MR. JAZIL: Your Honor, may I approach?

THE COURT: You may.

MR. JAZIL: I'm going to show the witness Defendants' Exhibit 1, 2, and 3.

BY MR. JAZIL:

Q. Mr. Brackett, look at me when you are done reviewing them.

Are these the documents that you are referring to, sir?

A. Yes, these are.

Q. If you take a look at documents 1 and 2, they lay out citations to the federal government's position.

A. Yes.

Q. Why weren't you persuaded by the position in the citations that were listed there?
A. So, well, I mean, these are -- like I consider these like one-pagers. I'm generally not persuaded by a one-pager in general. I always want to go see what the sources say. My training as a researcher kind of instilled that in me. So it's like, okay, well, this is what it says, but what does the evidence say?
Q. Mr. Brackett, does the GAPMS memo, which is the first part of DX6 accurately capture your conclusions?
A. Yes, it does.
Q. Did anyone anywhere tell you to arrive at those conclusions?
A. No, they did not.
Q. I would like to move on to a few other GAPMS reports.
At the time you were drafting the June 2022 GAPMS report, did you know whether AHCA had any other GAPMS reports related to the treatment of gender dysphoria?
A. I was aware that a couple of drafts had been done prior to my time to the Bureau. I think one was started while I was in the Bureau.
Q. At the time that you were asked to do this job, did you know whether any of them had been finalized?
A. I was not aware if any had gotten through the process, no.

Q. Did you review any of those reports before you started work on your GAPMS report?
A. I did not.
Q. Why not, sir?
A. So I wanted to take a look at the evidence with fresh eyes. I didn't want to see what any other analyst had come up with as far as conclusions went. I just wanted to go into it with a clean slate, not having reviewed really anything else other than what I kind of already had in my head, which wasn't much of anything on the subject.
Q. Have you since reviewed those prior GAPMS reports?
A. After we had gotten this report finalized, I did look at those.

MR. JAZIL: Your Honor, if I may approach with three exhibits for the witness?

THE COURT: You may.

MR. JAZIL: For the record, they are Plaintiffs' Exhibits 240, 242 and 244.

BY MR. JAZIL:
Q. Mr. Brackett, what is 240, sir?
A. 240, that is our GAPMS memo on puberty suppression therapy.
Q. That is a finalized memo, right?
A. Yes, that one is finalized.
Q. And what about Plaintiff's Exhibit 242?

A. That one is on cross-sex hormone therapy, and that's also a GAPMS memo.
Q. Is that a draft or a finalized one?
A. This was a draft.
Q. Explain to me the discrepancy --
MR. JAZIL: If we can pull up 242, please.
BY MR. JAZIL:
Q. There's a date here April 19, 2022, and the top right shows Rick Scott, Governor; Justin Senior, Interim Secretary. Explain that discrepancy to me, sir.
A. So, the GAPMS template that we use was a -- it was a Word document, and when the GAPMS template was created, it -- the date autopopulated whenever you open the document. If you were to open up these three documents today in our share drive, you're going to get today's date in that field.
MR. JAZIL: Can we pull up 244, please, Plaintiffs' Exhibit 244.
BY MR. JAZIL:
Q. Sir, can you tell me whether or not this gender confirmation surgery GAPMS was a finalized one?
A. No, this one was not finalized.
Q. You now have testified that you reviewed these GAPMS reports after writing your own. Having reviewed these three, is there anything in these three reports that would change your mind about the GAPMS report you wrote in June of 2022?

A. No, there wasn't anything in these three.
Q. Why not?
A. So to kind of take them piecemeal, we will start with the one from 2017 on the surgery, I did take a look at that. What I found when I reviewed it was that the conclusions of all the studies that were evaluated were taken more or less at face value. There wasn't any probing of the methodology used, whether or not the subject -- whether or not the studies were low or high quality. It was mostly like, here's the conclusion, and it just moved on. So because I felt like it was missing that aspect of -- that analytical critical aspect that can determine whether or not the evidence was, you know, really truly supported the conclusions, I couldn't be swayed by that one.

For the cross-sex hormone therapy, similar. Literature review is very thin. I think that one did acknowledge that the evidence was low quality, but it was also very thin. It didn't really go into depth onto those subjects. Given that I had also read the evidence for myself, I didn't see how that conclusion could match with what I had read.

And the similar goes to the one from 2016, as well.

I think one other -- one other thought that I had was, when I was reading them, was that we have a process for off-label usage, and I thought that the way the literature reads and the way these were written, I thought the evidence

in the narrative concluded -- conflicted with the findings.
Q. Sir, after the June 2022 GAPMS report was finalized, what did the Agency do next?
A. After the report was finalized, the Agency went to rulemaking.
Q. Did you play a role in that rulemaking?
A. Yes.
Q. What was your role, sir?
A. My role was to help provide feedback on the rule language. I also participated in the July 8th hearing, and I also prepared a comment summary afterwards.
Q. What is your understanding of why the Agency went to rulemaking after finalizing the report?
A. So, since we had determined these services to be experimental and investigational, we moved to go ahead and codify that to rule to demonstrate that, because we had determined them to be investigational and experimental, that we wanted to have them codified as excluded services under the Medicaid program.
Q. Was there a comment period under that rulemaking?
A. Yes, there was.
Q. When did that comment period open?
A. I think somewhere around mid June, maybe late June. It went through shortly after the end of the hearing on July 8th.

Q. Sir, do you know how many comments approximately the Agency received?
A. Oh, I think at least 600.
Q. Are these written comments or are you including the oral comments provided for --
A. Oh, these were the written comments that we received.
Q. And you mentioned a rulemaking hearing. When was that hearing, sir?
A. That was July 8, 2022.
Q. Where was it held, sir?
A. That was held at the Florida Department of Transaction's auditorium at its headquarters downtown.
Q. Why was it held at the Department of Transportation's auditorium and not at AHCA?
A. So DOT's auditorium had a large capacity. Also, it -- so it could accommodate a large crowd. We also anticipated that the Florida channel would probably also want to broadcast the hearing. That venue made for a much better setting to allow videography. And also because of the proximity of DOT's location to downtown and its accessibility compared to AHCA's.
Q. Why did you think there would be a large crowd?
A. Well, because we did receive a substantial number of written comments, and that -- because there had been a fair amount of media coverage behind our GAPMS report, we

anticipated a large crowd.
Q. Who from the Agency was at attendance at that hearing?
A. So serving on the panel, myself, at the time Assistant Deputy Secretary Jason Weida, Shena Grantham, and Cole Giering.
Q. Did the Agency invite others to attend?
A. Yes, we did.
Q. Who?
A. So to participate on our panel, we invited Drs. Andre Van Mol, Quentin Van Meter, and Miriam Grossman.
Q. Why did y'all invite those three doctors?
A. Since we anticipated a lot of comments, and we did anticipate some -- a fairly high quantity that would be in opposition to the rule, to be able to provide responses and feedback to those comments directly, we thought it would be best to have a few outside experts participate on the panel.
Q. Now, during the comment period at the hearing and the comment period for written comment, did the Agency receive comments that opposed its perspective?
A. Yes, it did.
Q. Who reviewed those comments?
A. Myself, our rules unit as well as Nai Chen.
Q. Do you recall the names of some of the prominent folks who commented against the rule?
A. Yes. So most notably, as far as written substantive

comments went, there was a group of faculty from Yale University as well as a couple of other universities that had written us a lengthy comment.

We also received comments from the Endocrine Society.

In addition we had also received comments from the American Academy of Pediatrics.

Q. When you received those comments from those prominent institutions and people, what did you do with them?

A. I read them very carefully.

Q. Did you do anything else beyond reading them very carefully?

A. Because they were very lengthy and very much based on scientific literature, research, and since I actually had been the one who had gone through and did the research for the report, I went ahead and started putting together analyses of each one.

MR. JAZIL: Your Honor, may I approach the witness with Plaintiffs' Exhibit 326?

THE COURT: You may.

BY MR. JAZIL:

Q. Do you recognize this document, Mr. Brackett?

A. Very much I do.

Q. What is it, sir?

A. That is our comment summary from the rule hearing from July 8, 2022.

Q. You testified a bit about why it is you prepared this document. Is there anything you would like to add to the why you prepared this document after having seen it just now?
A. So, because the Agency, I mean, because we did do exhaustive work on this project, we had gone through -- did a report, did a lot of research for that report, we had gone through the rulemaking process, that we do take outside comments very seriously. And we wanted to review them to determine whether or not they introduced anything that could particularly truly conflict where our GAPMS report, with our conclusions or our actions. So, it was -- this is part of what the Agency's responsibilities are, is to take into account comments from the public.
Q. If someone had as part of that comment process, provided you a high quality study, showing the efficacy and safety of puberty blockers, for example, to treat gender dysphoria, what would you have done with that comment?
A. It would have made me rethink my position.
Q. Now, Mr. Brackett, are you familiar with the tag line, "Let Kids Be Kids"?
A. Yes, I'm familiar with it.
Q. What is it, sir?
A. So that's the slogan that went on the web page that accompanied the GAPMS release.
Q. Are you aware of other instances where the Agency has

used slogans with policy initiatives?
A. Yes.
Q. Mr. Brackett, we've some heard testimony before about how the Agency has not used outside consulting experts as part of the GAPMS process.
Do you know whether the Agency has used outside consultant experts as part of other work the Agency has done?
A. Oh, yes, we have.
Q. Can you give me a couple of examples, sir?
A. Well, as our Bureau Chief testified earlier, we did use an outside consultant for the Canadian Prescription Drug Importation Program. We've also used outside consultants when working on behavior analysis and other policies on that treatment service.
THE COURT: Before we go beyond that, let me make sure I understood the premise of the question. The premise of the prior question was that the Agency had not used outside consultants in the GAPMS process. Is that correct?
THE WITNESS: That's correct, sir.
MR. JAZIL: Your Honor, I believe there was some earlier testimony from Mr. English that the --
THE COURT: Right. I knew there was prior testimony, but sometimes people disagree with prior testimony. I was just trying to make sure there wasn't any doubt about it.
MR. JAZIL: Understood, Your Honor.

BY MR. JAZIL:

Q. You gave us a couple examples of instances where outside consultants were hired. I asked you about the tag line, "Let Kids Be Kids," you said the Agency had used tag lines before. Do you have a couple examples for us of instances where the Agency --

A. Since I do work on the Canadian Prescription Drug Importation Program, there have been a couple of slogans associated with that, and the Agency initiatives on lowering prescription drug prices.

Q. Understood.

Mr. Brackett, do you know Jeffrey English?

A. Yes, I do.

Q. How do you know him, sir?

A. He was a co-worker of mine in the Bureau Medicaid policy.

Q. Are you familiar with his work, sir?

A. Yes, I am.

Q. How so?

A. There have been times I had to review it. I have also been his acting supervisor, but always because of my experience on GAPMSes, I have been periodically asked to review his work product.

Q. Were you asked to review a GAPMS report of his on computer-assisted musculoskeletal surgical navigational orthopedic procedures for total knee arthroplasty, sir?

A. Yes. I remember in March of 2022 being asked to take a look at that draft.

Q. What did you find based on your review?

A. I had found that he had plagiarized parts of it.

Q. Now, Mr. English has testified before in this case that he did not include citations for a draft document. So how then can you say that he plagiarized something when he just didn't cite something in the draft?

A. Because according to the Bureau of Medicaid Policy Procedures, when you have completed a draft of something and you have routed it to your supervisor for approval, and your supervisor signs off on it as having approved it and sends it to the Bureau Chief, that's a finalized draft. That's not a draft for review and feedback prior to routing. That's a finalized draft.

MR. JAZIL: Your Honor, I have no further questions.

THE COURT: Cross-examine?

CROSS-EXAMINATION

BY MS. DeBRIERE:

Q. Good morning, Mr. Brackett. I've been taking some notes, so I'm going to get myself organized. It will take just a second.

A. No problem.

Q. Thank you.

Okay. Let's start by talking about your education a

little bit.

You have an Associate in Arts from Tallahassee Community College; is that correct?

A. Yes.

Q. And you have undergraduate degree in history from Florida State University?

A. Yes.

Q. You have a Masters of Arts also from Florida State University; is that right?

A. That's correct.

Q. I think your thesis for your Masters was called, "Pensacola, Florida, During the Civil War and Reconstruction"?

A. That's right.

Q. Do you have a science degree?

A. I do not have a science degree.

Q. Do you have a medical degree?

A. I do not.

Q. Are you or have you ever been a health care provider?

A. I have not personally worked as a health care provider.

Q. Have you published in any scientific journals?

A. No, I have not.

Q. Have you published in any medical journals?

A. No, I have not.

Q. And you mentioned you were peer-reviewed. What was that

in?
A. So my peer-reviewed articles, those were historical. One was in the Florida Historical Quarterly, and the other one was in Southern Studies, which is an Interdisciplinary Journal of the South. That one actually was a public-health-history-related project.
Q. What was the title of that article?
A. "Cutting Costs by Cutting Lives."
Q. And what was it about?
A. It was about prisoner health and how it led to the abolition of Florida's penal labor system.
Q. And the other article you published in Florida Historical Quarterly, I believe the name of that article was "Wrongful Defeat: The 1934 Florida Senatorial Democratic Primary between Claude Pepper and Park Trammell"; is that correct?
A. That's correct.
Q. Do you have any experience conducting clinical research?
A. Can you please rephrase that?
Q. I can try asking it again. Does that work?
Do you have any experience conducting clinical research?
A. So are you referring to reading clinical-reviewed articles or are you talking about actually preparing research for clinical journals?
Q. Actually preparing research for clinical journals.
A. No.

Q. Do you have any education or training related to the evaluation of clinical or medical research?
A. So, when I did work at the Department of Health as a medical disabilities examiner, that job, in order to execute it correctly, you do have to have a degree of medical literacy. So you do spend a lot of time reading medical literature, going through medical science. You are collaborating with doctors. That job requires a high degree of medical literacy. If you don't have it, you can't execute it.
Q. When did you work in that position?
A. I worked in this position in 2014 and 2015.
Q. Did you go straight from being a teacher to going into being an adjudicator?
A. Yes.
Q. And what kind of teacher were you?
A. So I have caught a little bit of everything. I taught just about every social science thread, middle school, high school, I also taught college and university. When I --
Q. I'm sorry, Mr. Brackett. I was just speaking if the teaching position you held directly before becoming an adjudicator. What teaching position was that?
A. So I taught math and science at a school in Sweden.
Q. What type of school?
A. It was an international school, English speaking.

Q. What grades?
A. So I taught around ninth grade.
Q. Okay. And then the adjudicator position, did that require a degree in science to work at?
A. No. So the Department of Health brought in people with different backgrounds, and the Social Security Administration does have a program for people to go through to train to become one.
Q. So you received some training with the Social Security Administration regarding medical reviews; is that correct?
A. That is correct.
Q. How long was that training for?
A. That training was really ongoing for about a year. Of course, your first couple of months are just spent doing nothing but training, and then they start giving small numbers of cases. And as you train on those, you steadily get more and more well versed in medical literacy, policy. It takes about a full year before they work you up to a full caseload. So you train for a year.
Q. Okay. Turning to the case at hand, Mr. Brackett, the task given to AHCA by the governor's office in this matter was to take a detailed look at the available medical evidence or at least the peer-reviewed literature and see what it says. Is that an accurate statement?
A. Yes.

Q. And it's my understanding that Ann Dalton and Secretary Weida selected you and the Canadian Prescription Drug Importation Program team for that task; is that right?
A. That's right.
Q. You testified just a second ago you were chosen for that task in part because of your experience in special projects as well as your experience I think for ten months, you said, in GAPMS. Why was this a special project?
A. Well, for me, I considered this a special project, it was just a GAPMS, but since it was a job that was outside the Canadian Prescription Drug Importation. Special projects is kind of a term that I've used personally for myself, since it was a -- I just considered it a special project, considering it was a little outside what my position description required.
Q. So, it was something you defined yourself, but it was criteria that Ms. Dalton used to select you to draft the GAPMS, right?
A. Yes.
Q. Nai Chen, a pharmacist, was also on the Canadian Prescription Drug Importation Program team; is that right?
A. That's correct.
Q. And Mr. Chen is a pharmacist; is that right?
A. Yes.
Q. Mr. Chen's assistance with the June 2022 GAPMS report,

would you describe it as fairly limited?
A. As far as the work that contributed, that would be limited, but he and I discussed stuff every day.
Q. Okay. So his role my understanding was two parts: He created the map that you discussed earlier, and then he also occasionally sent you -- found and sent you an article. Is that accurate?
A. Yes, he did that as well.
Q. It's my understanding that the process you used to draft the June 2022 GAPMS was to collect and review the literature that you deemed relevant in determining whether gender-affirming care was experimental. Is that an accurate representation of your process?
A. So my assessment going through, determine whether or not -- finding sources that were relevant to the topic, that would be accurate, yes.
Q. Did you rely on all relevant medical literature regarding gender-affirming care when drafting the June 2022 GAPMS?
A. I relied on everything that I found and include on my works cited page.
Q. So everything you relied on is contained in that works cited page; is that correct?
A. That's correct.
MS. DeBRIERE: So, Your Honor, I would like to show what has been marked as Plaintiffs' Exhibit 141. It will take

just a second to appear on the screen. Bear with me.
BY MS. DeBRIERE:
Q. Mr. Brackett, this is a 2011 study from de Vries. The study pertains to puberty suppression in adolescents with gender identity disorder and published in the Journal of Sexual Medicine.
Did you rely on this study in your report?
A. I believe I did cite study. Yeah, this is one of the studies that we considered.
Q. And this is contained in your works cited?
A. I think that one is, yes.
MS. DeBRIERE: Can we bring up Plaintiffs' Trial Exhibit 18. Can we go to page 40, please.
BY MS. DeBRIERE:
Q. Mr. Brackett, what I would like you to do is review that. I believe it's in alphabetical order, so we can scroll down to page 40. Is that correct, it's in alphabetical order?
A. Yes, it's in alphabetical order.
Q. Right now we are talking about de Vries, the 2011 study. I do see --
MS. DeBRIERE: Go to page 40, please.
BY MS. DeBRIERE:
Q. I do see a study here 2014 de Vries, but I was asking about a 2011 study.
A. So in response to that question, is that there are 88

articles cited. Many of these I have not laid eyes on in a year.

Q. That's fine. I was trying to confirm: Did you rely on the 2011 de Vries study?

A. What's cited in the works cited is what I relied on --

Q. Okay.

MS. DeBRIERE: Can we bring up Plaintiffs' Exhibit 166, please.

BY MS. DeBRIERE:

Q. This is a 2013 Colizzi study. It's entitled, "Hormonal Treatment Reduces Psychobiological Distress in Gender Identity Disorder," and it was published in the Journal of Sexual Medicine. And I would just like to look at the study's conclusion at PLAINTIFFS6574. It states:

Our results suggested that untreated patients suffer from a higher degree of stress and that attachment insecurity negatively impacts the stress management. Initiating the hormonal treatment seemed to have a positive effect in reducing stress levels, whatever the attachment style may be.

Mr. Brackett, I can tell you this is not contained in your works cited page. Did you rely on this study in drafting the June 22nd GAPMS report?

A. No, I did not.

MS. DeBRIERE: Can we go to Plaintiffs' Trial Exhibit 176.

BY MS. DeBRIERE:

Q. This is 2021 Green study that discusses the association of gender-affirming hormone therapy with depression, thoughts of suicide and attempted suicide among transgender and nonbinary youth. It was published in the Journal of Adolescent Health. And looking at the conclusions of the study in PLAINTIFFS6676, it states:

Findings support a relationship between access to gender-affirming hormone therapy -- that's what "GAHT" stands for -- *and lower rates of depression and suicidality among transgender and nonbinary youth.*

So, again, Mr. Brackett, I can tell you this article is not contained in your works cited page. Did you rely on it in the June 2022 GAPMS report? We're happy to bring up the works cited page.

A. I've got it right here in front of me.

No, we did not look at this one, but we did look at studies similar to that.

Q. What study was that?

A. So I think that one would be -- because we did look at surveys. I think we used as an example of a study we used Geffen.

Q. I'm sorry?

A. On page 40, the Geffen study.

Q. And what was the name of that study?

A. Wait. No. I want to backtrack on that one.

No, we didn't. In our quality of evidence section -- I think I had the authors mixed up -- we did rely on -- we did do an analysis of a study that we relied on a large survey.

Q. Okay. But you did not rely on this particular study?

A. I did not.

Q. And the topic of this particular study?

A. Are you talking about the topic?

Q. The study that you evaluated, yes.

A. So I would not use this study -- as far as the topic on suicide, I would actually need to go back and look at some of the content in the GAPMS report to confirm for you whether we did or not.

Q. Okay. I'll move on.

I would like to show what's marked as Plaintiffs' Exhibit 151. This is 2020 study by Achille. This is a study on the longitudinal impact of gender-affirming endocrine intervention on the mental health and wellbeing of transgender youth. It was published in the International Journal of Pediatric Endocrinology.

Looking at the study's conclusion at PLAINTIFFS6284, it states:

Our preliminary results show negative associations between depression scores/suicidal ideation and endocrine intervention, while quality of life scores showed positive

associations with intervention, in transgender youths over time in the U.S.

Again, Mr. Brackett, I can represent to you that this was not contained in your works cited page. Did you rely on this study in drafting the June 2022 GAPMS?

A. I did not.

Q. Bringing up Plaintiffs Trial Exhibit 154. This is a 2021 Almazan study which reviewed association between gender-affirming surgeries and mental health outcomes. It was published in JAMA Surgery. Looking at the study's conclusion at PLAINTIFFS6320, this study's results -- excuse me -- the study's results demonstrate that undergoing gender-affirming surgery is associated with improved past-month severe psychological distress, past-year smoking, and past-year suicidal ideation.

Same question, Mr. Brackett.

A. We did not use this one in our study.

MS. DeBRIERE: I'm going to ask for Plaintiffs' Exhibit Trail Exhibit 155.

BY MS. DeBRIERE:

Q. This is a 2022 Ascha study. It evaluates top surgery and chest dysphoria among transmasculine and nonbinary adolescents and young adults, published in JAMA Pediatrics.

I have the same question for you, Mr. Brackett.

A. If it's not in our works cited, we did not use it.

Q. Okay. Just one more.

Looking at one final study, Plaintiffs Trial Exhibit 192, this study is entitled, "Experience of Chest Dysphoria and Masculinizing Chest Surgery in Transmasculine Youth." It's authored by Mehringer in 2021.

Looking at the study's conclusion at PLAINTIFFS6858, it states that, quote:

We *observed consensus that chest dysphoria is a major source of distress and can be functionally disabling to transmasculine youth. Masculinizing chest surgery performed during adolescence, including before age 18, can alleviate suffering and improve functioning.*

Last time, Mr. Brackett, was this a study you relied in the June 2022 GAPMS report?

A. We did not rely on this study.

Q. So you stated during your earlier testimony that your review was exhaustive. Do you maintain that your review of those medical literature was exhaustive as to gender-affirming medical care?

A. I still maintain that position, yes.

Q. So turning back to Plaintiffs' Trial Exhibit 18, in the June 2022 GAPMS report, you concluded that because the cause of -- excuse me. Let's get to the page first so you can read it. It would be page 14.

A. Okay.

Q. So in the report you conclude that because the cause of gender dysphoria has not been established, treatments that pose irreparable effects should not be utilized to address what is still categorized as a mental health issue.

There is no citation next to that statement, is there, Mr. Brackett?

A. No, there is not.

Q. So that's your independent conclusion?

A. Yes, that's my independent conclusion.

Q. Also, in the June 2022 GAPMS report, on page 21, you discuss the positions of the American Academy of Pediatrics and the American Psychological Association regarding gender-affirming care, and you conclude that stances like these can substantially influence practitioners in their treatment recommendations.

And, again, Mr. Brackett, there is no citation next to this statement; is that right?

A. That's correct.

Q. So this is your independent conclusion?

A. That's my independent conclusion.

Q. Are you a member of any professional medical organizations?

A. No, I'm not.

Q. In a couple of the sections of the June 2022 GAPMS report you discuss watchful waiting. If high percentages of

children diagnosed with gender dysphoria.

THE COURT: Give me the exhibit number of this again. I thought you said Plaintiffs 18, and --

MS. DeBRIERE: That's correct, Your Honor, it's Plaintiffs' Trial Exhibit 18. It's the June 2022 GAPMS report.

THE COURT: I got it.

MS. DeBRIERE: Page 12.

MR. JAZIL: Your Honor, if I may, it's also DX6. DX6 is the exhibit with all of the attachments.

THE COURT: I was just pulling up the wrong document on my machine. I'll figure that out at some point, but thank you.

BY MS. DeBRIERE:

Q. So as I stated, in a couple of other sections of the June 2022 GAPMS, you mention watchful waiting; for example, you state:

If high percentages of children diagnosed with gender dysphoria also have histories of trauma and attachment issues, should conventional behavioral health services be utilized without proposing treatments that pose irreversible effects? Would that approach not provide additional time to address underlying issues before introducing therapies that pose permanent effects.

And then you say, *For example, one of those approaches*

would be the watchful waiting approach.

Is that an accurate representation of your report?

A. I'm seeing the whole screen. I'm trying to follow you from where you were reading.

Q. Take your time to locate it. It's in the second full paragraph.

A. Okay. Can you scroll down so I can see the exact page number?

Okay. There we are.

Q. I apologize. There is --

A. I was reviewing the wrong page.

Q. It was my fault, Mr. Brackett. I apologize. I confuse things.

So, once again let me ask the question, because I'm sure at this point it's been lost.

There is a couple of times in this report that you refer to watchful waiting. This is an example of referring to watchful waiting.

When you were referring to watchful waiting, were you referring to the Dutch model?

A. Yes.

Q. And under the Dutch model, it's my understanding that after the waiting period the studies suggest that care should be started at some point for those who persist. Is that accurate?

A. According to those individuals, I think they do make recommendations for that, yes.
Q. Okay. Based on your report it seems like you're endorsing watchful waiting. Is that a correct characterization?
A. No. I can see how that paragraph can be read, though, when taken out of context, but no.
Q. Okay. Because, just to be clear, the watchful waiting approach at some point does recommend that care be started; is that right?
A. At some point, yeah, following the Dutch model.
Q. Okay. Thank you.
MS. DeBRIERE: Can we pull up Plaintiffs' Trial Exhibit 23, which is Rule 59G-1.035.
Your Honor, my co-counsel was asking if we would like to stop for lunch. I think I only have probably 20 minutes left. It's 12:30.
THE COURT: If we can finish, let's do. We can make it till 1:00 before we eat.
BY MS. DeBRIERE:
Q. Okay. So as my friend reviewed earlier, part of the Agency's standard process in assessing whether health services fall with Generally Accepted Professional Medical Standards is to determine whether the services are supported by evidence-based clinical guidelines. Is that a correct

characterization?
A. So, subsection 4(a), yes.
Q. Having read your report, I take it that you do not think WPATH guidelines are evidence-based. Is that a correct statement?
A. Well, I can -- when you take into account evidence at-large, well, yes, they are evidence-based, but that evidence is low, low, very low quality. So it's very weak evidence, and you can't build a solid foundation for guidelines on weak evidence.
Q. So that's why you didn't use WPATH as a determining factor under 4(a); is that right?
A. No, that's not correct. I did use WPATH. I took WPATH's guidelines extensively into my considerations. I read, re-read, and probably re-read again their guidelines. I did take them into high consideration, maybe more so than some of the other sources.
Q. Okay. Does WPATH maintain that gender-affirming medical care is experimental?
A. No, that's not WPATH's stance.
Q. Okay. So you did not adopt that portion of WPATH; is that right?
A. My findings didn't agree with theirs.
Q. Okay. Thank you.
And your findings -- so it's my understanding that your

finding did not agree with theirs because your determination of the low quality of the evidence; is that correct?

A. Right. My assessment of the evidence did not align with the strength of their recommendations.

Q. Okay. Last week plaintiffs' expert, Dr. Dan Karasic, testified that a 2016 study found that there was a high degree of certainty to support the provision of care in only 13 and a half percent of the time when a systematic review of all medical interventions was conducted.

Did you take that particular finding into consideration when you decided not to follow the WPATH's guidelines in your opinion?

A. Since I don't think we included that in our works cited, I don't think we took that position into account, no.

Q. Okay. Dr. Karasic further testified about another study, also a systematic review of a variety of medical interventions, not just gender-affirming care, which was done to determine the percentage of interventions that satisfied the high quality criteria of GRADE, dividing those interventions into simple and complex.

Dr. Karasic testified that the study found that, when looking at complex interventions which would include gender-affirming medical care, none had high certainty under GRADE, and the most common result was the medical intervention demonstrated was very low certainty.

Again, Mr. Brackett, did you consider that when you were adopting your conclusions in the June 2022 GAPMS report?

A. I did not consider that, but based on what you've read, that seems to mirror my findings upon my reading of the evidence.

Q. Okay. I was saying as to all medical interventions, not just gender-affirming medical care.

A. No. I understand where you are going with that, yes.

Q. You also just mentioned in your earlier testimony that, after learning that the 2017 surgery GAPMS -- GAPMS on gender-affirming surgery, was not, as you mentioned, probed and the studies relied on, guidelines cited, were taken at face value.

Did you decide at that point, seeing that that GAPMS was weak, that you would go back and review all GAPMSes to make sure there were similar weaknesses regardless of the type of care it was assessing?

A. No. That's not a job I would undertake.

Q. Looking at another factor under 59G-1.035, the criteria used to determine whether -- another factor under 59G-1.035 is evaluating whether there is other credible health coverage of the health service. That would be (4)(e).

So in reviewing the June 2022 GAPMS you assess coverage under Medicare, TriCare, the VA, and state Medicaid programs; is that correct?

A. That's correct.
Q. Did you include an assessment of whether gender-affirming care was covered by commercial or private insurers?
A. No, we did not.
Q. So, looking at this rule, where in this rule does it state to limit assessment to only government insurance programs?
A. It doesn't actually specify what insurance programs to look at. It just says other credible insurance payors.
Q. So the ruling does not contain the limitation as to only government insurance programs; is that right?
A. It's not a requirement, but it's -- this is also not the only GAPMS where did not look at private payors. It's a totally different business model.
Q. Fair enough. So in undertaking GAPMS, prior to the June 2022 GAPMS, was there ever a time AHCA did rely on private or commercial insurance coverage as part of the assessment?
A. There have been times with GAPMS reports in the past that we've taken a look at private payors. That's usually to supplement if we are having problems getting enough information from other Medicaid payors, but first and foremost it's always what do the other state Medicaid programs cover.
MS. DeBRIERE: I would like to pull up at Plaintiffs'

Trial Exhibit 331, this is a GAPMS on scleral contact lens in its final draft form. On page 7 -- scroll down a little bit, a little bit more. There we go.

BY MS. DeBRIERE:

Q. So here, consideration, yes, of commercial insurance coverage, AEtna, Blue Cross/Blue Shield, I think it continues on to the other page. So in this GAPMS you did decide to rely on commercial insurers?

A. I did not actually author the one on scleral lens, but this mirrors some of the GAPMS reports I did. I mean, when we don't have an exhaustive perspective of other state Medicaid programs or to strengthen that section, often we can add private insurance payors.

Q. Okay.

MS. DeBRIERE: Can you scroll up just a little bit, probably the page above.

BY MS. DeBRIERE:

Q. So here it says state Medicaid programs, 30 Medicaid programs include coverage for scleral contact lens. So here it looks like there was strong evidence within the state Medicaid programs, but you also decided to do an analysis of the commercial insurance; is that right?

A. Well, 30 states, yes. That's often at the analyst's discretion. It's not necessarily required.

Q. Okay. A final factor, under 59G-1.035 calls for the view

by -- excuse me. Let's start by saying:

Just reviewing through some of your earlier testimony about coverage not here in the U.S., but in European countries, you mentioned some European countries that have recently placed restrictions on gender-affirming care for minors. Is that an accurate representation of your testimony?

A. Yes.

Q. Have any of those countries barred provision of coverage of gender-affirming care to adolescents under all circumstances?

A. I don't -- as I recollect, I don't think so, but I think it's very, very extenuating circumstances if it's used.

Q. How would you define "extenuating"?

A. I don't know. You would have to -- I mean, given -- I'm basing that statement based on the guidelines that I read from the other countries, it would be up to like House of Lords in Sweden to make that determination.

Q. So touching on one final factor under 59G-1.035, which calls for the views by clinical or technical experts on the subject or field. Did AHCA contract with Dr. Andre Van Mol to assist with the June 2022 GAPMS report?

A. Yes, we did contract with him.

Q. At the time AHCA decided to contract with Dr. Van Mol, were they aware that he was affiliated with the American

College of Pediatricians?

A. I do not know if they were aware.

MS. DeBRIERE: Can we pull up Plaintiffs' Trial Exhibit 284.

BY MS. DeBRIERE:

Q. You see here some articles that Dr. Van Mol shared with Secretary Weida while working on the June 2022 GAPMS report. Some of these articles are about "Financing the Transgender Movement and Its Tactics," another title is "Who are the rich, White Men Institutionalizing Transgender Ideology." Do you see those there?

A. Yes.

Q. Are these the kind of articles that AHCA might take under consideration when they're deciding whether to contract with consultants to provide information about care for people who are transgender?

A. I can't speak to that.

Q. Would it have affected your personal decision to contract with Dr. Van Mol?

A. I don't know. Because this is an email, I don't know how it would apply to the large context of the discussions.

MS. DeBRIERE: Can we pull up Plaintiffs' Trial Exhibit 285.

BY MS. DeBRIERE:

Q. Here Dr. Van Mol writes to you: *I've read through*

several more. These four are the best of the lot that establish the connection to big pharma, biotech, philanthropy profiteering in the clothes of being rights advocates.

Including an article, you'll see in the attachments called, "A Founding Father of the Transgender Empire," as well as, "The ACLU Gets Fat on Pharma and Tax Funding."

So these articles were sent to you. Did they have any impact on your decision as to whether to rely on Dr. Van Mol's information provided?

A. Well, I never actually read anything that he sent us, so as far as those goes because they didn't really pertain to the subject I was evaluating. I was looking at the medical evidence. So the input that I got from Dr. Van Mol that helped were mostly more getting citations and some feedback or suggestions for peer-reviewed literature that were in academic journals.

Q. Did these articles that he shared with you, did it indicate he might be biased?

A. I mean, it indicated that I think he disagreed with the conclusions of a lot of medical evidence.

Q. Okay. So you did know that he disagreed with gender-affirming medical care when you were consulting with him; is that right?

A. As we worked with him, yes, I was aware of that position.

Q. Okay. Turning to the rule adoption process a little bit,

why did you -- you earlier testified. Why did you expect such a large opposition to the rule at the public hearing?
A. Well, as far as my experience and my role in the process since we had gotten so many comments -- I mean, we had like 600 comments -- hundreds before the hearing even took place, so we expected there to be a large turnout of people there; and just the fact that the report, when it was released, I mean, it was in the news. So this was a hot topic.
Q. Did that extensive opposition affect your decision to adopt the final rule?
A. No, it did not.
Q. Did AHCA confer with the GAPMS consultants about any questions they might receive from those testifying at the public hearing prior to the hearing?
A. There were a couple, I think, Zoom calls. Generally the ones I was on were just more basically on how the arrangements for the hearing would go. I don't think so there was an extensive Q and A prep with the experts. I think it was just mostly more, here's what's going to happen, here's what you can expect.
Q. Okay. So AHCA didn't suggest that the consultants provide specific answers to questions for the public hearing?
A. I don't recall them providing specific answers.
Q. Okay. Did the consultants ask if they should say anything in particular at the public hearing?

A. No, I don't think there was anything like that, no.

MS. DeBRIERE: Can we look at Plaintiffs' Trial Exhibit 303.

BY MS. DeBRIERE:

Q. Here you see an email from Miriam Grossman to Secretary Weida and it says:

Quick question: Is it okay if while answering a question at the hearing, I say something like, this rule will protect young people in Florida the same way similar kids are now protected in Sweden, Finland, et cetera. I applaud the State of Florida and hope many others will follow.

So that does seem like asking if she should respond in a certain way at the hearing. Is that your interpretation?

A. Yeah.

MS. DeBRIERE: Can we look at Plaintiffs' Trial Exhibit 292. Can you scroll down just a little bit, please. I'm looking specifically for --

THE COURT: Voices up where we can all hear.

MS. DeBRIERE: I apologize, Your Honor.

Actually, can you pull up 286. Again, my mistake. Thank you. Can we scroll down. We talked about this exhibit quite a bit. Keep scrolling, please. This is not the right one. Can you go to 286A, please, A as in apple.

BY MS. DeBRIERE:

Q. So you had previously testified that Dr. Van Mol had put

together a bibliography for you, and this is the document you were referring to; is that correct?
A. Yes.
Q. Okay.
MS. DeBRIERE: And I just want to note for the Court, this document is both at 286 -- if you can scroll down, please, Ms. Gonzalez, keep scrolling through the whole document just very quickly so we can all see.
BY MS. DeBRIERE:
Q. You know, as I'm looking at this, Mr. Brackett, there's actually a 286B, as in boy, as well. This looks like more than a bibliography to me. Do you disagree with that contention?
A. There are some summaries in there. I actually didn't really look at the summaries. I just looked at the sources.
Q. Okay. It's my understanding you paid someone -- Dr. Van Mol close to $35,000 to write a document, a pretty extensive document, that you then decided not to consult while drafting the June 2022 GAPMS report; is that right?
A. Can you repeat the question?
Q. I absolutely can.
So it's AHCA's decision to pay Dr. Van Mol several thousand dollars to draft this document; is that right?
A. My awareness was that he already had this document composed before he contracted with us, or at least most of it

composed. I don't think, given the time that we had spent between getting an agreement done and him sending this to us, he would have had enough time to do this project on his own.

THE COURT: Here's the question: This man got hired for a lot of money to work for the State. He sends you this long document talking about the very subject you're working on, and your testimony is you didn't read it or take it into account. Is that --

THE WITNESS: No, Your Honor, I'm not testifying to that.

THE COURT: All right. Then tell us the truth. Did you read this document? Did you consider it?

THE WITNESS: So, I read the document, but I was primarily interested in the articles. That was really what I was looking at, or the articles and the citations. The content summaries, I wanted to look at -- I look everything for my own eyes.

THE COURT: So he read it. There you go. Next question.

MS. DeBRIERE: Thank you, Your Honor.

Plaintiffs' Exhibit 291. Scroll down, please.

BY MS. DeBRIERE:

Q. I think you had just testified that Dr. Van Mol had already prepared the document and simply shared it with AHCA.

What I just showed, that was the master background

document; is that correct?
A. That was the document that he had sent to us. I mean, I don't -- no one has ever referred to it as a master background document. I'm not sure what's meant by that.
Q. Well, what is this master background document then that he refers to in his invoice?
A. I guess that would probably be what he sent us. I didn't see his invoice, so --
Q. So Dr. Van Mol may have charged you guys nine hours for completing a master background document that he had already drafting previously?
A. No. I think, given how long it is, it would strain fragility to say that he composed a 55-page document in nine hours.
Q. I just have a few more questions.
MS. DeBRIERE: Can we pull up Plaintiffs' Trial Exhibit -- what we have marked as Plaintiffs Trial Exhibit 365.
Your Honor, if I may turn to counsel, this, Mr. Jazil, is an exhibit that we shared with you last night and asked if there were any objections. It's a press release regarding Senate Bill 254. I'm gathering from your face that you did not see my email.
MR. JAZIL: Your Honor, I haven't seen the exhibit. Perhaps we can put it up and I can --

If my friend is going to represent this is from the governor's website, then I think the Court can take judicial notice of it. I think it's a press release. Are you --

THE COURT: Are you offering the document in evidence?

MS. DeBRIERE: I would like to, Your Honor, yes, please.

THE COURT: It probably doesn't have a number, yet. I don't know what the last number is. Give it the next number.

MS. DeBRIERE: We premarked it, Your Honor.

THE COURT: 365?

MS. DeBRIERE: Yes, Your Honor.

THE COURT: Is there an objection to 365?

MR. JAZIL: Your Honor, a quick question. Are we using it to attribute statements to the governor or to --

MS. DeBRIERE: So, Your Honor, I --

THE COURT: Look, let me just tell you. I'm sure you all have read my *Warren* opinion. One of the things I said is, look, when an official makes a decision, the official is welcome to put it out however they want; and, if you put some statement out for political reasons, that doesn't tell you why you made the decision. And so, if you made a decision for legitimate reasons and you issued a press release to maximize the political benefit, well, that's what people who run for

office do. Maybe that tells you something about how it got done, but not very much. So this isn't going to tell us very much. It's too small for me to read it, but --

MR. JAZIL: Your Honor, just a word of caution, I guess; that is, statements in press releases that are attributed to people ordinarily aren't said by those people, they are written by someone in the press shop, et cetera. So with that --

THE COURT: Well, I get it; but, if it got issued in his name, it's --

I'll admit it. Plaintiffs' 365 is admitted.

(PLAINTIFFS' EXHIBIT NO. 365: Received in evidence.)

MR. JAZIL: Thank you, Your Honor.

MS. DeBRIERE: Scroll down, Ms. Gonzalez, the second page please.

THE COURT: And go ahead at some point and file 365 on the CM/ECF system so that it's part of the record.

BY MS. DeBRIERE:

Q. Mr. Brackett, as we just discussed, the governor's office issued a press release yesterday about Senate Bill 254, which in part prohibits the use of State funds like Medicaid to pay for gender-affirming care. Are you at all familiar with that bill?

A. Only what I have seen in local news.

Q. Are you familiar with the press release other than seeing

it here today in front of you?
A. I am now. No, I had not seen the press release.
Q. I just want to point out that in this press release it does use the slogan "Let Kids Be Kids."
Did AHCA solely develop the "Let Kids Be Kids" slogan?
A. You mean when we did the --
Q. Yes, for the --
A. -- GAPMS?
Q. -- June 2022 GAPMS.
A. I'm under the impression that AHCA created that, yes.
Q. Okay. And so the AHCA-created slogan has now been adopted by the governor's office regarding Senate Bill 254?
A. That appears to be the case.
Q. And you had mentioned that AHCA had developed other slogans for programs; is that right?
A. Yes.
Q. Okay. What were those slogans?
A. I think "lower Prescription Drug Prices." I think that's the one I can think of off the top of my head. Our website, I think, we have like one for visitation rights. I mean, our website has lots and lots of slogans and banners for various programs we do.
Q. Okay. So we would be able to find those slogans on AHCA's website?
A. You should. We definitely have archive versions of

these. I mean, we come up with new slogans every quarter, so --

Q. Okay. Thank you. Just one last set of questions.

It's my understanding that you were in the GAPMS position for 11 months; is that correct?

A. Ten months.

Q. Ten months. Thank you.

Jeff English, it's my position, was in that position for three years?

A. Yes.

Q. And he left that position voluntarily?

A. To my knowledge, yes.

MS. DeBRIERE: Thank you, Your Honor. That's all I have.

THE COURT: Redirect?

REDIRECT EXAMINATION

BY MR. JAZIL:

Q. Mr. Brackett, my friend asked you about studies that were not included in your GAPMS report. Do you recall that testimony, sir?

A. I do.

Q. One of the studies that my friend brought to your attention was a study called, "Top Surgery and Chest Dysphoria Among Transmasculine and Nonbinary Adolescents and Young Adults," from JAMA Pediatrics.

Do you recall questions about that?
A. I do recall her questions.
Q. If you go to page 43 of DX6, your GAPMS report, the third one down, sir.
A. Yes.
Q. Was that an article concerning top surgeries and dysphoria?
A. Yes, it was.
Q. My friend mentioned the de Vries article, but your -- does your works cited include an article by the same author, just from a different year?
A. It does. And that was the reason why I was little confused when that one was put on the screen versus what we had actually cited. Titles can be kind of combobulated sometimes.
MR. JAZIL: Can we pull up Plaintiffs' Exhibit 176, please.
BY MR. JAZIL:
Q. Do you recall my friend asking questions about this article, sir?
A. I do.
MR. JAZIL: If we can go to the next page. Can we blow up the procedures section.
BY MR. JAZIL:
Q. Take a look at that, Mr. Brackett, and look up at me when

you're done.
A. Okay.
Q. Did you in your GAPMS report look at other articles that used the survey method to obtain information?
A. We did.
Q. And did you find them -- why -- did you find them persuasive?
A. No, I did not.
Q. Why not, sir?
A. While it's a survey, it does have a very large, large sample size. I mean, I think the citation I was looking for was on page 41, and it was by Herman. So, you have 34,700 plus sample size. They recruited through various social media means, Snapchat, et cetera, so they are looking through online communities. But regardless of how they are sampled, it's a momentary snapshot. It's how these youths are feeling at any given moment. It's just a momentary snapshot. We don't have longitudinal histories. We don't know the participants' backgrounds. We don't know their profiles.

So -- and I think these surveys, most of them are usually anonymous. So we don't really know who they are even. So that makes it quite problematic. But it's a snapshot, okay, this is interesting, but there's a lot more information that's needed.

MR. JAZIL: No further questions, Your Honor.

THE COURT: Mr. Brackett, they asked you a lot of questions about your background. I want to fill it in a little bit.

You were a teacher in Sweden immediately before you came to AHCA. Where else have you taught?

THE WITNESS: Your Honor, I also spent four years teaching in Jacksonville, Florida.

THE COURT: Where did you teach in Jacksonville?

THE WITNESS: So I taught at a charter school called River City Science Academy.

THE COURT: Say again.

THE WITNESS: Oh, it was a charter school called River City Science Academy. It was kind of like south side, Beach Boulevard area, if you're familiar with Jacksonville.

THE COURT: Some kind of science emphasis?

THE WITNESS: The school had a science emphasis, yes.

THE COURT: Where else? Sweden and that school in Jacksonville. Anywhere else?

THE WITNESS: I've also taught at Florida State University, Tallahassee Community College, and I also taught at St. Johns River State College.

THE COURT: What did you teach at FSU?

THE WITNESS: History.

THE COURT: Were you on the facility at FSU teaching history?

THE WITNESS: No. I was a TA.

THE COURT: So you were a student, and you were a TA, helping out -- I was an undergraduate at Florida State, so I had back then we called them graduate assistants. That's what you were, a graduate assistant?

THE WITNESS: Well, I was not assisting a professor. I was the teacher of record. So I prepared all of the lectures, exams, grade all the content. I was the teacher of record for those courses, sir.

THE COURT: And you were a student at the same time?

THE WITNESS: I was a student at the same time.

THE COURT: When you got involved in this GAPMS project, what did you understand about where the assignment came from; why it was that the Agency was doing a GAPMS study on the subject?

THE WITNESS: So, initially, when I got the assignment, when I was asked to do it, I figured there were some other factors at play. I wasn't really aware of those. I also knew it had been a long time since we looked at it. So I figured it was probably coming from Agency leadership.

THE COURT: Ms. Dalton gave you the assignment?

THE WITNESS: Yes, Your Honor.

THE COURT: She didn't tell you where the assignment came from? She left that for you to figure out on your own?

THE WITNESS: I don't -- often we ask these

questions, and we don't always get the answer. I figured it definitely came from like senior leadership.

THE COURT: But Ms. Dalton didn't tell you that?

THE WITNESS: It just didn't come up, Your Honor.

THE COURT: Did you have any reason to think it came from the governor's office?

THE WITNESS: I suspected that it probably did.

THE COURT: You live here in town, I'm going to guess you read the newspaper.

THE WITNESS: Yes, Your Honor.

THE COURT: You must have known that trans issues were a hot topic with this administration. True?

THE WITNESS: I was aware of that, yes, Your Honor.

THE COURT: Did you know when you got the assignment what result the administration would prefer?

THE WITNESS: I had an idea, I mean --

THE COURT: I haven't gone back and tracked the chronology, but people who took a position that didn't match up with what the administration wanted, haven't fared very well in the State. Were you aware of that at that time?

THE WITNESS: No, I was not.

THE COURT: Is it your understanding that being trans is a mental health issue?

THE WITNESS: Based on the DSM-5 diagnosis, being trans by itself, according to the definition, that's not.

THE COURT: I want to know what you believe.

Do you believe that there are people who are, in fact, trans people who have one native sex, biologic sex, sex assigned at birth as it's sometimes referred to, but who, in fact, identify as the opposite gender?

THE WITNESS: I do, Your Honor.

THE COURT: I've been involved and reviewed a number of public hearings. I don't think I have ever seen one that seemed to be so orchestrated in advance as this one.

First, have you been involved in any other public hearings that were as orchestrated as this one?

THE WITNESS: No, I haven't been involved in a public hearing that large or anything like that, no.

THE COURT: Who orchestrated this, or choreographed it? Who decided the order in which people were going to speak?

THE WITNESS: I don't know, Your Honor.

THE COURT: One of the questions on cross was about the -- I think they were Zoom meetings you said -- the discussions with the experts, and you said something that frankly struck me as curious. I want to follow up on it.

You said, "I don't think there was extensive Q and A prep with the experts." If there wasn't any Q and A prep with the experts, that's an odd way to phrase it. If there wasn't any extensive Q and A prep with the experts, was there at

least some Q and A prep with the experts?

THE WITNESS: So I wasn't present for all of the calls, all of the Zoom meetings, so I would be speaking to events for which I wasn't present for. The calls I participated on were not Q and A prep sessions. There were just more logistics, getting to and from the venue, how things would transpire.

THE COURT: How things would transpire, that we're going to have a long list of speakers in favor or what was that?

THE WITNESS: No, Your Honor. It would be more how we go into the building, where we'd sit, things like that.

THE COURT: And this has nothing to do with the merits, but DOT, where is DOT? I'm not sure I know where DOT is.

THE WITNESS: Your Honor, it's right there by Cascade Park.

THE COURT: In one of those that used to be Caldwell.

THE WITNESS: I think it might be the Caldwell building. I don't know. It's definitely one of the historic ones.

THE COURT: One of those --

THE WITNESS: 1950s, it's very nice.

THE COURT: When I used to go to the Public Service Commission over there, I'm not sure anybody described it as

very nice, but I'm with you. All right. Thank you.

Questions just to follow up on mine?

MR. JAZIL: Your Honor, just one.

REDIRECT EXAMINATION

BY MR. JAZIL:

Q. Mr. Brackett, if you had come to the opposite conclusion in your GAPMS report, in other words, supporting the use of puberty blockers, cross-sex hormones, gender reassignment surgeries, do you think you were going to get fired from your job?

A. No, definitely not.

Q. Why not?

A. So, I'm a career civil servant. My position is classified as such. I was performing a task as I was assigned, which was to do a GAPMS report on treatments for gender dysphoria.

MR. JAZIL: Nothing further, Your Honor.

THE COURT: Thank you, Mr. Brackett. You may step down.

MS. DeBRIERE: I have one follow up.

THE COURT: Sure.

RECROSS-EXAMINATION

BY MS. DeBRIERE:

Q. Mr. Brackett, just for the clarity of the record, do you know if the request to undertake the GAPMS came from the

governor's office?
A. To undertake to do the GAPMS specifically?
Q. To do the review of gender-affirming care -- Medicaid coverage of a gender-affirming care.
A. I think it did. I'm not certain.
MS. DeBRIERE: If we can bring just up -- hold on.
BY MS. DeBRIERE:
Q. So you say you are not sure.
A. I mean, I think from my understanding was that the governor's office asked us to also take a review as the Department of Health did. As far as to do a GAPMS specifically, they are not that familiar with our processes.
Q. But it is your understanding that the initial request for Medicaid to undertake a review of gender-affirming care came from the governor's office; is that right?
A. I think so.
MS. DeBRIERE: Thank you. That's all I have.
THE COURT: Now, thank you, Mr. Brackett. You may step down.
We are going to take a lunch break. Where do we stand? We're done for the day?
MR. JAZIL: Your Honor, we just have Dr. Scott left who is going to appear by Zoom Monday morning.
THE COURT: So we don't need a lunch break. We just need to quit for the day.

Anything else we need to discuss?

MR. GONZALEZ-PAGAN: Not from the plaintiffs, Your Honor.

THE COURT: Do we have time? Nine in the morning probably works in England.

MR. JAZIL: Yes, Your Honor.

THE COURT: All right. I will see you back at 9:00, Monday morning.

(*The proceedings adjourned at 1:11 p.m.*)

* * * * * * * *

I certify that the foregoing is a correct transcript from the record of proceedings in the above-entitled matter. Any redaction of personal data identifiers pursuant to the Judicial Conference Policy on Privacy are noted within the transcript.

Judy A. Gagnon *5/20/2023*

Judy A. Gagnon, RMR, FCRR Date

Registered Merit Reporter

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UNITED STATES DISTRICT COURT
NORTHERN DISTRICT OF FLORIDA
TALLAHASSEE DIVISION

AUGUST DEKKER, et al.,	)	
	)	
Plaintiffs,	)	Case No: 4:22cv325
	)	
v.	)	Tallahassee, Florida
	)	May 22, 2023
JASON WEIDA, et al.,	)	
	)	9:00 AM
Defendants.	)	Volume VII
_____	)	

TRANSCRIPT OF BENCH TRIAL PROCEEDINGS
BEFORE THE HONORABLE ROBERT L. HINKLE
UNITED STATES CHIEF DISTRICT JUDGE
(Pages 1263 through)

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P R O C E E D I N G S

(Call to Order of the Court at 9:00 AM on Monday, May 22, 2023.)

THE COURT: Good morning. Please be seated.

Mr. Jazil, please call your next witness.

MR. JAZIL: Thank you, Your Honor. The defense's next witness is Dr. Sophie Scott.

THE COURT: Dr. Scott, good morning.

THE WITNESS: Good morning.

THE COURT: I'm Judge Hinkle. Before the lawyers start asking you questions, let me ask you this: Are you there in a room all by yourself?

THE WITNESS: I am, yes. I'm in my office. I'm on my own.

THE COURT: If somebody comes in, we'll deal with that. Otherwise, we'll assume you're there by yourself.

If you would, please, raise your right hand.

DR. SOPHIE SCOTT, DEFENDANTS WITNESS, DULY SWORN

THE COURT: Please tell us your full name and spell your last name for the record.

THE WITNESS: My name is Sophie Kerttu Scott, and my surname is Scott, S-c-o-t-t.

THE COURT: And tell me again -- maybe spell the middle name.

THE WITNESS: K-e-r-t-t-u.

THE COURT: Mr. Jazil, you may proceed.

MR. JAZIL: Thank you, Your Honor.

DIRECT EXAMINATION

BY MR. JAZIL:

Q. Dr. Scott, what do you do?

A. I'm a cognitive neuroscientist at University College London.

Q. Dr. Scott, what does a cognitive neuroscientist do?

A. A cognitive neuroscientist works in the area of brains and brain structure and brain function and relating that to human experience and human behavior. So it's an area of neuroscience, and we work with brains. But we're sort of a -- analogous to psychologists.

Q. Dr. Scott, you said that you work at University College London.

MR. JAZIL: I'd like to pull up what's been admitted into evidence as Defendants' Exhibit 33.

BY MR. JAZIL:

Q. Dr. Scott, this was a CV attached to your expert report. Was that CV a fair and accurate summary of what you've done to date?

A. Yes.

Q. Now, Doctor, you mentioned that you work at the Institute of Cognitive Neuroscience at University College London. On your CV, it says that you are the director of that.

What does the director of the Institute of Cognitive Neuroscience do?

A. I'm responsible for the day-to-day running of the building. So, you know, if there is a problem with staff or an issue with safety, then that's my responsibility, and I'm also responsible for the scientific direction of the research and the teaching that's carried out here. So I have a broad scientific perspective. In addition to that, I'm also running my own lab here at the institute.

Q. Do you also do your own teaching at the university?

A. Yes, yes, I teach a couple of modules.

Q. I understand.

Doctor, just going through your résumé, it says that you were previously the Wellcome trustee or fellow for several years --

A. Yeah.

Q. -- at the Institute of Cognitive Neuroscience.

What is that?

A. The Wellcome Trust is a big biomedical charity that funds biomedical research, and they fund people at different points in their careers as what they call research fellows.

What that means is if you apply for one of these grants and you are awarded it, it pays for your salary. So you are an independent research fellow at the university. It also pays for other staff working on your grant and also for all your research

expenses, so, you know, the cost of brain scanning, for example, and all your other costs, like travel and publications.

So they are very competitive grants to get, and they're fantastic grants to get because it really lets you build up your lab and build up your research profile.

Q. And, Doctor, is it correct that you've been a professor since 2006 at University College London in neuroscience?

A. Yes.

Q. Doctor, just going down, you've got a list of prizes and recognitions.

Doctor, what is the Michael Faraday Prize by the Royal Society?

A. The Michael Faraday Prize is one of the prizes given by the Royal Society for excellence in scientific research, but also excellence in communicating science. So it's for my work both scientifically and also my work communicating research.

Q. And was the work related to neuroscience or something else?

A. Yes, it's all neuroscientific research.

Q. Doctor, it also says that in 2020, you were appointed Commander of the Most Excellent Order of the British Empire for services to neuroscience.

Do you see that?

A. Yes.

Q. Who appointed you Commander of the Most Excellent Order of the British Empire for services to neuroscience?

A. It's awarded by the monarch. So my -- I was appointed commander of this -- CBE, it's called -- on the Queen's birthday in 2020.
Q. Understood.
It says that in 2016, you were elected a fellow of the British Academy.
First, can you tell us what the British Academy is?
A. The British Academy is one of a number of learned societies in the UK which are there to promote academic research and also researchers. So the British Academy is broadly covering research into the humanities, so it includes psychologists and people at the -- sort of the humanity end, if you like, social end of the sort of research I do, and it goes across linguistics and also historians and philosophers.
Q. And what were you elected as a fellow for?
A. I was elected for my research into -- yeah, into human communication.
MR. JAZIL: Can we go on to the next page?
BY MR. JAZIL:
Q. It says that in 2012 you were elected a fellow of the Academy of Medical Sciences.
Doctor, what's the Academy of Medical Sciences?
A. The Academy of Medical Sciences is another learned society. It's a more recently developed one, and it's people doing research and working in the fields of medicine and also related

disciplines. So there are a lot of medics who are members of the Academy of Medical Sciences but also lots of people like neuroscientists or epidemiologists who do research which relates to biomedical science, like me.

Q. Doctor, there is a section in your CV that talks about supervision of graduate students. It says that you've supervised 14 Ph.D. students at University College London and 35 master students at University College London and two students at City University and one at the University of Reading.

Was the subject that all these students were studying neuroscience?

A. Yes.

Q. And later on in your CV, it lists where some of your students went. They went on to work at Oxford, the University of Amsterdam, and the Max Planck Institute; correct?

A. Yes, I'm very proud that everybody who has worked on my lab has gone on to a good job in academia or a related discipline.

Q. Understood.

Doctor, there's section in here about editorial work. It lists five journals.

First, can you tell us what editorial work means?

A. Editorial work for a peer-reviewed journal, and four of those journals are peer-reviewed journals. So *The Psychologist* at the top, that's a -- that's a journal for people who are members of the British Psychological Society.

All the other journals, my work there as an editor was to oversee the peer-review process. So people would submit papers to the journal; I would read the paper; I would decide whether or not it was appropriate to send out to review; I would select the reviewers and invite them. When they reviewed the paper, I would get those together, read the paper, read their reviews, and then come to a decision about whether the paper could be accepted, whether it should be rejected, or whether changes were needed. And then I'd oversee that whole process, and that is the peer-review process.

Q. Understood.

Doctor, have you ever done work for the U.S. National Institutes of Health and the National Science Foundation?

A. I have. I've been on panels overseeing the grant review process for a couple of ad hoc grants for the NIH, and I was on the -- an NSF panel for several years looking at psychology according to neuroscience grant applications.

And what you're effectively doing on those panels is people have written grants and submitted them to these different grant causes, and what your job is to do is to read the grants that have been submitted. Some of those will have been allocated to you to represent to the panel. So you read them in more detail, and you have to present them to the panel for discussion. And it's very -- in effect, what you're letting -- what you're doing is you're helping the funding body, NSF or NIH, decide how to

spend their money, what is the research that we should be funding.

It's an extremely interesting job to do because what you have to do is, of course, read in great detail, a bit like when you're an editor of a journal -- you have to read papers and these grant submissions in great detail. It might not necessarily be precisely in your own area of research. So it gives you a very useful, much wider view over the sorts of research going on in what discipline that you're a part of.

Q. And you've done the same work for the Royal Society?

A. I have, up until last year. For six years I was on the Dorothy Hodgkin Fellowship panel, and that's actually a panel that goes across all of science. So we're seeing grants submitted about computer science or oceanography or physics or genetics, and the panel reflects that. And for the six years, I was the person representing sort of behavioral neuroscience, cognitive neuroscience, psychology, anything to do with behavior and organisms.

And you're doing the same thing. You have to read the grant applications, and you have to represent them to the panel, and you have to interview the person who has come -- in this case, who actually is there to be -- who has submitted the work, who is going for this fellowship.

And that's extremely interesting because it's even broader than those NSF panels I was on, because any -- all possible

areas of science are being represented, and you have to be able to discuss different areas of science across a wide range of disciplines.

Q. Understood.

And, Doctor, looking at your CV, you've got approximately 150 refereed articles in there.

Can you tell what you say the term "refereed articles" mean?

A. Refereed articles, it's the same as a peer-reviewed article. So it's been through a formal process. You've submitted it to a journal, and it has been edited and sent out for peer review, and it's gone through some, potentially, period of revisions before being accepted.

Q. Were all those articles in the field of neuroscience?

A. I think all of them are in psychology and cognitive neuroscience with the exception of one, which is in poetry.

MR. JAZIL: You can take that down.

BY MR. JAZIL:

Q. Doctor, what were you asked to do in this case?

A. I was asked to provide some expert testimony about the -- the use of puberty blockers, gonadotropin-releasing hormone, agonists, and antagonists in teenagers -- four teenagers both in terms of the possibility of teenagers to be able to engage with what was -- understand the possibilities of what this kind of medication could mean, but also in terms of what the effects

could be on the developing teenage brain of GnRH agonists.
Q. Were you also asked to look at Dr. Edmiston's trial testimony in this case?
A. I was.
Q. Were you asked to review Florida law concerning the treatment of gender dysphoria?
A. I was not.
Q. Were you asked to review any clinical guidelines or best practices on the treatment of gender dysphoria?
A. I was not.

MR. JAZIL: Your Honor, I'd like to ask Dr. Scott her opinions in the field of neuroscience, brain development, brain structures, and neurochemistry, not poetry.

THE COURT: Questions at this time?

MR. SHAW: Yes, sir.

VOIR DIRE EXAMINATION

BY MR. SHAW:
Q. Good morning, Professor Scott. Good to see you again.
A. Morning. Nice to see you.
Q. Professor Scott, you're not a medical doctor; right?
A. I'm not.
Q. And you don't have any training in adolescent healthcare?
A. No.
Q. You've never treated a patient with gender dysphoria?
A. No.

Q. And you've never conducted any clinical research on gender dysphoria?
A. No.
Q. You've never published any peer-reviewed articles on gender dysphoria?
A. No.
Q. Your main area of research looks at the effects of speech, laughter, and sound on the brain; right?
A. Yes.
Q. And none of that --
A. And to do that, what I have to -- sorry.
Q. No, no. Please.
A. So what I have to do to study that is both understand the physics and the acoustics and the linguistic aspects of speech, but also I have to understand brain structure, brain function, brain neurochemistry, and brain development to be able to look -- looking at how speech is processed, for example, in the human brain.
Q. And none of that -- none of the things that you study -- speech, laughter, and sound, none of that relates to gender dysphoria; correct?
A. No.
Q. About puberty blockers, you testified that you're not a doctor. So is it safe to say that you've never prescribed puberty blockers?

A. I'm not a medical doctor, and I have not prescribed puberty blockers.
Q. And you've never conducted any clinical research on the effects of puberty blockers on the brain?
A. Other than reading the literature, which is, of course, research, I haven't conducted any basic science in that area, no.
Q. But never any clinical research yourself?
A. I've applied the research. I haven't done the research, no.
Q. And you've never conducted any clinical research on the effectiveness of puberty blockers in treating gender dysphoria?
A. Other than reviewing the literature, no.
Q. So is it fair to say that your knowledge of puberty blockers is based on your review of the literature?
A. Yes.
Q. And you submitted a report in this case; right?
A. Yes.
Q. Did you -- in your report, did you discuss any of the literature that looked at the effects of puberty blockers in treating -- in treating gender dysphoria?
A. No. I was looking at the animal research and what little human research there is on the actual brain effects of the puberty blockers.
Q. So, no, you did not discuss any human research in your

report related to gender dysphoria?
A. In the report, no. No.
Q. Are you aware of the Staphorsius 2015 study on executive functioning?
A. I am. Would you like me to talk about it?
Q. You didn't put that in your report, though?
A. I didn't, because if you look at the mice research -- I'm sorry; it wasn't research -- the mice study that was looking at -- it was conducted, I think, in 2018, 2019, as part of the case review looking at the evidence for the benefit of puberty blockers in treating gender dysphoria, which concluded that there were no benefits, partly because the evidence was very poor, and the Staphorsius paper was an example of very bad evidence for showing, for example, no difference in the effect of puberty blockers.

So it was a study using the Tower of London test where you are asking people to move -- it's a test. It's like a problem-solving test. And they were doing a functional imaging study of teenagers with or without gender dysphoria, and within gender dysphoria, some of them were on puberty blockers and some were not, and what they found was no overall difference.

But this was a study of functional imaging, which is hard to find robust differences in different populations, whoever they are, because it's quite noisy data. So it's not strong data either way. I wouldn't -- with that bit of functional

imaging study, I wouldn't choose to say whether or not that was something that was showing positively that there are no differences or definitely that there are differences. It's not a good dataset, and that's -- I'm quoting the mice study on that.

Q. Thank you.

You did not mention any of that in your report; correct?

A. Because of its poor evidential value, I did not.

Q. Right.

Well, you did not mention Staphorsius at all?

A. I did not for its poor evidential value.

MR. SHAW: Your Honor, in light of the fact that Professor Scott has no experience with gender dysphoria, no experience treating patients with gender dysphoria, no experience administering or clinically studying puberty blockers in any setting, we would move to exclude Dr. Scott's testimony.

THE COURT: Mr. Jazil.

Part of what I'm interested in in that exchange is she's now given testimony that was not in her report. Why does she get to come to trial and discuss something that's not in her report?

MR. JAZIL: Your Honor, a couple of points there.

One, the study that my friend mentioned, that is a study that she is -- that was not included in her expert report. It's a study that, I believe, was referenced in Dr. Edmiston's

testimony.

THE COURT: Why does that matter? If it's not in her report, why isn't it excluded on the ground -- I don't care how good a report it is, and I don't -- why does it matter if her testimony is true and relevant and helpful? If it's not in her report, isn't the answer it should be excluded?

MR. JAZIL: Your Honor, testimony regarding that one specific report, yes, but her testimony will be more than about just that one specific report.

THE COURT: Got it. We'll double back to that.

But if I understand what she just said, her report does not discuss studies on humans.

MR. JAZIL: No, Your Honor, that was incorrect. Her report does not discuss studies on humans for the treatment of gender dysphoria. Her report does discuss studies on humans for -- pardon me, Your Honor. Her report does discuss studies that talk about the use of puberty blockers for other things like precocious puberty, et cetera. So she looked at the available --

THE COURT: Point taken.

So, plainly, she can't give medical testimony about treating patients, and certainly not trans patients for gender dysphoria, but she can give testimony within her area, and -- and some of that testimony is certainly relevant to the issues here.

So she can testify about cognitive neuroscience within the scope of her report, and if particular questions come up that the plaintiffs think aren't within her expertise, object and I'll deal with it then. But the motion to exclude her testimony entirely is denied.

MR. JAZIL: Thank you, Your Honor.

THE COURT: And I'm not going to consider the testimony she gave in response to the voir dire question on subjects she did not include in her report. She -- her testimony should be received only as consistent and addressed in her report.

MR. JAZIL: Your Honor, clarification on that. At the end of Dr. Edmiston's testimony, there was a colloquy with the Court on some issues related to transgender identifiers in the brain. There was a question asked by one of my colleagues that elicited a response from Dr. Edmiston.

Would it be appropriate for her to comment on that exchange, which was, frankly, outside the scope of both sets of expert reports, but --

THE COURT: Maybe, and we'll deal with it when we get to it.

There is a difference between testimony offered by the proponent, by the party that hired the expert, when that testimony is outside the scope of the report on the one hand and testimony elicited on cross-examination by the adverse party on

the other hand.

And there is a difference between testimony elicited by the party that hired the expert on the one hand and an answer volunteered on the -- during the voir dire examination by the opponent on the other hand.

I don't recall the exchange involving Dr. Edmiston, but if it was something that your side asked, then your side certainly doesn't have an objection that it's beyond his report. If it's something he volunteered in response to a question that didn't call for it, that's different.

I also don't want to give the impression that I'm unduly strict in the application of the requirement to tender a full 26(a)(2) report. It's a dynamic process. Things come up during a trial. They certainly know that Dr. Scott is a cognitive neuroscientist, and they know generally what it is she's here to testify about.

So whether you can ask the question about the subject that Dr. Edmiston dealt with really depends on what it is and how close it is to what she's already disclosed, but I do understand how a lawyer would not come to court expecting to cross-examine her about this particular study when she didn't discuss that study or anything like it in her report, just comes up on voir dire. And so Mr. Shaw is not ready to cross-examine on that subject because he had no reason to think that's what we were going to be talking about.

MR. JAZIL: Understood. And, Your Honor, just so the Court's clear, Dr. Scott, in her expert report, talked about animal studies, human studies. The human studies were about giving -- as I explained earlier. So, I mean, to the extent that we're talking about animal studies and human studies, it's a broad category.

THE COURT: I get it, and I -- this is probably a longer discussion than Dr. Scott wanted to sit through or maybe than we needed to have. Let's get to the actual questions, and it may turn out none of this makes any real difference. I'll hear what Dr. Scott has to say.

MR. JAZIL: Thank you for the indulgence, Your Honor.

BY MR. JAZIL:

Q. Dr. Scott, I'd like to start with brain development.

A. Uh-huh.

Q. What are the phases to brain development?

A. There's three broad phases over life span of big changes in development of the brain. The first is during gestation and through to the end of being a child up to puberty, and that's when you get really big changes in the structure of the brain.

There's then another period during -- from puberty through to the end of adolescence, and then that takes you through to about the early 20s and then you have basically an adult brain, which is still a work in progress. That's still a flexible organism, but it then doesn't go through any big changes until

the end of life.

Q. And can you walk us through how brain structures evolve during those three phases?

A. So to think about this, you have to let me just very briefly touch on what we -- what we talked about when we're talking about brain structure. We're talking about neural tissue which is made up of brain cells called neurons, and all living things are made up of cells, and cells can be very different in different animals and different parts of the body, but brain cells are particularly unusual.

They have a cell body, which is containing the cell nucleus, and they're often surrounded by lots of little projections, some of them big, some of them small. And then there's normally one very long, slender projection that goes from that cell body that can go off and make connections elsewhere in the brain, and this is how your brain can make connections over relatively long distances, because the cell bodies have got these long axonal projections.

Now, if you look at the brain, these brain cells aren't just mushed in there. What they do is they form distinct layers. So the cell bodies sit in what's called grey matter, and that's the cortical mantle that sits on the surface of your brain is one big layer of grey matter, and then there are little nuclear grey matter sitting underneath that.

The cell connections, these long axons, form sort of

information superhighways, which are connecting different brain areas and sit underneath that cortical mantle. And that looks white, and it gets called white matter for this reason, whereas the cell body layers look grey, and they're called grey matter.

And if we look at the structure of the brain, what you're seeing is something that when you're born you have almost all the brain cells that you're ever going to have. You have nearly 90 billion brain cells, and you're born with almost all of them.

And what you see between sort of birth to about the age of 6 is that brain gets four times bigger, not because you're growing new brain cells, but because the brain structure is very rapidly growing and those brain cells are growing. They're growing longer, and they're starting to make many more connections.

So between birth and puberty, what you see is quite a dynamically changing brain with the relative size of the grey matter and the white matter areas changing quite a lot. And then as you go into puberty, you have this remarked change in the way that the brain structure's starting to evolve where you start to see a consistent thinning of the grey matter layer in the cortex and a relative deceleration in the growth of the white matter. So you're picking that up as an overall change.

If we think about what's actually underpinning that juvenile period and that change through adolescence, that's being driven by two very main ways that the brain is changing,

the relationship of the brain cells are changing.

So, first of all, the brain is changing in terms of the number of connections that the brain cells can make with each other. That varies a lot through adolescence, and it continues to change -- so through childhood, it continues to change through adolescence.

And you're also seeing a change in the myelination of those long axonal projections. What myelination means is that the brain cells -- these long projections start to get coated in a thin, fatty sheath called myelin. And what that lets the brain cells do is send signals much more efficiently and much more quickly.

So if you track this profile going through childhood and then on through adolescence, what you see is a change in these connections moving towards an adult-like brain and also a change in myelination, and both of these features progress through the brain very roughly in the back, different direction, such as the part of the brain that shows an adult-like pattern of connections, and an adult-like pattern of myelination is the front of the brain that comes in last.

Then in your early 20s, you're starting to see something that has this more adult-like profile, but, as I say, that's not fixed; that's still dynamic. Your brain is changing throughout your whole life span because anything that changes in your brain -- anything that you learn will affect the kind of

connections that your brain has. Anything you remember from the conversations you'll have today is because your brain has changed yet again. But you don't get these huge changes, both in size and growth pattern, that you're seeing in the period from birth to puberty and then from puberty to adulthood.

Q. Doctor, as puberty is affecting the brain during the phase that you just described from the beginning of puberty -- to I'll call it the end of adolescence, your 20s, as you said, how, if at all, does that period affect decision-making in the human being?

A. There was a recent review in nature of neuroscience that described sort of decision-making as being distinctly different in adolescents in a way that's a sort of critical defining feature of adolescents. So adolescents are amazing humans. They are creative; they're intelligent; they are full of fantastical ideas of things to do.

The challenge that the adolescent brain has is that the decisions that adolescents can make can be, in some circumstances, more impulsive, but more generally more risky. And the problem here seems to be not that there are some risky things that attract adolescents more. It's more that teenagers and adolescents can struggle to understand or engage with what potential outcomes of behavior could be.

Now, that might be something trivial like not taking an umbrella with you when it might rain, or it might be something

really serious that might affect your health. And that's something that is associated with not necessarily a one-to-one way, but it seems to be linked to the fact that, as I say, these changes in the brain go from back to front in terms of connectivity and in terms of myelination. And the frontal lobes, which is the last to show this pattern of adult connectivity, and myelination are the brain areas which are strongly involved in decision-making, in emotion regulation, in managing behavior.

Q. Understood. And, Doctor, you say that you looked at Dr. Edmiston's testimony in this case. Now, Dr. Edmiston discusses decision-making in a hot context, in a cold context, and seemingly disagrees with your assessment of risk-taking.

What's your response, Doctor?

A. I think my response is twofold. First of all, Dr. Edmiston is, I mean, correct in that you can identify tasks that are more hot where decisions can be more driven by emotion, and you can identify tasks that are more cold, more rational.

In the real world, I've certainly worked in areas of cognitive psychology, but are strongly influenced by the idea that actually, in the real world, all decisions involve emotional aspects. You can't not have an emotional contribution to how you reason about the world, how you decide what to do in the world.

And I think the second point of our disagreement with

Dr. Edmiston is that he is framing risky decisions as impulsive decisions, and decisions don't have to be impulsive to still be risky. Decisions could be very well thought through and thought through for a considerable amount of time and still be very risky in their potential outcomes.

Q. Understood.

Now, Doctor, are you familiar with gonadotropin-releasing hormone agonists?

A. Yes. Yes.

Q. And if I just call them "puberty blockers," will you know what I mean?

A. Yes.

Q. All right. Walk us through the effects of these chemicals on the human brain. How do they impact the brain?

A. There -- so the gonadotropin-releasing hormone is something that's released, I think, in the pituitary gland, and it has its effect on the hypothalamus. And this is triggering cascading effects, that they can give you an increased release of sex hormones from the ovaries and the testis. So both estrogen and testosterone start to be increased as a result of this.

The GnRH analogues, which can be agonist and sometimes antagonist, they are sitting on the receptors and stopping, blocking, literally, that hormone having its effect. The GnRH --

MR. SHAW: Objection, Your Honor.

Professor Scott -- objection. Professor Scott doesn't have any expertise, has never clinically studied puberty blockers or studied how they affect the brain.

THE COURT: Well, Dr. Scott, tell me how you know about what GnRHa does.

THE WITNESS: Because I have to, as part of my job, understand brain structure, brain function, and brain neurochemistry. GnRH acts as a neurotransmitter, and the -- so any neurotransmitter is picked up by receptors that -- there's no other way for neurotransmitters to have their effects on the brain.

And there are different ways that you can disturb the uptake of a neurotransmitter by its receptors. And in the case of the GnRH agonist, what they're doing is they're blocking the -- they're sitting on the receptors and stopping the hormone from getting in there.

So I understand this because I understand how neurochemistry works and how neurotransmitters work.

THE COURT: Well, I guess two responses: First, it seems to me that this isn't the doctor's area and, second, do you even disagree with that?

MR. SHAW: I'm sorry?

THE COURT: Do you even disagree with what she just said?

MR. SHAW: I -- we would disagree to the extent that

she does not have the -- the expertise to understand. She gave a very general explanation of --

THE COURT: I get it. I'm going to overrule the objection.

But, look, I guess here's part of my response that probably doesn't affect the ruling, but it's as if the witness just said, I know the light was green, and the question -- the question whether the light was green is really not debated. Everybody -- it's just clear the light was green, and you object, Well, she doesn't have any reason to know the light was green. Well, if she doesn't have a reason to know the light was green, that's a good objection, and I would sustain it.

But it's a bench trial, and I'm trying to figure out where we're going. And if everybody agrees the light's green, I'm not sure what we're worrying about.

MR. SHAW: Understood.

THE COURT: The objection is overruled.

BY MR. JAZIL:

Q. Doctor, would you like to add anything to what you've already said about how the GnRHa agonists affect the brain?

A. No. Other than the original hormone, the GnRH hormone, has a very short half-life. It's made, and it has its effects that disappear very quickly, and the blockers seem to work by having a longer half-life. They are around in the system for longer, so they're able to have this effect. They have this blocking

effect for longer.

Q. Understood.

Doctor, are there any animal studies that look at the long-term effects of using the GnRH agonist on the human brain?

A. On the human brain?

Q. I'm sorry. Pardon me. On the brain?

A. Yes, there are -- the majority of the studies that we have -- and there still aren't many -- looking at the effects of puberty blockers on brain development during the peripubertal period going into adolescence is on nonhuman models, because you can do experiments with nonhuman models that you can't do with humans. For example, you can do post-mortem analyses.

So there are, I think, five studies on sheep, there is a study on yaks, and there is a study on mice.

Q. Okay. Let's take those five sheep studies, Doctor.

What do those five sheep studies show?

A. I think the first three studies are basically on the same sheep. So there was a study showing that administering puberty blockers around puberty in male and female sheep, male sheep go into puberty earlier than female sheep, which is the opposite with humans, so they have to treat them actually at different points, slightly early for the male sheep.

And then it was looking at effects on behavior, and it found that there are effects on sort of emotional behavior, emotional reactivity in the sheep. And it goes in the opposite

direction. So the male sheep become more reactive, and the female sheep become less reactive.

There are two follow-up studies, I think, on that same -- my impression is that it's the same population of sheep. One was looking at gene expression in brain areas that seem to be a delaying and finding differences in the amygdala caused by administering the GnRH analogues. And this, if I remember correctly, had a greater effect on the female sheep than the male sheep.

And then if you look at the anatomy -- and this was done with structural magnetic resonance imaging -- a brain area that was very important in terms of social processing, learning, and emotional behavior is the amygdala. It sits in the middle of the temporal lobes and in front of the hippocampus. And administering the puberty blockers led to an increased size in the amygdala for both the male sheep and the female sheep. The effect was more exaggerated for the female sheep possibly because there is already a sex difference in the size of the amygdala, and the sheep male amygdala are larger than female amygdala. So you are seeing a growth in this area in all the treated sheep, and it's more exaggerated in the female sheep.

Q. Why do we care about the changes in the size of the amygdala, Doctor?

A. Because it's leading to a difference. It's leading to a change. This is not having no effect on the brain. If puberty

blockers were a pause button that led to, like, kind of a neutral period where you could sort of -- things are changing, there should not be these alterations in brain structure. There is an effect happening there.

Q. And what does the amygdala control?

A. The amygdala -- it's not very big, but it's a very important area in terms of behavior. I used to work a lot with people who had damaged their amygdala. They do have very affected behavior. You don't want to damage your amygdala. It can lead to big changes in your ability to deal with social situations. But it's actually comprised of a lot of tiny little nuclei.

So all we have from the study on the sheep is a measure that is bigger. What we don't have is a very clear study of actually saying which components of the amygdala, which are tiny, whether they're actually changing that's driving that. So we don't actually know what's underlying this.

Q. Doctor, did the sheep studies deal with spatial cognition at all?

A. There are a couple of other sheep studies, these ones just in rams, so just in male sheep. And what they did was they administered puberty blockers in half of the sheep around puberty, and then they looked at the sheep's ability to learn spatial navigation in mazes. And they were looking at this because spatial navigation in mammals really relies on the

structure that sits just behind the amygdala called the hippocampus, and it's very important in spatial navigation. So they are taking spatial navigation as a proxy for potential effects on the hippocampus.

And what they found when the sheep were being treated with the puberty blockers was that the sheep who were treated had difficulties with spatial navigation. They took longer to learn their way through mazes.

And there was some suggestion that they also showed emotional reactivity, but what they did is they then applied testosterone to those sheeps, and they were replacing the testosterone that their bodies aren't making. And when they did that, it improved their emotional reactivity, but it didn't affect their ability to learn the mazes.

So then you sort of start to pull out, What's the effect of the puberty blockers? What's the effect of lacking testosterone?

Significantly, this lab also went back -- because this is missing from the rest of the literature in a way that's quite frustrating. They went back and they asked questions about what happened to those sheep when they got older, because they only applied the puberty blockers for an amount of time. They didn't keep the sheep on this.

So the studies in the first paper were all done around sort of 40, 50 weeks. They went back at 80, 90 weeks when the sheep

who had been treated are no longer on puberty blockers, and they looked at their spatial cognition. And what they found there was that the sheep had problems with their long-term spatial memory. They were taking longer to solve mazes that they had previously learned, even though they're no longer on puberty blockers. And they interpreted from that that there was a longer term effect on the brain caused by the puberty blockers even after the puberty blockers had ceased.

Q. Understood.

And, Doctor, again, you reviewed Dr. Edmiston's testimony in this case; right?

And she commented on the sheep studies, and my understanding of her testimony is that she found no differences in spatial cognition.

How do you respond?

A. I didn't agree with Dr. Edmiston's interpretation of that study. He had argued that the first study showed no difference in spatial ability, and that's not what the paper shows, and it's not what is argued. And it's certainly not what the data show. He also didn't pick up on the follow-up study at all.

MR. JAZIL: And, Your Honor, I apologize. I believe I referred to Dr. Edmiston by the wrong pronoun. It was unintentional.

MR. GONZALEZ-PAGAN: Thank you.

THE COURT: Before we're done, I assure you, I'll call

people by the wrong name. I do it almost in every case I preside over, so this case probably wouldn't be any different.

MR. JAZIL: And I meant no ill by it. It was just a slip of the tongue.

BY MR. JAZIL:

Q. Doctor, moving on to studies in other animals, were there any mice studies?

A. Yes, there's a study by Anacker and colleagues. And what they did with the mice is they had, again, male and female mice, and they administered puberty blockers, I think, by daily injections. And they studied what was elicited in terms of the mice's behavior, and they also looked at elements of brain function in the mice, the postmortem.

And what they found was that, A, there were effects of the puberty blockers on the treated mice. The brain and the behavior measures were different. What was clear was that for every difference that they found, you either found it in the male mice or the female mice. None of the effects they reported were showing you something where both the males and the females were affected or anything that looked like the males were becoming masculinized or the females were becoming -- I'm sorry -- the males were becoming more feminized or the females were becoming more masculinized.

So, for example, they found that the male treated mice were more likely to want to spend time with an unfamiliar male mouse

than unfamiliar female mouse, and that's unusual in adult male mice. They tend to prefer to be around female mice.

So there is a difference, which, in fact, in the paper they attribute to aggression, because male mice are quite aggressive towards other mice, and that seems to be -- a perception that seems to be reduced in the treated mice.

The female mice show different patterns of behavior around anxiety and what is used in mice as now like a despairing behavior. So they were more likely to be nervous about eating food in a novel environment. And if you place them in water in what's called a forced swim task, they were more likely to stop swimming altogether and just float, which is used as a measure of the mouse feeling hopeless.

So you see this pattern through all the behavioral measures that they had an effect on male mice or female mice. And at the brain level, they looked at the dentate gyrus, which is part of the hippocampus. And what they were looking at was gene expression that is associated with recent activities in those areas, and they did find differences, that is, increased activity in the hippocampus, for the treated female mice, but, again, no difference for the male mice.

Q. Understood.

MR. SHAW: Objection, Your Honor. There was no discussion of any mice study in her report.

THE COURT: Is that so?

MR. JAZIL: That is, Your Honor.

THE COURT: The testimony about the mice study is struck.

BY MR. JAZIL:

Q. Doctor, we did talk about the sheep studies.

Let me ask you this question: Why should we give any credence to these sheep studies when we are talking about the human brain?

A. Because we are able to do wholly controlled studies with the sheep that are able to illustrate aspects of behavior change or brain change. We can do analyses with the sheep that we can't do with humans. We can do postmortem analyses, for example, gene-expression analyses.

It's tempting to imagine that because sheep are animals that we farm that they are uninteresting -- the sheep are highly social mammals. Like all mammals, they go through puberty. They have an extended period of being juveniles, and they go to sexual maturity, which involves changes in behavior. And that gives us a good model for looking at puberty. And although it is a completely different area, they studied evidence that, in terms of sexual orientation, male sheep are somewhat more complex than human males.

So sheep are definitely not -- I'm not claiming that sheep have anything like gender identity, but it is certainly not the case that sheep are sort of boring robots.

Q. Understood.

And, Doctor, in your report you also looked at some human studies.

Can you tell us what those studies were and what conclusions you draw from them?

A. There is a study of precocious puberty, and precocious puberty is more -- puberty itself has a range, so it's not like everybody goes into puberty at the age of 12. So some people go into it early and some people later. Some people go in very young. And so precocious puberty is defined as girls or boys going into Tanner Stage 2, which is the appearance of breast tissue, around the ages of 6 or 7. And it can be associated with quite serious outcomes. For example, your height can be very badly effected if you go through puberty too young. So it's very commonly treated with puberty blockers.

There is only one study that I'm aware of that has gone in and asked questions about the effects of these puberty blockers that wound up being used to delay puberty in -- normally going into puberty, but puberty was happening early, the effect of that on behavior and on measures of cognition.

And this study showed that on many measures -- so, I should say, in this study, you've got two groups of girls. So it's all girls. They've got girls who are going through precocious puberty and are being treated with puberty blockers as a result, and then you've got a group of controlled girls who have no

problems at all, so they are just a group of average girls.

They were tested on a measure of emotional processing and sort of distractibility. And on one aspect of that, the girls with precocious puberty did show a different response. They seemed more distractable under certain circumstances with emotional faces.

They also did measures of IQ, and the girls in the control group had an average IQ of 101, which you would expect to see. Average IQ should be around 100. The girls with precocious puberty who were being treated with puberty blockers had an IQ -- an average IQ of 94.

Now, that did not come out as being statistically significant in this study when they compared the two, although statistical significance is hard when you have small groups, as they had there. And, also, statistically significant is just a measure of how lucky something is to have happened by chance. It doesn't mean to say it couldn't be meaningful.

But I think it is striking that IQ isn't just relevant in terms of is it different between two groups, because IQ is a scaled score. What your IQ is also matters.

And the girls with precocious puberty had an average IQ of 94. That's seven points lower than the controlled group of girls. And, also, in the subtests of the intelligence test that they used, none of those girls with precocious puberty who were on puberty blockers scored higher on average than the controlled

group of girls.

I'm not the person to point this out. Somebody -- Dr. Hayes wrote a commentary on this paper, pointing out that there was no reason for being complacent around an IQ difference of seven points. I think if somebody told you you were going to take medication that would knock seven points off your IQ, you might think twice about it.

And the study itself is also not ideal, because in the way that it's designed, you can't determine the effects of the puberty blockers. Or are you looking at the effects of precocious puberty because you can't -- the girls have both? So we don't have another condition where there are untreated girls who have precocious puberty.

So it's -- you know, as you tend to find with human studies, it's not perfect, but it's certainly -- there is enough evidence to make at least one other person say, This is slightly concerning.

Q. So, Doctor, based on your knowledge and experience of brain development, brain structures, neurochemistry, and your review of literature that you've described, what, if any, opinions have you formed regarding the effects of puberty blockers on the human brain?

A. I think, first of all, what we can't do is be complacent and assume that there's nothing happening here. All the evidence that we have from human studies is that there are

effects on brain development if puberty blockers are administered around puberty, and that's already concerning.

From my reading of the literature around the use of puberty blockers in gender dysphoria, it's initially -- was certainly suggested in the UK at Tavistock Clinic, just up the road from here, to be something that was going to be brought in at the age of 16, because after puberty had happened --

MR. SHAW: Objection, Your Honor. None of this was in her report.

THE COURT: Are we off the report again?

MR. JAZIL: Your Honor, we are off the report on the Tavistock discussion, so --

THE WITNESS: Okay. Okay. I am to leave that bit out, but I'm going to go back to what's in my report, yep.

BY MR. JAZIL:

Q. So, Doctor, based on your review of the studies we discussed, the sheep studies --

A. Yep.

Q. -- and based on your review of the human studies that you just discussed with the Court, and based on just your general knowledge of how neurochemistry works, what conclusions have you reached about the use of puberty blockers on the human brain?

A. They are not a pause button. They are having changes on the brain, and we are seeing this in the mammal models. We've got no reason to imagine that this would be different in the

human brain. There is nothing in the literature that would suggest that.

So I think the problem is twofold. It's having an effect, and we don't know what the effect means. All I can say is that I can't think of another situation in which you would be complacent about the potential effects of drugs on brain development, particularly occurring at a very critical point in development.

Q. And are these changes reversible or are they irreversible, the effects that you're seeing on the brain?

A. From the studies that we've seen on sheep, they are -- there's at least some evidence that it's irreversible. The brain -- remember, you're born with all the brain cells you're ever going to have, and changes in your brain are due to growth in those brain cells and changes in how they're myelinated and changes in how they talk to other brain areas. That's all there is.

So by the time you're an adult, the brain that you were -- we've all got different brains. Part of the reason for that is the different experiences and the different things we've done with those brains. You can't just go back to some default state. The brain is changed by experiences and by these sort of things that can affect the brain, and they don't -- it doesn't just snap back like an elastic band.

Q. Understood.

MR. JAZIL: No further questions, Your Honor.

THE COURT: Cross-exam?

CROSS-EXAMINATION

BY MR. SHAW:

Q. Professor, you mentioned that puberty blockers have the potential to cause a decrease in IQ; is that correct?

A. Yeah.

Q. And you cited a number of studies in your report on that, and one of them was the Mul study from 2001?

A. Sorry. How is that spelt?

Q. M-u-l.

A. Sorry. I don't have my report.

Is it okay for me to open my report up? I've closed everything on my computer.

Q. Do you not recall citing that in your report?

A. I don't remember the name. Is it possible for me to open up my report?

Q. Sure. We can bring it up.

A. That would be great. Thank you.

MR. SHAW: Ms. Gonzales, if you could bring up the Mul study.

If you'd go to the first page, please.

BY MR. SHAW:

Q. This is the --

A. Oh, yes, I do remember. So this was cited by Hayes, wasn't

it?
Q. And for the record the study is called "Psychological assessments before and after treatment of early puberty in adopted children."
Do you see that?
A. Yes, I do. Thank you.
Q. And this is a human -- this is a study on humans?
A. Yes.
Q. Yes?
And it looks at the effects of puberty blockers in children with precocious puberty.
Do you recall that?
A. Yeah.
Q. And you reviewed this study before you cited it?
A. I did look at it because Hayes had mentioned it, yep.
Q. Did you review this study before you cited it?
A. As I said, I looked at it because Hayes had mentioned it.
Q. Because -- okay.
The study explicitly says that there is no relevant decrease in IQ among the treated children; correct?
A. It says: *Intelligence quotient levels decreased significantly during treatment*.
Q. Right.
MR. SHAW: If we could go to the PDF, page 4.

BY MR. SHAW:

Q. Second column, under *Intelligence*, it says --

A. Yeah.

Q. -- *the IQ levels for the whole group decreased significantly, but this was not clinically relevant. A comparable significant decrease was present in both groups. There was no significant differences between Groups A and B.*

Did I read that correctly?

A. You did.

Q. Did you mention this finding in your report?

A. No, because it's within the same range as the change in the paper by Wojniusz with the -- the one we were talking about just before.

So when you're talking about a clinical change in intelligence tests, what you're normally talking about is something that's starting to go in units of ten. So something that went under 90, under 80, that would be starting to become clinically relevant, or in the opposite direction.

Q. You didn't mention any of that in your report?

A. No, because, as I said in the report -- and it's the same case with the study with Wojniusz -- that's -- just because it's not falling outside of the parameters of something that would be clinically relevant. So, for example, if you have a head injury, then you probably will have a much larger decrease in IQ, but it doesn't necessarily mean, as Hayes was arguing in

their article, that this is something about what you should be complacent.

Q. You've just mentioned Hayes, and you're referring to the Hayes commentary of Wojniusz's 2016 study; correct?

A. Yeah.

Q. I want to talk about Wojniusz's study.

But, first, did you know Hayes was a political scientist?

A. No.

Q. No.

Do you often rely on the expertise of political scientists in your research on the brain?

A. If I don't know who's a political scientist, then how could I know that?

Q. I'm sorry?

A. If I don't know if someone is a political scientist, how could I know -- how could it be having a view on what I'm taking to be data about the brain?

Q. And you didn't know he was a political scientist?

A. I think I said that.

Q. Okay. Let's talk about the 2016 Wojniusz study that Hayes comments on.

MR. SHAW: Ms. Gonzales, can you bring up that study?

And for the record, Wojniusz is W-o-j-n-i-u-s-z.

BY MR. SHAW:

Q. This study is called "Cognitive, Emotional, and

Psychosocial Functioning of Girls Treated with Pharmacological Puberty Blockage for Idiopathic Central Precocious Puberty"; right?

A. Yes.

Q. And this is another study of humans?

A. It's the only study of humans, other than the Mul one.

Q. And it looked at the effects of puberty blockers in girls with precocious puberty --

A. Yeah.

Q. -- right?

Just as an aside, you would agree that puberty blockers are standard treatment for precocious puberty?

A. They are, yes. As I say, the effects of precocious puberty are not trivial.

Q. And you would agree that puberty blockers have been used for decades to treat precocious puberty?

A. It doesn't go back that far. We've only known about these hormones since the '70s. But, yes, they've been used for a while.

Q. Do you think we should stop using puberty blockers to treat precocious puberty?

A. I suspect that what you'd be looking at here is weighing up the different risks, because, as I say, the precocious puberty in and of itself is -- it's a risky condition for the girls. It can have serious outcomes. So I'm not aware of any other

studies, other than these two, looking at issues around common side effects of this. It might be interesting to have a conversation about what would be the different risk factors that are involved here using them or not using them.

Q. But my question was: Do you think we should stop using puberty blockers to treat precocious puberty?

A. As I said, I don't think that's something that is -- it's certainly -- the question is should you stop it now, or you should start doing that. If it's going to be considered, then it would have to be considered in the light of what are the problems of precocious puberty.

Q. Okay. I'll move on.

A. You'd be weighing up the options.

Q. On Wojniusz's 2016 study, Wojniusz concluded that the puberty blockers had no effect on cognitive functioning; correct?

A. Other than they described it as interesting; that there were these differences on one of the emotional measures.

MR. SHAW: Ms. Gonzales, can you go to PDF page 7? And blow it up. Yep, there.

BY MR. SHAW:

Q. So the last paragraph, it says: *No significant differences between the CPP and the control group were seen with regard to cognitive performance neither on paper and pencil nor in computer-based tests concerning memory, spatial ability,*

attention, and executive functions.

Did I read that right?

A. Yes. You'll notice there is also a difference in the next sentence about the Trail Making Test, so there is a difference there.

Q. Yeah, I'll read the next sentence. It says: *Only in the Trail Making Test-Number Sequencing, assessing --*

MR. SHAW: If you could go down, Ms. Gonzales.

Keep going.

BY MR. SHAW:

Q. *-- processing speed, the CPP group showed a significantly poorer performance. This finding is difficult to explain since neither the very similar Trail Making Test-Letter Sequencing nor any other of the processing speed tests showed significant differences between the groups. Taking into account that the p-values were not corrected for multiple testing, it is possible that this finding is accidental.*

Did I read that right?

A. You did.

Q. Okay. Thank you.

MR. SHAW: Ms. Gonzales, if you could go up, please, back up to the previous page.

BY MR. SHAW:

Q. And on IQ specifically, the second-to-the-last paragraph in the right column, it says: *The puberty-blocker-treated CPP*

girls estimated IQ in the current study was within the normal range and somewhat lower, although not significantly than that of the controls; correct?

A. Yes, as I said before.

Q. Okay. And I just want to stay on this study for one more point.

You mentioned in your testimony something about puberty blockers affecting emotional reactivity; isn't that correct?

A. Yes, yeah.

MR. SHAW: Ms. Gonzales, if you could go to page 9.

BY MR. SHAW:

Q. And it's not highlighted, but it's on the screen. The last sentence above the "Cardiac function and emotional regulation" section, it says: *In summary, although part of the findings suggest differences in emotional reactivity between the groups, the results are not conclusive.*

Did I read that right?

A. Yes.

Q. And I misspoke. I want to stay on this study for one more point.

You mentioned something about -- did you -- you mentioned in your report that puberty blockers may cause a decrease in heart rate. Do you recall mentioning that in your report?

A. Yes, yeah.

Q. And you mentioned this study for that --

A. Yes.
Q. -- correct?
A. Yeah.
Q. A lower heart rate can mean that a person is more relaxed; right?
A. Yes, or healthier.
Q. So a lower heart rate is a good thing?
A. Well, as you'll notice towards the bottom of that paragraph, like they say, through interpretation of the puberty blockers as being something that's actually changing the emotional regulation capacity as you're measuring by heart rate. What you have to do is rule out a direct role for the puberty blocker itself on heart rhythm, and they point out that you can't do that if you bear in mind that the original GnRH is a neurotransmitter and it's having its effect on the hypothalamus.

But, actually, you find GnRH receptors in a much wider area of the brain. It's not only found in areas that are directly controlling the things that are happening in the ovaries and the testes. It is working as a neurotransmitter. When you block that, you could be also changing other aspects of how the body is going to start working, because we don't know what this is.

That's precisely what they're saying here. You can't tell whether this is something to do with the precocious puberty, the actions of the blocker, or the actual direct action of that drug.

Q. But you'll agree that the study says it's the -- in the last paragraph: *Consequently, the lower heart rate and higher heart rate variability would suggest that treated CPP girls have better emotion regulation capacity and higher adaptability to changing contexts than controls.*

A. I wouldn't agree with that --

Q. I read that right; right?

A. -- without the context of the next sentence, and the fact they say "could." Then they are definitely saying that this is one mechanism, but you cannot be certain.

Q. Do you have any training in puberty blockers that makes you certain either way?

A. No, but I have a little bit of expertise in how emotion effects the brain and the body, and that's one of things you're measuring here with the heart rate variability. So I'm commenting on this as something that's affecting the brain and the body.

Q. So you're familiar with heart rate variability?

A. Yeah.

Q. And heart rate variability is a measure of emotional control; right?

A. It can certainly be linked to that. It can -- there are a lot -- the heart is unbelievably reactive in terms of its moment-to-moment changes, but also it's -- how it's influenced by longer scale phenomena that can affect you. So, for example,

if you are in a fight-or-flight state of extreme fear, then your heart rate will be high, but your heart rate will also be less variable. So you are in a different emotionally reactive state and at some ball points in between. So it's not -- it's like a world of complexity starting to understand heart rate and heart rate variability.

Q. Heart rate variability is associated with lower levels -- excuse me. Let me rephrase. A higher heart rate variability is associated with lower levels of anxiety; correct?

A. When you hold other things constant, yes, and that's because what you're seeing is the heart rate is becoming -- is being more reactive. That's why it is being more variable.

Q. And the first sentence -- it's still on the screen. The first sentence under "Cardiac function and emotional regulation": *GnRHa-treated CPP girls had significantly lower resting heart rates and significantly higher heart rate variabilities than controls.*

Did I read that right?

A. Yes.

Q. Moving away from puberty blockers, you made some comments in your testimony about adolescent behavior; correct?

A. Yeah.

Q. And you made the point in your report, and I believe in your testimony, that teenagers are more prone to impulsive behavior?

A. I think the bigger emphasis I was making was on risk and risky behaviors. So their behavior can be impulsive, but the bigger problems are when it's associated with the riskiness of things whether or not they are impulsively decided.
Q. Would you agree that teenagers are able to assess -- to properly assess those risks when in the company of other adults?
A. No. If you think about the overall differences between how everything we understand about the adolescent brain differs from the adult brain, one of the cardinal features is that it can be extremely difficult for adolescents to engage with the potential consequences of actions whether or not they are being impulsive, whether or not they're being guided by adults. The meaning of those consequences can simply be less salient and less engaging to them.
Q. Would you agree that teenagers are able to properly assess the risks when speaking or working with medical doctors?
A. No, I think the same problem would still be there. If you -- if you can't understand what the import and the valence and the severity or the potential severity of outcomes could be, then it doesn't matter how well you are being supported by a medic or not. It's still going to be very difficult for teenagers to fully engage with that.
Q. So would you recommend that teenagers should not take any advice from a medical doctor?
A. No, I'm not saying that. I think you've got a situation

where the outcomes are potentially extremely serious and, actually, the medical doctors don't necessarily have the best advice. Then you -- and the outcomes could really be something that could have life-altering possibilities. Then I don't think that that's something that a teenager -- in most of the situations, we would protect teenagers from the consequences of their decisions because of that.

MR. SHAW: Pardon me one moment.

(Discussion between the attorneys.)

BY MR. SHAW:

Q. Professor, one final question. Do you know, in the United States, that it's the parents' responsibility to consent to medical treatment?

A. Yes. But I would imagine, in this situation, parents aren't going to be trying to get their children on puberty blockers without the child agreeing to it.

MR. SHAW: No further questions.

THE COURT: Redirect?

REDIRECT EXAMINATION

BY MR. JAZIL:

Q. Doctor, you discussed with my friends some issues concerning neurotransmitters and the effects on the hypothalamus. I'll confess I got a little lost in that discussion.

Are you saying that puberty blockers are a mechanism to

block neurotransmitters, and the neurotransmitters that could be blocked are in places other than the hypothalamus? Help me understand that --

A. Yeah.

Q. -- exchange there.

A. So from when they were first discovered, GnRH, gonadotropin-releasing hormone, was assumed to be having a very precise role in the hypothalamus because that's triggering, you know, these sex-hormone changes and the way that they behave.

But it turns out that, certainly in primates, if you look for the receptors that are sensitive to gonadotropin-releasing hormone, you don't only find them in the hypothalamus. You find them in basal ganglia. You find them in the basal forebrain. So you're finding them in a more distributive network. We still don't know what that means.

For example, several of the sheep studies that were looking at the effects of puberty blockers onto the brains and behavior in the sheep were doing that precisely, because there is the potential for these neurotransmitters -- so for the blocking of the function of this neurotransmitter to have an effect on cognition and behavior in a way that's more widespread than the effect it's having on -- in a direct way on sex hormones.

Q. So just to make sure I understood this, When we started studying puberty blockers, we were concerned about the effects on the hypothalamus. But since then, we've come to see that the

effects would be more widespread on the brain.

Did I get that right?

A. Exactly, exactly. There is the potential of it actually having an effect on a wider network of behavior and cognition.

Q. And, Doctor, my friend showed you some excerpts from the Wojniusz study.

Did any of those excerpts change your perspective on your testimony earlier about the conclusions you drew from the Wojniusz study?

A. No. It is interesting. If you read all the papers that I've mentioned, every one of them, including Wojniusz, says, We don't know what this means; we need to have more data, particularly because these drugs are being used in adolescent populations at a time when the brain is changing. So it's not changing my thoughts about this. The effects are not big, but they are there, and they are there in a direction that is worrying.

Q. Understood.

MR. JAZIL: No further questions, Your Honor.

THE COURT: Dr. Scott, one probably insignificant question to start with: Have you ever done any studies using sheep?

THE WITNESS: No. I've done some studies with horses, but not sheep.

THE COURT: One thing you noted in your testimony was

that precocious puberty is not trivial, and so I think you said, in response to Mr. Shaw's question about whether we should stop using GnRHa on patients with precocious puberty, that we should evaluate the risks -- the patient should evaluate the risks; true?

THE WITNESS: Well, ideally, I think the medical profession would be the best place to be gathering evidence and evaluating the risks so that they can then present to the families and the children concerned. But, yes, it is certainly, at least potentially, the case that there are things to think about here, and it may be that the severity of precocious puberty is so great that it is worth taking those risks.

THE COURT: Certainly for the patient and the patient's parents to evaluate the risk, they need the input of the doctor, and the doctor needs to know what the medical profession as a whole knows.

You're nodding your head yes, and I think that's what you just told me.

So precocious puberty is not trivial, and I suspect everyone would agree with that.

Is gender dysphoria trivial?

THE WITNESS: No. No, that's not trivial. However, at the moment -- and this is in my report -- we have no way of knowing. We have no biomarkers. We have no behavioral measures. We have no way of telling which adolescents

presenting with gender dysphoria are going to be the ones who benefit from treatment with puberty blockers.

So mental health is at risk in untreated gender dysphoria, but it's also significantly worse in treated gender dysphoria. So it really is the case that we're dealing with people who are in a very dire situation, and they deserve much better health care than they are receiving, absolutely.

But there's no clear evidence -- sorry.

THE COURT: Go ahead.

THE WITNESS: I was just going to say, there's no clear evidence that puberty blockers help, other than anecdotal evidence that there are some people for whom it does help, and that's still a level of anecdote. So at the moment we really don't know who are the people who are going to benefit from this for whom the risks really probably are worth going through for this treatment.

I recently read a book by Hannah Barnes with people absolutely making that case who are now in their 20s who are very happy they went down this path, and there are also the case that the vast majority of people with gender dysphoria are not going to have their symptoms improved by this treatment.

THE COURT: My question is this: If patients and their parents and doctors should evaluate the risk and make a decision whether to use this drug when the patient has precocious puberty, why isn't it the patient and parent and

doctor who should evaluate the risks and benefits and make the decision whether to use this drug when the person has gender dysphoria?

THE WITNESS: I think that's probably because we know that in precocious puberty it works. What that does is it delays the progression from Tanner Stage 2 all the way through puberty, and it delays it for long enough that you can then take the girls or the boys off it, and they go into puberty at a more normal age, and you've delayed the changes in height that can be associated with that.

We do not know this with the treatment of gender dysphoria with puberty blockers. What we do know is that the evidence we do have suggests that it does not work. It is not effective, so I think --

THE COURT: Let me see if I understand this.

You think -- you've never treated a gender dysphoria patient. I've heard evidence of many hundreds of gender dysphoria patients who are substantially better off after having had this drug, but what you're going to testify under oath is that none of them are better off?

THE WITNESS: No. That's not what I said. I said we know that there are some people for whom this is beneficial. What we cannot tell, and what the evidence is not there for, is who those children are going to be. So we don't know, in advance of it working, whether or not this is going to be

somebody for whom this will work. And for the people whom it doesn't work, it does not improve anything. It doesn't improve mental health. It doesn't improve a quality of life --

THE COURT: Fair enough.

THE WITNESS: -- so --

THE COURT: If it doesn't work --

THE WITNESS: (Indiscernible crosstalk.)

THE COURT: If it doesn't work, it doesn't work; I get it.

THE WITNESS: And we can't tell in advance.

Sorry.

THE COURT: Well, you can't. I've heard from doctors who think they can, but I don't want to get in a debate with you. I know you're not the treating doctor.

THE WITNESS: Absolute --

THE COURT: Questions just to follow up on that?

MR. SHAW: No.

MR. JAZIL: No, Your Honor.

THE COURT: Thank you, Dr. Scott.

THE WITNESS: Thank you.

THE COURT: I appreciate your availability, and we're going to disconnect you now.

That testimony is completed.

THE WITNESS: Thank you.

(Dr. Scott exited the Zoom conference.)

THE COURT: Please call your next witness.

MR. JAZIL: Your Honor, the defense rests.

THE COURT: Rebuttal case for the plaintiffs?

MR. GONZALEZ-PAGAN: No more witnesses, Your Honor.

THE COURT: All right. Let's take a 15-minute break, and we'll do closing arguments.

10:40 we'll start back.

(Recess taken at 10:25 AM.)

(Resumed at 10:40 AM.)

THE COURT: Please be seated.

Closing argument for the plaintiffs.

MR. GONZALEZ-PAGAN: Briefly, Your Honor, before closing arguments, if it's okay, my colleague, Ms. Dunn, would like to correct something.

MS. DUNN: Ms. Dunn, Chelsea Dunn.

Your Honor, when we submitted the deposition designations, we neglected to include the completed errata sheets. We were notified by Mr. Beato, so we refiled those deposition designations, but we also have copies for the Court to include with the binders that we submitted.

THE COURT: Got it. Okay.

MR. GONZALEZ-PAGAN: Good morning, Your Honor.

THE COURT: Before you -- good morning.

But before you start -- before I forget it -- let me tell you one thing.

We've had discussions before about the relationship between this case and the Doe case that's pending on a submitted motion for preliminary injunction. My tentative plan, at least, is to rule on both of these at the same time. There will be a lot of overlap between the decision in this case and decision in that case. There are obviously some differences, but there's a lot of overlap.

Here's my suggestion to both sides: If you appeal -- and it certainly seems likely to me that one side or the other or both will appeal -- I'm not sure the procedures at the circuit for notifying the circuit that there are these related cases.

I recently sat with the circuit. We had a case. We prepared. We heard oral argument. It turned out the exact same issue with the exact same lawyers had already been argued to another panel and nobody told us. So they -- they may not have the same rule that we have here that require you to notify us of related cases -- or if they do have that rule, the lawyers in that case just missed it -- but that was a lot of unnecessary work.

So if these cases both wind up going up, figure out what you need to do to let the circuit know that both cases are pending so that they can deal with it, however it is appropriate for them to deal with it, but somebody there needs to decide how to do it.

MR. GONZALEZ-PAGAN: Understood, Your Honor.

Thank you very much.

May it please the Court, Omar Gonzalez-Pagan for the plaintiffs. Your Honor, over the past two weeks we have been building a trial record demonstrating that subsection 7 of Rule 59G-1.050 of the Florida Administrative Code, or what we will call the AHCA rule, and section 3 of the recently enacted Senate Bill 254, which prohibits state funding for medical care that affirms a person's gender identity if inconsistent with their sex assigned at birth, are unlawful.

Both of these provisions independently serve to prohibit the Florida Agency for Health Care Administration from providing Medicaid coverage for gender-affirming medical care, care that only transgender people need as treatment for gender dysphoria.

In building this record we have shown that gender-affirming medical care is not only safe and effective but that it is not in any sense of the word experimental. This is so because under *Rush v. Parham*, based on current medical knowledge, the State's determination that gender-affirming medical care is experimental is not reasonable.

As previewed at the beginning of this trial, AHCA's overt -- very own regulation to determine whether a treatment is experimental, that which dictates Generally Accepted Professional Medical Standards, shows that the only conclusion

one can reach is that the State's conclusion in this instance is grossly unreasonable.

We have provided extensive and, in many instances, uncontroverted evidence that under the six factors of subsection 4 of Rule 59G-1.035, gender-affirming medical care, meaning puberty-delaying medications, hormone therapy, and surgery as treatment for gender dysphoria meets Generally Accepted Professional Medical Standards. And, again, while those factors are not binding on this Court, we do think they're instructive, and they emphatically illustrate that gender-affirming medical care is safe, effective, and not experimental.

Factor one, which the Court is very familiar with already, the existence of evidence-based Clinical Practice Guidelines. It is uncontroverted that there are primarily two evidence-based Clinical Practice Guidelines for the medical treatment of gender dysphoria.

These are the WPATH standards of care, specifically Version 8 published in 2022, and the Endocrine Society guidelines published in 2017. Plaintiffs' eight experts -- two psychiatrists, a pediatric endocrinologist, a clinical researcher and adolescent medicine physician, a surgeon, a bioethicist, a neuroscientist, and a public health researcher -- all testified to this fact.

These evidence based guidelines set forth that gender-affirming medical care, which is only provided after the

onset of puberty, is appropriate and indeed necessary when medically indicated.

In making such a determination, one looks to the patient, the particular needs of the patients after conducting an individualized assessment and for which the guidelines provide detailed guidance on how to conduct that assessment.

The State's experts, and AHCA's employee responsible for the June 2022 GAPMS report, Mr. Brackett, all acknowledge that the WPATH Standards of Care and Endocrine Society guidelines are already applicable clinical practice guidelines. They point to no competing guidelines in the United States, let alone guidelines that are widely accepted.

As outlined in trial Exhibits 36 through 43 and 45 through 49 and the testimony of plaintiffs' experts, these guidelines are viewed as authoritative and have been endorsed by the American Medical Association, the American Psychiatrist Association, American Psychological Association, the American Academy of Pediatrics, American Academy of Child and Adolescent Psychiatrists, the Endocrine Society, the Pediatric Endocrine Society, and many more.

While defendants point to no recognized competing guidelines in the United States, they point to three reports from three different countries; namely, Finland, Sweden, and the UK. But these reports have no weight, Your Honor. For one, each of the reports only apply to medical care for adolescents

and not adults, and each provides for the medical treatment of gender dysphoria based on an adolescent patient's individual needs.

In this sense, as the U.S. Court of Appeals for the Eighth Circuit recognized in *Brandt v. Rutledge*, the reports really do not differ significantly from the WPATH Standards of Care.

For another, even if the reports were contradictory, they are in opposite. That's because, unlike the WPATH Standards of Care and Endocrine Society guidelines, each of the reports is unpublished, it's not peer-reviewed, and it's incomplete. Defendants have not identified or provided full copies of each of these reports. They've provided summaries, interim reports and, with regards to Finland, a summary -- a translated summary of an unknown origin. Maybe it is because they have no bearing.

In addition, the three reports were drafted by government bureaucrats in these other countries and not medical professionals. And as the State's own expert, Dr. Stephen Levine, testified, standards of care and Clinical Practice Guidelines are, quote, to be constructed by people in the field, closed quote.

He gave the example of the standard of care for low-grade prostate cancer and said that it is written by urologists and people qualified with the expertise in evaluating

that quality, the quality of that evidence.

That is what happened with the WPATH Standards of Care and Endocrine Society guidelines, not the three reports to which defendants refer.

Finally, Dr. Levine also testified that clinical guidelines tend to be much more regional, much more local. If that is so, then three unpublished, non-peer-reviewed, incomplete reports from three foreign countries should have no bearing on what the clinical practice guidance and standards of care for the treatment of gender dysphoria in the United States should be.

As outlined in my opening statement, this first factor weighs heavily in favor of the provision and coverage of gender-affirming medical care and shows that this care falls squarely within Generally Accepted Professional Medical Standards.

Next, we look to the publication of reports and articles containing authoritative medical and scientific literature that relate to the health service at issue. Plaintiffs' experts, in particular Dr. Olson-Kennedy, who conducts clinical research regarding the treatment of gender dysphoria, testified to the abundance of peer-reviewed, scientific literature supporting the safety and efficacy of the medical interventions for the treatment of gender dysphoria.

When it comes to adults, as Dr. Olson-Kennedy

testified, the amount of published literature documenting this safety and efficacy is, in research language, significant and, in layperson's language, enormous.

Not one of the defendants' experts discussed this literature regarding adults, and instead, each focused on the care of minors. But when it comes to adolescents, there is more than ample scientific and medical literature documenting the safety and efficacy of puberty-delaying medications, hormone therapy, and surgery to treat gender dysphoria, particularly chest-masculinizing surgery.

Dr. Olson-Kennedy walked us through numerous cross-sectional and cohort longitudinal studies across the United States and the world documenting the safety and efficacy of gender-affirming medical care to treat gender dysphoria.

This included two of her own studies, studies that she published and have been peer reviewed that pertain to hormone therapy and chest-masculinizing surgery for older adolescents and young adults. Her testimony is corroborated and backed up by the testimony of each of plaintiffs' other medical experts, including Dr. Shumer, Dr. Janssen, and Dr. Karasic, as well as the reviews, systematic review, of literature regarding hormones conducted by Dr. Baker.

As anticipated, the defendants' experts critiqued a handful of these studies, not all of them, but a handful of these studies, because the studies have limitations.

Your Honor, every study known to science has limitations. It is impossible to design a scientific study without limitations. That is why, as plaintiffs' experts testified, we look to the body of literature as a whole. And here the body of literature goes back decades, both for adolescents and adults.

By contrast, when asked for a single study that would support the State's position that gender dysphoria could be effectively treated with gender -- with psychotherapy, the State's experts could not come up with one example, not one.

That is understandable because there is none. There is no peer-reviewed scientific literature supporting the defendants' position. The entire body of scientific and medical literature, when taken as a whole, provides strong and unrivaled evidence in support of puberty-delaying medications, hormone therapy, and surgery as treatment for gender dysphoria. This factor also weighs in favor of the plaintiffs.

Number 3, the effectiveness of the health service in improving the individual's prognosis for health outcomes. I've just discussed the overwhelming universe of medical literature that shows that this gender-affirming medical care is effective to treat gender dysphoria.

But as -- just as Dr. Janssen explained, it is a little drier, when talking about the effectiveness of gender-affirming medical care from the data perspective, when

compared to the profound positive impact we see when patients get access to this care.

The positive impact of gender-affirming medical care is corroborated not only by the clinical experience of plaintiffs' experts, but by the experiences of plaintiffs themselves and their factual witness.

Plaintiffs August Dekker and Brit Rothstein both testified as to the positive impacts of being able to access hormones and chest-masculinizing surgery and the impact that it had on their mental health, their dysphoria, and their quality of life.

And Jane Doe and Jade Ladue testified on the similar impact, positive impact, that puberty-delaying medications had on their adolescent children, Susan Doe and K.F.

August Dekker testified that his gender dysphoria felt like he had a constant void in his chest, like he had been walking around with a leaden ball in his stomach that informed everything else that he did and became unmanageable. He didn't want to sleep. He didn't want to eat. He didn't want to do anything that was even remotely human because he was, in his words, so disgusted with himself and the way that people perceived him. He was depressed and anxious as a result. Your Honor, this is on the trial transcript pages 656 through 657.

By contrast, once he was able to obtain medical

treatment for his gender dysphoria, his depression and anxiety ameliorated, and he was happier. He was more secure in himself. He was confident. He wanted to go outside and meet people. He wanted them to know who he was and wanted them to see how he presented himself because he felt proud of who he was and of himself.

Being able to obtain chest surgery meant like the world had been lifted off Mr. Dekker's shoulders. He felt like that was the way things were supposed to be all the time. It felt natural. He had confidence in his body and was not able to go -- was now able -- was now able to go swimming at the beach or even wear a white shirt to this trial. In his words, it was probably the best thing he has ever done for himself.

The plaintiffs' experiences are like that experience relayed by Kim Hutton, whose son, now 20, had been receiving gender-affirming medical care for ten years, puberty-delaying medications and hormones, as well as the experiences observed by plaintiffs' medical experts of their patients. This includes the testimony of Dr. Karasic, Dr. Shumer, Dr. Schechter, Dr. Olson-Kennedy, and Dr. Janssen.

Speaking of the effect of puberty-delaying medications, Dr. Shumer testified about how adolescents -- it's always a challenging time. But if you throw in gender dysphoria on top of that, it becomes even more challenging and difficult.

And when he sees an adolescent patient, they've

oftentimes been -- have been circling that appointment on their calendar for many, many months. Again, this illustrates that this care is provided with care and not immediately or by chance. People plan and take time to get to know each other, to get to know themselves and work with their providers to access this care.

And Dr. Shumer testified that his patients express how they've been suffering, how they're not fitting in the world because the body is changing in a way that is not consistent with who they are. And that their parents, who are there because they love and support them simply want to allow their adolescent to live the happiest, healthiest, most fulfilling life that they can live.

And that one of the greatest things of Dr. Shumer's job is that he gets to see these patients back in follow up and see them doing so well that he gets Christmas cards five years later from patients of the college, having that healthy, happy, productive life that they didn't think was possible when they first came. All of that, Dr. Shumer testified, was a result of gender-affirming care.

By contrast, the State could only produce, primarily, experts who have never treated or studied gender dysphoria. They couldn't really speak to its effectiveness because they didn't know how. The one expert they produced who had some experience treating gender dysphoria, Dr. Levine, provided

additional support for gender-affirming medical interventions for both adults and adolescents. To be sure, he recommends a more careful assessment of the patient, but so does the standards of care, which recommends the bio-psychosocial careful assessment of adolescent patients.

Finally, the State could not produce any evidence that gender-affirming medical care was harmful and could not produce any evidence beyond their say-so that treatment for psychotherapy alone is sufficient or effective. Gender-affirming medical care is efficacious to treat gender dysphoria. Mountains of literature document as much, the clinical experience of plaintiffs' experts shows as much, and the testimony of plaintiffs illustrates as much. This factor goes to the plaintiffs.

Next up are Factors 4 and 5, utilization trends and coverage polices by other credible insurance payor sources.

Dr. Kellan Baker testified about how, over the years, we have seen an increase in the utilization of gender-affirming medical care. He testified that this increase is attributable to both greater of an ability of coverage and the fact that the consensus about this care has led providers who are providing this care to be explicit in their coding without fear of triggering an exclusion.

That also relates to Factor 6. Dr. Baker testified that the trend among all types of payors in the United States,

all types, is to cover gender-affirming medical care as necessary. This includes private insurance in the marketplaces, employer-provided insurance, Medicare on a case-by-case basis, and state Medicaid programs.

For example, he testified that a --

THE COURT: Surely the trend among Medicaid payors is the other direction?

MR. GONZALEZ-PAGAN: Well, Your Honor, he testified --

THE COURT: And that's whether that's a political movement or what.

Yeah, he said that. Look, I read the papers, and I don't pay attention to what the newspapers say when I'm evaluating my cases. Sometimes I skip over stories on purpose. But just -- I have looked at what's going on in other states. I mean, you know, I read the decisions, but I also see the statutes and so forth that are being passed. And just in the last month, there have been two or three states that have taken action.

Surely you don't assert that the trend is all your way?

MR. GONZALEZ-PAGAN: Your Honor, if one were to take a step back from this one last year alone, the answer is, yes, it is.

THE COURT: All right.

MR. GONZALEZ-PAGAN: Because some of those were states

that already had exclusions, like Texas, for example. And the reality is that even today, as we stand here today, of the 56 U.S. jurisdictions, 46 or 47 do not have any exclusions whatsoever. A few of them in the last year have adopted them, but it is still less than 10. And at the same time, 27 U.S. jurisdictions have adopted policies requiring affirmative coverage of gender-affirming medical care.

THE COURT: I get it. And I asked partly -- you've probably heard me say something like this before. You know, sometimes it's not nearly so important what the particular subject that's being addressed by an expert is or what the facts are. Sometimes it just tells you something about the expert and the expert's credibility, and it was part of the reason I asked the questions I did at the end of Dr. Scott. When you get experts that just won't recognize plain facts, it tells you something. When you get somebody that says the trend is all one way, it's just not.

MR. GONZALEZ-PAGAN: Understood, Your Honor.

I don't believe that was Dr. Baker's testimony. Dr. Baker was taking a holistic, universal view and testified as to the -- not just Medicaid, but Medicare insurance payors, the fact that, in the marketplaces, over 90 precent of private insurance being sold has actually no exclusions whatsoever. And that, in Florida, of the six insurance companies that operate and provide insurance, only one had a limited, vague exclusion,

the rest had none, and some of them had affirmative coverage.

We all, I think, understand that Dr. Baker would acknowledge that there are policies being passed right now in certain states because of political reasons. But I think if one were to take a step back, one would see that over the decades that this care has existed, the trend has always been for more coverage. And, yes, now we face these questions of whether that should be reversed, but that is different than what the trend was at the time that this exclusion was excluded and the overall graph that we would look at right now.

THE COURT: Yeah, I get it. And if one lived in Europe, one would say that the trend was on the defense side -- on the plaintiffs' side, and now it's turned around a little bit. And in the United States, the trend was certainly on your side, and now it's turned around a little bit. I don't know --

MR. GONZALEZ-PAGAN: Only one of six factors, Your Honor, to look at.

THE COURT: I get it.

And I'll say this to both of you: It's almost -- sometimes it's almost like you think that you should only say the things that support your side, and you ought to ignore everything else. That's fine. You can do it that way, but I have to deal with everything.

So it would really help me -- on both sides, it would help me if the experts actually looked at what was going on

instead of just cherry-picking what helped their side, and the same thing for the lawyers.

Look, it's not all one way. There are facts that support one side and facts that support the other side. Just come to grips with them. Don't pretend like I'm not going to find them out. I'm going to do my best to find them out. And if you just pretend like it doesn't exist, you kind of forfeit your chance to be heard on the question.

So on this, for example, I get it. The argument is, oh, yes, the trend is against us. Recently, it's political. It might very well be that it's political. But if you just don't acknowledge the trend, you don't even get a chance to say it's political. And I would have figured that out by myself, but some things I wouldn't figure out by myself.

So, frankly, all through this, if you'll address the real issues on both sides, it will help me.

MR. GONZALEZ-PAGAN: Understood, Your Honor. Absolutely.

And my next point was the following: Florida's exclusion, just like the recently adopted exclusions in other states like Texas, they represent extreme outliers within the realm of the 56 U.S. jurisdictions. Sure, some of them have gone more extreme now than before, because Dr. Baker testified that the few places that had exclusions, they were all different, if you will, that there were exclusions that were

total, categorical, like that has been adopted in Florida, whereas other places that adopted exclusions were limited to only certain treatments, say, for example, surgery, and some of which have age exclusions, specifically.

But, overall, if one were to take a look at the whole map and take a step back, the numbers have always been in support of a trend in this care. And, of course, we are now faced with the situation that we now live in politically where certainly some states have sought to restrict this care in multiple ways: Passage of gender-affirming care which is under litigation in several states as well as Medicaid exclusions in some states. Most of those states already have them. They were part of that ten or so jurisdictions, but they were states that have now made it even more difficult, not dissimilar from the actions in Florida here from passing the AHCA rule -- adopting the AHCA rule and then enacting Senate Bill 254 at the same time.

In sum, while this factor is somewhat mixed, one would argue that, overall, particularly utilization trends and the fact, if one were to look at private insurance policies and private creditors, none of which were discussed or acknowledging the GAPMS report, those factor -- these factors actually weigh in favor of the plaintiffs.

And then the last is the recommendations or assessments of clinical or technical experts on the subject or

field. This implies that these experts have experience. Most of the experts provided by the State had no experience in this care. And, indeed, the process leading to the GAPMS report was a sham process where only opponents of this care were selected to provide input.

Here plaintiffs presented the Court with the testimony of five providers of various disciplines who treat gender dysphoria. Each of them has treated hundreds of transgender patients of varying ages for gender dysphoria. Collectively, they have treated thousands of transgender people with gender dysphoria throughout the country from California to Illinois, from Michigan to New York.

And they, Dr. Shumer and Dr. Karasic, reviewed the medical records of the plaintiffs and testified that they have a diagnoses of gender dysphoria and that their care was consistent with the standard of care. Each of these experts are recognized as leaders in their field of gender-affirming care. They are experienced. They are published. They are peer reviewed. And they provided extensive testimony about the efficacy of gender-affirming medical care from a research perspective and a clinical experience perspective.

Their testimony was further supported by the testimony of a bioethicist, a public health researcher, and a neuroscientist, those being Dr. Antommaria, Dr. Baker, and Dr. Edmiston, all of whom have studied and rated about this

care.

I believe one can break the State's experts into buckets, if you will. They are the experts that had no experience providing this care, have not published, and had what can charitably be called or referred to as extreme biases against transgender people.

They also had other witnesses like Dr. Kaliebe who had some experience, but it was very limited experience and was not published in the area. Dr. Kaliebe's testimony said he's provided treatment to four people in the form of psychotherapy.

THE COURT: Yeah, I said that when I was asking questions. It may have been 4 he didn't treat out of his 12.

MR. GONZALEZ-PAGAN: Four that he had a prolonged relationship of treatment, and 16 overall that he has diagnosed with gender dysphoria.

THE COURT: I just didn't want you repeating back my number because I thought I might have had it wrong. But, anyway, it wasn't a big number. It was part of his 12.

MR. GONZALEZ-PAGAN: Yes, correct, Your Honor.

THE COURT: Maybe it was four adolescents. I can look back at the transcript, but it was a small number.

MR. GONZALEZ-PAGAN: And he could not provide any testimony in support of his position that psychotherapy alone -- any evidence, pardon me -- that psychotherapy alone is sufficient or effective in treating gender dysphoria.

This leaves us with Dr. Steven Levine, whose testimony, in large part, not in all parts, supports the plaintiffs. To be sure, Dr. Steven Levine advocates a more cautious and prolonged approach to assessment of gender dysphoria for adolescent patients, in particular. But he does not dispute that there are positive effects of gender-affirming medical care and the effect that it has had on even the patients that he has seen. And he believes that the decisions regarding this care should be left to patients, their families, and their doctors -- we agree -- not the government. And he has provided letters to support adolescent and adult patients obtaining gender-affirming medical care.

To be sure, Dr. Steven Levine is a critic of the standards of care as they stand now and would actually argue for a more cautious and, if one will, prolonged therapy approach before accessing medical care.

But at the end of the day, that goes to the tailoring question, not whether a categorical rule that prohibits all coverage of this treatment should exist. And Dr. Steven Levine is one of many people who have experience in this care, and we have provided a significant number of others who testify in support of the current standard of care in Clinical Practice Guideline approach.

THE COURT: Dr. Levine is probably correct that politics have affected the organizational endorsements of this

care; isn't that right?

MR. GONZALEZ-PAGAN: Your Honor, I would disagree with that. I just want to distinguish between politics -- about gender-affirming care in the political sense and what is occurring with governments versus, like, internal debates on politics about what the care should look like.

Plaintiffs' experts testified that -- those that were involved in the development of Standards of Care 8 testify that there are varying degrees of views. One would argue that Dr. Steven Levine is on the more conservative side of how the care should be provided, and certainly some organizations have rejected that.

But at the end of the day, that is part of the debate in science, and one could say that Dr. Steven Levine does engage in that debate. He has published literature in this area.

THE COURT: Lots of people engage in it. But I guess -- let me give you a chance to address this, and it goes to both sides.

I mean, on the defense side they can say that Mr. Brackett didn't know what result he was supposed to reach. Okay. His boss knew.

On your side you can say, Look, the folks that have participated in developing these guidelines, the folks at the American Pediatric Society who endorsed these guidelines, weren't affected by the higher political, moral, religious

disagreement about transgender individuals. Dr. Levine said he hadn't seen this level of political disagreement affect any other medical assessments, standards-of-care discussions. Frankly, to me that rings true.

Are you going to tell me, no, that's not it, that nobody in the American Pediatric Society would be worried about speaking up for fear of being labeled a bigot?

MR. GONZALEZ-PAGAN: No, I cannot categorically say no, Your Honor, of course not.

What I will say is this, though: This is a reason why a ruling is necessary to get the government away from banning this care, and let the debate happen among the medical providers and scientists.

I will say this: I believe, and I believe the testimony shows and the evidence provided shows, that Dr. Steven Levine disagrees with some of the plaintiffs' experts, certainly. And that is part of the debate that can happen and should happen. But he doesn't represent a majority view within the medical provider community, and there's no evidence that he does.

I don't disagree that there is significant debate around this, but part of that has to do with the fact that this care is being banned by states like Florida or being prohibited from being covered by states like Florida and injected politics into what would otherwise be routine medical care.

This may be outside -- completely outside the scope of what my closing is, Your Honor, but arduous debate in science is actually the norm. Some of my co-counsel and I were talking about this recently, because we spotted a pileated woodpecker, and I can note for the Court that there is vigorous debate as to whether the ivory-billed woodpecker is currently extinct or not, and scientists go at each other's throats at that fact.

But it's not a political issue that should be handled by the government. And the scientists put forth research, put forth papers about that, and they then, as a community, debate what makes sense.

Here -- here the standards of care were not just drafted in a vacuum. It involved 119 individuals all debating internally about what they should look like, having divergent views. The standards of care were actually published for public comment and then finalized. And in doing so, for the finalization, they were subjected to the peer-review process. That is how science should work.

So I do agree there are some folks that disagree with this care; they do. That is fact. But the fact that that is a reality doesn't mean that plaintiffs and transgender Medicaid beneficiaries should not have access to the care that their doctors believe is appropriate that they need and believe is appropriate and that we have shown has been documented to be effective, efficacious, and safe for their gender dysphoria.

I don't disagree with Your Honor that there is debate about this care in multiple spheres, but the overwhelming view of experts in this field is that this care is appropriate. And even the State's expert, that would be in the more conservative end of people who have some experience with this care, would agree that it is appropriate in some circumstances.

This rule prohibits coverage of that care in all circumstances. It just doesn't meet the moment and endangers the safety and lives and health and well-being of transgender people in Florida who are low income or are disabled and, therefore, rely on Medicaid for access to care.

Your Honor, I would argue that this discussion of the six factors illustrates that even under AHCA's own regulations, gender-affirming medical care conforms with Generally Accepted Professional Medical Standards and is not experimental.

Given this, AHCA's rule and Section 3 of Senate Bill 254 discriminate on the basis of transgender status and sex. They, therefore, violate Section 1557 of the Affordable Care Act and are subject to having -- under the Fourteenth Amendment.

Further, because these treatments are not experimental and they ameliorate gender dysphoria, Florida must cover these services where they're medically necessary for beneficiaries under the age of 18 -- of 21 under the Medicaid Act. Beneficiaries under the age of 21 are entitled under the EPSDT requirements of the Medicaid Act to have access to any care that

will ameliorate a condition.

Finally, because these services are covered for the treatment of other conditions for adults, Florida must cover the services as treatment for gender dysphoria under the Medicaid Acts comparability requirement, which prohibits discrimination among individuals with the same medical needs stemming from different medical diagnoses -- medical conditions. I can point the Court to *Davis v. Shah,* 821 F.3d 231, a decision by the Second Circuit in 2016.

Turning back to the equal protection argument, the State has intimated, but not shown, that care is being provided without caution. To be clear, the State has provided no evidence that this is the case in the state of Florida. But plaintiffs are not here to argue that every medical or healthcare professional out there is perfect or that they do things all the time by the book. That is neither their burden nor what is required of them under the Constitution and these laws.

Rather, plaintiffs have shown that when care is provided consistent with Clinical Practice Guidelines, it is safe and effective to treat gender dysphoria. That has been their experience, and that has been the experience of plaintiffs' experts.

It is the State's burden to show that their actions are substantially related to an important governmental interest

and that they had an exceedingly persuasive justification for doing so. The defendants cannot. Defendants point to the experience of the transition and have provided one out-of-state witness who testified to her own experience with the transition, Ms. Hawues (phonetic).

But the transition does not necessarily mean regret, although I believe in Ms. Hawues's case she testified that it does, and everyone acknowledges that the transition or regret may happen. It is a fact that no one denies. However, the uncontroverted evidence is that the transition and regret are extremely rare. We are talking 1 percent each. And this is for a population that is already so extremely small. This is born by the fact that defendants cannot find a detransitioner from Florida, notwithstanding that it is the third largest state in the country.

Defendants have repeatedly referenced the experience of one of the clinicians who offered a letter in support of Mr. Dekker to obtain chest-masculinizing surgery, that of Ms. Rolf. They ignore -- and that is -- the letter from Ms. Rolf is Exhibit 237A admitted into the record.

They ignore that a student clinician at the time, Ms. Rolf, was operating under the supervision of not one, but two licensed and well-practiced clinical mental health professionals, and they also fail to mention or ignore that it was an unnecessary letter. It was a second letter on top of the

first letter that Mr. Dekker obtained from his own psychiatrist with whom he had a long-standing relationship with. Mr. Dekker did that as a belt-and-suspenders approach to avoid being denied coverage.

I don't think the State would be arguing that medical residents cannot practice medicine if under the supervision of another doctor. Otherwise, how would they get experience? It is true as well with mental health counselors.

In sum, these two arguments or examples are wholly insufficient to support the State's actions, let alone to meet their burden under intermediate scrutiny to show as exceedingly persuasive justification, and one that is substantially related to the actions that they have taken.

Finally, Your Honor, it is worth noting the intentional nature of the State's actions. Not only was the AHCA rule a predetermined outcome of a fixed process, but the rule in SB254 is part of a constellation of actions by Florida officials seeking to erase transgender people from Florida. In signing Senate Bill 254 -- if I may, Your Honor -- the Governor signed other measures targeting LGBTQ people and transgender people in particular, and he also stated he -- and he also used the same slogan as AHCA did in adopting the rule: "Let kids be kids."

The implication, Your Honor is that a trans kid is not a normal kid. I believe that is wrong. Indeed, the Governor's

own words demonstrate as much. In signing Senate Bill 254, he stated: *As the world goes mad, Florida represents a refuge of sanity and a citadel of normalcy.* This thinking permeated an influence, the numerous deviations of process at AHCA, as they pursued the rule. These deviations were confirmed by the testimony of Jeffrey English as well as the State's own witnesses, Ann Dalton and Matthew Brackett.

Jeffrey English would have been the person who ordinarily would have handled the GAPMS report at that point in time. He was excluded. Never had AHCA hired consultants in the process of promulgating a GAPMS report. For the first time they did so here, and they chose only individuals with opposing views to gender-affirming care. In fact, they chose five to include attachments and two additional ones to serve as advisers.

At the end of the day, Your Honor, transgender Floridians are just a part of the fabric of this race date as any other person. Their medical needs are as important as those of any other person. They're as important as to those -- of any other person in Medicaid. This Court has now heard from them and from those who love them and those who care for them. August Dekker, Bri Roth, Susan Doe, and K.F. can see a future for themselves because they had access to gender-affirming medical care that they needed. It is our responsibility to ensure and protect that future for them.

For this trial, we have demonstrated that medical

treatment for gender dysphoria, which AHCA previously covered, is not only safe and nonexperimental, it is effective and necessary. Lives are at stake.

Your Honor, we thank the Court for allowing us to present this case and for hearing our arguments. We also thank all of the court staff for their care and attention throughout these past two weeks.

We ask that the Court declare AHCA's rule and Section 3 of SB254 unlawful and that it permanently enjoin defendants from enforcing them.

Thank you, Your Honor.

THE COURT: All right. Thank you.

Mr. Jazil.

MR. JAZIL: Thank you, Your Honor. May it please the Court, Mohammad Jazil for the defense.

Your Honor framed the issues in this case around the *Rush versus Parham* test, whether, based on current medical opinion, Florida's determination that certain treatments for gender dysphoria are experimental is reasonable.

The State's contention is that its conclusion was reasonable, and, Your Honor, I'd like to start with Dr. Levine's testimony. On page 982 of the record, there was a back and forth with the Court in follow-up to some questions from direct, and the testimony from Dr. Levine on page 98 [sic] essentially lays out the framework that -- the frameworks that can be used

to treat gender dysphoria.

I like to think of it as a continuum, because that's how the testimony comes across to me. On one end of the continuum, you've got the reversion model. This is pejoratively referred to as conversion therapy, where you're telling folks that they ought to revert back to their natal gender.

On the other end of the model is -- other end of the continuum is the affirmative model, where you're telling folks, Look, we are going to recognize the gender you've selected. We're going to acknowledge that this is your new gender, and we're going to work with you along that way.

And then there's the middle ground, the psychotherapy model, which I'll refer to as the ambivalence model because you're not trying to revert someone back to their natal sex and you're not trying to affirm someone into their new recognized sex. So that ambivalence model, the psychotherapy model, is what Dr. Levine was advocating for, in essence, in his testimony. And Dr. Levine talked --

THE COURT: He did say rather clearly that some people need medical treatment, puberty blockers, cross-sex hormones; true?

MR. JAZIL: Yes, he did, Your Honor. And he said that -- as his testimony was developed, he said that, Okay. They do. If I use a psychotherapy model, I see them for years. After I do my careful evaluation, I may write a letter

recommending that if they want to chose surgeries or medical treatments, et cetera, they should go forward and get those. What he did refute, though, was that -- look, this isn't something that you can just pick up on, even if you have a multidisciplinary team, in a matter of minutes. It takes years.

THE COURT: Absolutely, absolutely. You have to do it right.

And if the Florida Legislature adopted a statute consistent with Dr. Levine's testimony, we wouldn't be here, or if we were, the plaintiffs would be in a much weaker position. But that's not what the legislature did.

And I guess the question you need to answer -- and this is a constitutional question, not just a *Rush versus Parham* question. When I said what I did there, I was dealing with a preliminary injunction, and the statute hadn't been adopted. So the constitutional issue is now here, dead center of the case. What you need to deal with is: Why is it that the State of Florida -- that the Legislature and the Governor get to decide the medical care that an individual gets when even your own expert says this kind of care is sometimes needed?

MR. JAZIL: Understood, Your Honor, and I'd like to approach that two ways.

One, Dr. Levine talked about the three models, and he talked about what people believe they know, not what they actually know, and he was advocating for one of those three

models. He said also that the affirmation model has gotten a lot of credence and has become sort of a model du jour.

And Dr. Levine then talked about some of the concerns that are associated with that model, because the Court asked the question and said that I should be prepared to address this at closing; that, look, at the end of the day, if the affirmative model is supported by low-quality evidence or very low-quality evidence but we're giving certain treatments -- puberty blockers, surgeries, et cetera -- why -- what then -- what kind of evidence supports the model that we' advocating for, which is the no puberty blockers, no surgeries, other model?

And so this question was also -- a variation of it, as I recall, was framed for Dr. Levine, too, and Dr. Levine, in advocating for his caution model -- and this appears in the next page, 983 of the transcript, said that, Look, if we're talking about the affirmation model and we're quick to start with the puberty blockers, the surgeries, et cetera, we're talking about possible long-term negative impact on fertility, sexual dysfunction, et cetera. So that was his discussion.

It was like, okay, if we're doing the affirmation model and we begin with supposition that we should prescribe puberty blockers, cross-sex hormones, et cetera, we are then entering into an area where there's a greater chance of these other issues happening. That's where Zoey Hawues and Yacov Sheinfeld's testimony comes in.

So if we take that, Your Honor -- that testimony at a 10,000-foot level, what Dr. Levine is saying is caution is the watchword. Caution is the watchword. Then, in Dr. Levine's perspective, that caution should come without blanket prohibitions, but should come with exceptions for those instances where these treatments are and aren't required.

From the constitutional perspective, the question then becomes -- and from the *Rush versus Parham* perspective, the question then becomes if caution is truly the watchword, who gets to draw that line, and how do we figure out where to draw that line? Now, Your Honor, I would submit --

THE COURT: Draw it anywhere other than just flat prohibiting care that's going to make lots of people much better off than they are without it. So draw a line. But that's not what the legislature did.

MR. JAZIL: Understood, Your Honor. That is not what the legislature did. And, frankly, Your Honor, I am not certain about the line that the legislature has drawn, because at the preliminary injunction hearing when we were talking about just the rule, I brought up the variance and waiver process, and the variance and waiver process would have aligned with Dr. Levine's perspective, because someone --

THE COURT: Only if it was real. But I get it. And, frankly, other than you, I haven't heard from anybody suggesting that the exception, which applies to rules in general, ever had

any chance at all to be applied here. You brought it up, and I told the other side when they started to take issue with you, Do you really want to take issue with that? Because, look, this is good for you. And here we still are, so I guess they haven't gotten an exception, even though they've presented pretty good facts.

MR. JAZIL: Your Honor, here -- one, it was a legal argument, so I think it's appropriate for me to be the one who provides the agency's perspective on it.

Two, no variances and waivers were submitted.

Three, had a variance or waiver been submitted and granted, I think it would have strengthened my case and the perspective that I've presented.

THE COURT: It would have.

In any event, the legislature put the end to that because there is no exception to the statute; right?

MR. JAZIL: Well, Your Honor, there, too, I'm a little confused, and I think it would be worth having a variance or waiver as a test case to see how this works, because the way that provision reads is that state funds cannot be expended for these treatments under Medicaid, state funds.

I went back; I checked. So the Medicaid program is intended to be a matching program. The question in my mind, from an accountant's perspective, comes down to can the funds be segregated into state funds and the federal matching funds. If

the answer is yes, the variance and waiver could theoretically apply. So, Your Honor, I'm just -- I'm being candid with the Court.

THE COURT: Whose check gets cut to the hospital when they provide care? I was going to ask one of your witnesses that, and I forgot. But -- we can go look it up, but I think the answer is it's a state check.

MR. JAZIL: And, Your Honor, I don't know, and the legislation happened and got signed in the middle of my case, so I haven't had the --

THE COURT: But the way this is set up is the State pays for it and gets reimbursement from the federal government, I think. We can look at that up.

Look, if the argument is this is really not a flat ban --

MR. JAZIL: It probably is.

THE COURT: Yeah, I think it probably is.

MR. JAZIL: Your Honor --

THE COURT: Let me ask this: Is preventing individuals from being trans, from having a gender identity different from their natal sex, is that a legitimate State interest?

MR. JAZIL: I do not think so, Your Honor. I don't think that would be a legitimate State interest.

THE COURT: So when, for example, the folks on your

side argue -- and I don't know if you've adopted this, but one of the things that keeps being said is, Oh, 90-plus percent of the people that get puberty blockers go on to get cross-sex hormones. Actually, I do think that's in your briefing.

MR. JAZIL: And, Your Honor, that didn't come from me. That was Dr. Olson-Kennedy when asked on cross-examination if you start on puberty blockers, what percent go on. 98 percent is the plaintiffs' number, not ours.

THE COURT: And that's fine. And if, in fact, this is appropriate treatment for a trans individual, the fact that they got appropriate treatment at stage A and then continued into stage B seems to me to only back up the theory that this was the appropriate treatment and we're on the right track.

98 percent, probably, of people that get the first round of chemo for cancer when they got assigned to a 3-chemo set or a 12-chemo set, if 98 percent or 99 percent go on to round two, that doesn't tell you something was wrong at stage 1. That tells you something was right at stage 1.

But when the defense comes in and argues, Oh, look, we know something's bad here because if you get puberty blockers, 98 percent go on to cross-sex hormones, it seems to me that that's bad because that's recognizing trans identity, and the State's really opposed to that.

That's what I take out of that argument. When the defense comes in and says, Oh, the sky is falling, because if

you get puberty blockers, you're also going to get cross-sex hormones, I take that as an argument that the sky is falling because these people are going to keep being trans.

Am I missing something?

MR. JAZIL: Yes, Your Honor. From my perspective, what you just highlighted starts out with the supposition that the trans identity and the gender dysphoria diagnosis are intertwined and that if you are transgender, you have gender dysphoria and, therefore, you need to go down this road. And I don't think that was the testimony.

THE COURT: No, no. I'm not the one that believes that. I understand that one can be trans and not have trans -- gender dysphoria.

MR. JAZIL: So, Your Honor, if we start by saying that one can be trans and not have gender dysphoria, and then we say, Okay, if you have gender dysphoria, you're on puberty blockers, and once you're on puberty blockers, there's a 98 percent chance you're on cross-sex hormones.

So to go back to Dr. Levine's perspective, we're not giving folks the opportunity to explore, you know, the reasons for this and that in creating the room for possible desistance, if that's going to happen naturally without, you know, reverting to the reversion model, and that was the point of the State, Your Honor.

That if -- if we're doing the puberty blockers -- if

we assume that the gender affirmation model is the one and only true model and that gender affirmation model requires that puberty blockers be prescribed, then once we prescribe the puberty blockers, we're taking away that opportunity for the person to, as Dr. Levine may say, explore what's going on, and naturally desist if given the space or naturally go onto the next step if that's what they want. That was the point, Your Honor.

THE COURT: All right. That's why I asked. I understand the argument.

MR. JAZIL: So, Your Honor -- and, again, I'd like to just circle back to the point about line-drawing. I know the Court may disagree with it, but my position is this: That if we assume that caution is appropriate, then the State gets to choose where it's drawing its line. If the State has chosen to draw its line towards a complete prohibition, that, too, can be defensible because we're dealing with a health, safety, welfare regulation. And I think it would be appropriate to defer to the State in that instance. A way to look at it is if I'm going to fix the road, at some point I have to stop the traffic and sort of reassess.

And, Your Honor, I point out --

THE COURT: Why did they shut down the research?

MR. JAZIL: Your Honor, I don't think there is testimony saying that we shut down the research.

THE COURT: Didn't you shut down the research? I mean, they were treating patients at Florida and doing research, and now they're going to have to disband the clinic because they can't treat patients at all with these drugs.

MR. JAZIL: Your Honor, I'm not sure that that is testimony that came in during the course of the trial. I know the section 3 would say that postsecondary institutions can't be reimbursed for prescribing these treatments, but I'm not entirely sure that there is testimony saying that the research is shut down.

There's testimony from one of the parents -- I think Ms. Lapado -- that she had an appointment at the St. Petersburg Johns Hopkins clinic, and those appointments didn't go forward.

THE COURT: Here's my understanding -- and I haven't gone back to recheck this. Been a lot of information coming in, so I may not have sorted it out accurately.

Here's what I thought: There was originally a proposal to allow research -- this may have been at the rulemaking process at the board of medicine. The proposal was we were going to allow research, and then that got pulled back out, and the research exception is gone. And if it's illegal for a doctor to provide this, it certainly -- there's no way for anybody to study it.

MR. JAZIL: There's no way for some -- Your Honor, you're right. If there's a prohibition on minors for the use of

these treatments, then there's no group for the research institutions to study. But, Your Honor, I point out that -- as my friend pointed out, there is a movement going around in the various United States dealing with this issue. My friend pointed to Texas and some of the other states that have perhaps aligned with Florida on the issue, but there are others, like California, who are going the other way.

And, Your Honor, I wanted to bring a California provision to the Court's attention because it does also go to the child custody issues that we discussed on Friday that deal with section 1 of the legislation that was passed.

And it's Senate Bill 107, Chapter 810. It was signed by the governor of California on September 29, 2022. And, Your Honor, section 5 of that bill is a mirror image of the Florida child custody section. In Florida the child custody section says if you're going through a divorce, you know, the courts have the ability to take temporary jurisdiction over your kid if the kid is getting or threatened with gender-affirming care.

California goes the other way and says that the courts of the state can take temporary emergency jurisdiction if the child has been unable to obtain gender-affirming health care or gender-affirming mental health care. So what you're seeing in the states is you've got a true opportunity for the laboratories of democracy, and more so just laboratories generally.

California is taking the approach, based on this statute and the others they've passed, that gender affirmation is the model we're going to use. Gender affirmation is the thing that will be done. So California can provide us a subset of studies that say, Okay, what happens when gender affirmation is what we're doing and how we're treating folks?

Florida, Your Honor, we have approved, and we are still reimbursing for, a whole list of mental health treatments, and so you can do a psychotherapy approach and see what happens, and we can use this to fill the gaps in the data.

THE COURT: And for those adolescents now whose doctors say, after a -- after a team approach that meets all the requirements, This adolescent is going to be far happier, less anxious, less depressed, have a better long-term outcome if we give this treatment -- and we have lots of clinical experience that says that will be true for many people -- at least for a period of time. There are no 50-year studies because this hadn't been going on for 50 years.

But for as long as we've had this, we've got clinical experience, widespread clinical experience, saying this works. For the adolescent in Florida who needs that care, the answer is, Let him eat cake. He's either going to move out of the state or he's going to be less happy, more anxious, more depressed. He cannot get the treatment that his doctor and the widespread clinical experience says is best. That's what the

State has said.

MR. JAZIL: Your Honor, I reframe that as the State saying, Look, when you're saying and your physicians are saying that you need these treatments in adolescence, you cannot get it. You can get it once you reach the age of majority, right, because that's --

THE COURT: Too late.

MR. JAZIL: And I guess what the State is also saying that that person who truly needs it in the adolescent stage is the exception, not the rule.

And so if we're crafting a statutory scheme, Your Honor, I would suggest that if the State is right about the rule, then the exception itself should not defeat the statutory scheme.

Your Honor, I'd also like to talk about the clinical experience. We heard from Dr. Shumer. We heard from the others who work on multidisciplinary teams. You also heard from Dr. Kaliebe. On some level Dr. Kaliebe's experience is also relevant because he's a line psychiatrist. He is dealing with these folks in -- he's dealing with patients, lots of patients in lots of different settings, and he's telling you that I just don't have the time to spend a lot of time with folks and go through the years long psychotherapy approach that Dr. Levine was advocating for.

So I think it's important to note that as well. If we

could go to some of the plaintiffs' medical records -- not on the public screen, please.

So, Your Honor, I'd like to start with K.F., and if we could scroll through.

Now, Your Honor, this is an institution that even Dr. Shumer recognized is outstanding. It's where he did his training. Here we've got the medical records for a young patient. 25 minutes were spent, and this is Plaintiffs' Exhibit 235, and the Bates number is 4243. This is the endocrinology visit. The risks were discussed.

Can we go onto the next page, please.

Now, this is another statement from the visit where the long-term side effects of the medical treatment was discussed, and there was going to be issues on future fertility, et cetera. This is the material that Dr. Shumer said he thought was somewhat conservative. He wouldn't have discussed issues this way.

So you've got -- you've got folks who are providing the gender-affirmation treatment who are discussing these issues with patients in 25-minute visits, and there isn't absolute uniformity in what it is they're telling folks.

And, Your Honor, this is -- this is something that came up as well. The patient's mother testified before the Court about a visit on August 6th. And what you can see from this document, Your Honor, is -- and this is in the record, is

that the visit was done by a telemedicine, right?

So it's a telemedicine visit, and the patient's mother testified that the patient, who was 11 at the time, was concerned about, well, is this going to hurt. 11-year-old concerned about, Is this going to hurt? But then the last sentence on the first blowup says, *He desires having kids in the future, specifically not birthing them, and does not desire ovarian preservation at this point.*

So this is an 11-year-old. We're having a discussion about future fertility, whether or not there's a desire to birth kids and whether or not ovarian preservation is necessary. And, Your Honor, again, just to pull out for a minute, this is an 11-year-old. We don't trust 11-year-olds to drive, to drink, to vote, to watch PG-13 movies, but we're talking about ovarian preservation.

THE COURT: You suppose a parent was involved in these discussions?

MR. JAZIL: For sure, Your Honor, a parent was involved in this telemedicine discussion about a --

THE COURT: Look, telemedicine -- this is August of 2020. It's -- COVID is raging, and there is no vaccine. So, yeah, people were getting medicine over the video, but, I mean, I take the point.

Look, I didn't need the expert to tell me that adolescents' brains don't work the same as adults and that

they're more likely to engage in risky behavior. It was more than 50 years ago, but I was an adolescent once, and I don't know that they've changed that much, so I get it. Adolescents, and certainly 11-year-olds, aren't in a position to make the same decisions they would be able to make later in life, but that's why we have parents involved.

I mean, what we had discussed before -- and I don't know that we're going to get much farther discussing it -- but here's the problem: A decision is going to be made, and if the child is 11, the child is 11. So the child and the parents are going to make a decision. There's going to be medical treatment -- and by that I mean puberty blockers and cross-sex hormone treatment -- or there's not.

You can't say the 11-year-old and the parents aren't able to make a good decision, and so we're going to decide for option B instead of option A. It's going to be a decision, and the same people are going to make it unless, of course, the Governor and legislature make it for them. And that's really the question in the case.

When you have someone who may need treatment, the decision whether to get treatment or not is going to be made because it has to be made at that point. So who's going to make the decision? Is it going to be the parent and child in consultation with a doctor who does this all the time and knows all about it or is the decision going to be made by the

legislature and Governor?

MR. JAZIL: I take your point, Your Honor. I'd simply add on to that that it's a little bit more complex. If we take Dr. Levine's testimony, and we assume that the gender affirmation model is the one that -- you know, is the one that's being trumpeted as the one and only model, and doctors are afraid to disagree from it because they might be labeled bigots, are the doctors giving the best possible information to the parents and the patients?

If gender affirmation -- we start out that gender affirmation is it and the Levine psychotherapy model is not it, so if that is the starting point, are we then putting the patients and the children in the best possible position to make the decision?

THE COURT: Absolutely a concern. Absolutely a concern.

And you heard I asked some questions earlier about, you know, not everybody goes to the University of Michigan or the University of Florida. And what -- am I to be concerned about somebody else, some lesser quality of care? It's -- it's absolutely a concern. And the solution to that is make sure this gets done right.

You keep saying, by the way, the gender-affirmation model as if that's the only way to do it and without psychotherapy, and that's not what the testimony is at all.

There's psychotherapy for all of these patients. That goes hand in hand with the administration of these drugs. Nobody has suggested otherwise.

And nobody has said everybody that appears and says they identify in the other gender is going to be rushed right in to these medicines. The testimony is exactly the contrary, that we're going to make the evaluation, and only some patients are going to get this.

I'll grant you -- and I asked the question to the other side -- and sometimes you have to evaluate the evidence in the record, but you have to consider some common sense along the way. And I've lived in this world. And so it -- does it concern me that maybe at the medical society people were afraid to speak up for fear of being labeled a bigot? Absolutely it does.

Do I think there are no bigots in the world involved on this issue? I don't think that either. I'm pretty sure there are some bigots. When you put on witnesses who don't believe that there is such a thing as being trans and that gender identity is really not a thing, that's not very impressive. I shouldn't label that person a bigot. Sometimes that is a sincerely held religious belief. I understand that.

I'm old enough to remember when people had sincerely held religious beliefs that Blacks and Whites shouldn't be able to go to school together or eat at the same restaurant. People

have all kinds of religious beliefs, but that's not -- upholding that religious belief is not a legitimate State interest.

MR. JAZIL: Understood, Your Honor. And I apologize for not being more precise when I was talking about psychotherapy.

What I mean to say is what I'm calling the ambivalence model where you're not using psychotherapy or any other kind of treatment to push folks one way or the other, and that's what I mean, Your Honor.

And I would like to point the Court to the Endocrine Society guidelines, which are DX24, page 15.

Can we pull up DX24, page 15, 1-5?

Can we blow up the section that says *Evidence*.

So, Your Honor, we saw this before, and this section talks about how, in prepubertal kids, the dissidence rate is 85 percent. And then it goes on to say that: *If children have completely socially transitioned, they may have great difficulty in returning to the original gender role upon entering puberty. Social transition is associated with the persistence of gender dysphoria/gender incongruence as a child progresses into adolescence.*

And this is from the Endocrine Society guidelines. And, Your Honor, I think this aligns with what Dr. Levine was talking about. If we don't take the ambivalence approach, if we take the affirmation approach, we sort are of pushing kids --

THE COURT: Yeah, look, you're talking about a different stage in life and a different problem.

I don't suggest that a doctor needs to be what you call ambivalent when a child appears in early childhood. So the 7- or 8-year-old shows up at the doctor's office with parents concerned about this kind of thing, I don't suggest that there is anything wrong with a doctor being a little bit skeptical. Most people are cisgender. And most times when something has happened that may concern a parent, it's just -- it's not an indication of real transgender identity.

I get it. And so I'm not suggesting there is anything wrong with a doctor being skeptical, and that's consistent with what Dr. Levine said. I don't think he said you have to be completely ambivalent. I think he said you have to make a good, honest evaluation. It has to be a good, honest evaluation. You can't start out, as I think some of the folks on your side would, by saying, Oh, this can't be real. But you certainly don't have to jump right into it. Surely, you can be skeptical. Surely, you can do a long-term evaluation.

And if the State had standards that required that, I don't know how the plaintiffs would challenge it. But that's not what the State has done.

MR. JAZIL: Understood, Your Honor.

And, again, I'd like to get back to the point that everyone is getting these diagnoses at wonderful

multidisciplinary centers. The evidence in this case doesn't bear that out.

We have Mr. Rothstein who was diagnosed with gender dysphoria by a woman named Debra Grayson -- we don't need to use these -- a woman named Debra Grayson who is not an M.D., whose services included hypnosis as one of the services she provided. Surely, that is not someone of the caliber of a Dr. Levine, a Dr. Karasic, a Dr. Janssen, or a multidisciplinary team in Michigan making these diagnoses.

THE COURT: And I guess my point is -- here's my question to you: Why isn't the solution to that imposing better standards rather than prohibiting the treatment?

MR. JAZIL: So, Your Honor, that is one possible solution, but it is not the only solution.

And I guess the point I keep coming back to is that if we know that there is a need for regulation, how perfect does the regulation need to be for us to say that it's constitutional? And that gets us into the discussion about, well, if it's a rational basis, we have a lot more leeway as a state to get around to figuring out what the regulation ought to be. But there is a rational basis, because there is a problem. We're trying to solve it. There's a rational basis.

If it is intermediate scrutiny, then it needs to be -- it's not perfect tailoring; it's reasonable tailoring. And depending on which case one looks at for intermediate scrutiny,

you can find a test that favors me, a test that favors them. The articulation isn't always perfect.

Your Honor, my point in simply highlighting the hypnotist who made a diagnosis and the intern who -- you heard from the plaintiff himself, Mr. Dekker: *I saw Abbie. I didn't see the others*. So if we take that into account, that these diagnoses are being made in a less than perfect way through doctors or interns or other providers who are not skeptical -- let's just use that word -- then there is a need for regulation. And if there is a need for regulation, well, then what's the test for the State?

And, again, I submit that it's the rational basis test. Your Honor and I had a colloquy about whether or not it should be the intermediate scrutiny test.

But, Your Honor, unless you have more questions about that --

THE COURT: No, we went through that.

MR. JAZIL: But, Your Honor, I've been thinking about that exchange a lot, and I just want to take another crack at one point. And, Your Honor, we talked about *Geduldig*, *Dobbs* and *Adams*. And in *Adams*, it was a bathroom policy. Natal males use the male bathroom. Natal females use the female bathroom. *Adams* said that is sex-based discrimination. It's subjected to intermediate scrutiny.

In *Geduldig*, the question was, okay, we've got

pregnancy, and the insurance isn't covering disability for pregnancy. And the pregnancy diagnosis included only women, right, and not males. But the Court said, Well --

THE COURT: Nobody got paid for pregnancy.

MR. JAZIL: Yes.

And then in *Dobbs*, it was abortion, again, affects only women.

My point with *Geduldig* and *Dobbs* is that the case and their discussion about the groupings don't make sense unless we take the diagnosis into account as well. And if, in this case, we take the diagnosis into account as well -- so it's gender dysphoria, not gender dysphoria -- gender dysphoria includes just trans. Nongender dysphoria includes both trans and natal males, females. Just wanted to make that clear, Your Honor.

Your Honor, I'd like to move on to the process issues. The plaintiffs' star witness on this point was Jeff English and, more specifically, Jeff English's email to Dr. Cogle. Your Honor said that we should be prepared to address that document in closing, and so I'd like to begin by first explaining --

THE COURT: I understand why Ms. Dalton assigned that the way she did.

MR. JAZIL: Okay.

THE COURT: I thought she was very credible.

MR. JAZIL: Understood, Your Honor.

THE COURT: She also said she knew what the preferred result would be.

MR. JAZIL: Your Honor, in fairness --

THE COURT: And somehow Mr. Brackett didn't know that.

MR. JAZIL: Your Honor, in fairness to her -- and I think the question was framed as: Do you read the newspapers? And isn't it -- that was sort of -- there was a setup to it. And I just caution, Your Honor, that newspapers aren't always the best first draft of history.

THE COURT: No, no, and I don't suggest they are. But if you lived in this town through this period, I just think it's a little unrealistic to think that somebody didn't understand which side of this issue this administration was on. And that's why I asked.

I mean -- and she knew. And as I said, she was very candid about it. That doesn't mean that she would have slanted the result or provided an untrue result. She just -- but she acknowledged that she knew.

Look, here's the -- you can run, but you can't hide. I think the record establishes beyond any question this came from the Governor's office. This came down from the Executive Office of the Governor. It was a response to what came out of the Biden Administration. So you had -- the Biden Administration took a position. It came to the attention of the Governor, and the Executive Office of the Governor pushed this

down, and things started happening.

That's not how this usually happens. I don't suggest for a minute that it's beyond the authority of the Governor to say, Look, we need to look at this. And the State had been paying for this for years.

But if the Governor says, Let's take another look at this, that's perfectly okay.

Then we get down to Mr. Brackett, and he's able, with just a few minutes' look, to know that he knows more than a group of 21 professors from Yale. That's --

MR. JAZIL: Understood, Your Honor.

And the Court has the 30(b)(6) depo designations where Mr. Brackett was designated. And as the Court goes through that -- and which are included in evidence -- the Court will see that, yes, the Biden Administration had come out with some of these policies in March of 2022. And the Governor's office did have a meeting on, well, what's the response?

The depo designations will also show that it was a lawyer at AHCA who came up with the idea of why don't we go through the GAPMS process. That's what it's here to do, evaluate the evidence. And so, Your Honor, we are not running from it. It is in the depo designations. And then you work through that process.

Now, Mr. Brackett did conclude that there was low-quality evidence to support the use of these treatments.

Mr. Brackett isn't wrong about that, and I don't think their experts disagree with that either.

THE COURT: I fully agree.

Let me say that I think the GRADE system, that G-R-A-D-E system -- that's an acronym. It stands for something. I don't take issue with the system. I think it was a very unfortunate choice of terminology, because someone who is politically opposed to a position then can holler low quality, and it obscures the actual evidence.

And it goes back to this question that you and I just talked about a minute ago. A decision is going to have to be made, and the only evidence on either side of the question is going to score out low or very low or nonexistent on the GRADE system. And so evidence can be the very best available evidence, the evidence that any honest, caring parent would take into account in making a decision, and yet score out as low quality.

MR. JAZIL: True, Your Honor. And as the guy who was charged with writing the GAPMS report, when you take a look at one of the two yardsticks that's being thrown at you as the basis for providing these treatments and one of those two very clearly just lays out low quality, low quality, very low quality, et cetera, it's not unreasonable for him to come to the conclusions that he came to.

And I'd suggest that doesn't -- his conclusions and

the fact that he relied in part on the Endocrine Society themselves to come to them doesn't suggest that he had any kind of animus as he was going through the process.

THE COURT: What should I make out of the idea that he didn't know which result was preferred by the administration?

MR. JAZIL: Your Honor, he is a civil servant technocrat. He's not the guy talking to Tom Wallace or Secretary Marstiller or the Governor's office on a daily basis that deal with these things.

THE COURT: What should I draw -- in terms of the honesty of this process, what inference, if any, should I draw from the fact that the consultants who were hired were all politically motivated opponents known to be opponents of this kind of care before he ever started into it?

MR. JAZIL: Your Honor, a couple of points there.

You can draw whatever conclusions you want to draw, but I note that not every single one of the consultants was labeled as someone who has an entrenched perspective on the issue.

Brignardello-Peterson, whose attachment is the very first one, she just did a systematic review of what's what. She's someone at McMaster University. And Your Honor will see this in the next case. She gets criticized for being a dentist, but she's also an epidemiologist. I note that the NIH director is also a dentist and a researcher. But setting that aside, she

was never smeared the same way. And I make that point, number one, Your Honor.

Number two, the fact that the Van Mols and the Miriam Grossmans of the world provided their perspective as the GAPMS report was being worked through, in and of itself, isn't outcome-determinative because there's still a rulemaking process. The entire rulemaking process is designed to solicit input from others, and there was input from the Endocrine Society, WPATH, and various others that was put in. It was considered. Mr. Brackett ultimately concluded that he didn't see a high-quality study, as he put it, that he was looking for.

So, Your Honor, I simply note that if the fix was in, there's a lot easier ways to do the fix. But you couldn't just start rulemaking and come to the conclusion and skip the GAPMS process.

THE COURT: Well, unless you were trying to sugarcoat it, but I get it.

Ultimately this -- now we've got a statute, so the rule process may have some relevance, and we discussed that before, but now we're dealing with a statute. So the --

MR. JAZIL: Understood, Your Honor.

And I'd simply like to point the Court to a relatively recent U.S. Supreme Court case, *Department of Homeland Security v. Regents of the University of California*, 140 S. Ct. 1891, from 2020. It talks about the animus question. And,

Your Honor, if we are dealing with the animus of agency action, whose animus are we looking at? And it's the animus of the ultimate decision-makers, which would be the secretary and Tom Wallace, the guy who signed it, right. And everything else is almost like circumstantial intent of the animus of these people it's being derived from --

THE COURT: There's a whole cat's paw theory, but I don't think anybody suggests that it applies here. The folks at the top of this probably weren't being manipulated by somebody -- by the cat's paw, so I don't think that matters. I get it.

MR. JAZIL: Understood, Your Honor.

And as we are moving on to the legislation, that, in and of itself -- we go through the *Arlington Heights* analysis. It's for historical background, sequence of events, procedural departures, contemporary statements of legislators, impact/availability of less discriminatory alternatives. But there is another component in that, Your Honor, that the Eleventh Circuit has been adding on: The legislative presumption of good faith.

Now, this concept arose in a redistricting context, has been extended outside of redistricting to elections context. And the language that the Eleventh Circuit used in its most recent *League of Woman Voters* case doesn't limit it to elections cases. It just says there is a legislative presumption of good

faith that needs to be overcome. And that legislative presumption of good faith, as we are working through the *Arlington Heights* factor, I posit, Your Honor, applies to every one of those factors.

And so, for example, Your Honor, the statements -- the unfortunate statements from one legislator during the bill development process came up. That in itself doesn't sink our battleship, in essence, is the point.

THE COURT: It doesn't. It's one legislator who said out loud what I suspect that others in our society, if not in our legislature, think.

Tell me what there is in this record that suggests that the Governor, anybody at AHCA, anybody at the Board of Medicine, anybody in the legislature thinks that there are, indeed, trans individuals who -- whose real gender identity is different from their sex assigned at birth.

MR. JAZIL: Your Honor, I would make a couple of points there.

Number one, the rule itself -- if we focus on the rule, the rule itself says you can't do three things -- right? -- the puberty blockers, cross-sex hormones, and the surgeries. But the fact that it leaves open a whole list of psychotherapies I think is evidence that we are not trying to prohibit transgender individuals accessing the care they need even if it is to affirm their preferred gender.

And, Your Honor, here I highlight one other point. I think everyone agrees that for prepubertal children, no medicine, no surgeries; right?

THE COURT: Absolutely.

MR. JAZIL: And so for that, those -- category of people, the prepubertal children, that's usually, approximating, up to the age of 12, psychotherapy. We're not banning it. It's there. You can use it. So from that age, then, of 12 to majority, we switch over to the statute. 12 to majority, no puberty blockers, no cross-sex hormones, no surgeries. The therapies are still there, including the therapies that may affirm your gender identity; right?

And then when we go from 18 on, there is no prohibition in the statutes that are part of 254 -- I think, Your Honor, it's important for the Court to take all of 254 into account as you're considering the animus question. I think that's just what the law says. So if we're taking all of it into account, that notion of, okay, if you're over 18, we're going to let you do what you want to do and get the treatments you think you need -- that part of it I think also goes to the point that, look, we're not going after transgender individuals. We're not saying that, you know, they shouldn't exist or they're -- well, I won't use the phrase that the legislator used, but Your Honor gets my point.

In addition, Your Honor, there is a grandfathering

provision in some of the other agency actions that are being undertaken here. So if you're on these treatments, we're not going to take you off them. And there's an emergency rulemaking provision in the statute, in 254, that deals with these issues as well.

THE COURT: So I understand your answer to say, Well, we didn't -- we didn't ban as much stuff as we could have. I'm not sure you could of when the anti-trans community has won a constitutional case on the therapy issue. So it would have been a little hard to try to say that we can ban therapy in support of trans identity when you've already got an Eleventh Circuit case saying there's a First Amendment right on the other side. That one would have been -- that would have tested your advocacy skills quite a bit. Leave -- leave that out of it.

My question was: Has anybody -- anybody in any of those areas I talked about -- Governor, anybody in the Governor's office, anybody at AHCA, anybody at the Board of Medicine, anybody in the legislature -- ever said, We understand there are actually trans people? Sometimes a person's gender identity really doesn't match the sex assigned at birth.

And you told me it wasn't as bad as it could have been, but you didn't point me to anything out of any of those places where anybody said anything suggesting that they actually believed there are trans people.

MR. JAZIL: Your Honor, I don't know the answer to

that. I don't know if anyone from those different agencies, those different branches of government has said that there are trans people.

I would note, Your Honor, that at the end of the day, if the claim is an animus claim and the idea is that the State is doing this to harm trans people, then the other side has a burden of showing that the Governor, the legislature, depending on which thing we're looking at, whether -- if it's the rule, it would be the Governor and the executive branch; if it's a statute, it would be the legislative branch. If folks in those two branches are taking actions not necessarily to impact trans people, but with the intent of it affecting the trans people -- and I don't think that evidence is put forward in this case, and so I --

THE COURT: I don't think my question was limited to the animus issue.

But however one frames the legal issue, if the decision-makers just believe there's no such thing as an actual trans identity, and the evidence, even from your own experts, to the extent they're credible, is that there are people whose actual gender identity doesn't match up with sex assigned at birth, doesn't that call into question the evaluation of risks and benefits that were made by the State? I mean, if you don't think the situation is real, then it's pretty easy to say there shouldn't be any treatment for it.

MR. JAZIL: Your Honor -- and I guess the testimony you heard from all of the witnesses, both defense and the plaintiffs, is no one is questioning that there is a gender dysphoria diagnosis; right? So if no one is questioning there is a gender dysphoria diagnosis, I think that presupposes that no one is questioning that transgender people actually exist; right?

THE COURT: I don't think that lines up, and one of your -- one the experts -- and I don't --

MR. JAZIL: It was Dr. Hruz.

THE COURT: I didn't memorize their names as they came through. I can look back and find it.

But one of my questions to one of your experts, he kind of danced all around it, and, frankly, I thought it was an evasive answer. I think there is a difference between saying there is such a thing as gender dysphoria; there is not such a thing as actual gender identity not aligning with natal sex. I probably haven't articulated it very well, but I hope I get across what I'm talking about.

I think you've -- I think that expert and maybe more than that think that this is all just a false identity. One of your experts signed a brief that said that: They're just masquerading; it's false identity. Well, the more credible of your experts said, Oh, it's not false identity. There are people whose gender identity doesn't match sex assigned at

birth.

And I just -- and my question was, you know: What's in the record? I'm not asking you to speculate what's in some legislator's mind, other than what they've said. But my question was: Is there anything in this record that suggests that any of the decision-makers agree, for example, with Dr. Levine as opposed to the expert who said this is all false identity and they're masquerading?

MR. JAZIL: Your Honor, the closest I get to is Matt Brackett, who was on the stand. He's not one of the decision-makers. He just wrote the report. He said -- he recognizes there's a transgender identity.

Second, Your Honor, the decision-makers didn't let me hire Dr. Levine, so I suppose that's a sideways way to suggest that they're not disagreeing with it.

That's my best answer to that question, Your Honor.

THE COURT: Yeah, I got it. You know, I'll have been through the entire record by the time I enter a ruling. So if there's something there, I think I'll find it.

MR. JAZIL: Understood, Your Honor.

THE COURT: The fact they didn't say it doesn't mean that there aren't some who believe it. I get it. They -- politicians speak a lot, but they don't have to speak about everything.

MR. JAZIL: Fair enough, Your Honor.

Your Honor, I just highlight a couple of other things from the record. I would commend for the Court's consideration the Endocrine Society guidelines, the portion on the unresolved questions concerning the effects on the brain. I think that's important.

You heard from Dr. Scott. Dr. Scott is -- at the very end I asked Dr. Scott what she meant by the effects of the neurotransmitters on the hypothalamus, and she went and explained that, look, really we thought it was going to affect just the hypothalamus, but it's affecting other parts of the brain. And, yeah, there are sheep studies that deal with these issues, but, you know, we're seeing changes in the amygdala. The amygdala is important because it controls other things that happen.

And so, Your Honor, I highlight that because Scott's testimony did align with the Endocrine Society guidelines and the need for further caution when we're assessing the effects of puberty blockers on the brain. It's a big unknown, and I highlight that for the Court.

Your Honor, finally, we put this in our summary judgment papers, which we then asked the Court to consider as our trial brief, the 1983 argument. I understand the Court's pretrial order concerning it, and the Court laid out some of the more recent cases. And I'd note that the Court was careful in saying that some of those cases didn't decide the issue but went

on to the discuss the merits.

And, Your Honor, again, I'd point out that the Supreme Court heard a case November 8th dealing with whether or not 1983 actions are appropriate to enforce spending clause issues or spending clause statutes, and I have a feeling this case will come out this summer. It has to. So I simply note that for the Court, and I just want to make sure I preserve the argument if it goes up.

With that, Your Honor, unless the Court has further questions, I have nothing further.

THE COURT: No. Thank you.

Rebuttal?

MR. GONZALEZ-PAGAN: Thank you, Your Honor. Just very briefly.

I would just note that the rule at issue in this case and the provision in section 3 regarding State funding from SB 254 applies equally to minors and adults. So it is not just wait until you are 18 if you are low income or disabled. It's you're not able to get this care in the state of Florida for your entire lifetime.

THE COURT: You can get the care after 18, but you have to pay for it.

MR. GONZALEZ-PAGAN: Or leave the state because you are low income. You're on Medicaid.

THE COURT: I understand. I get it. If you're on

Medicaid -- if you don't have any money and you have to pay for it and there's no source of reimbursement, then --

MR. GONZALEZ-PAGAN: Yeah.

THE COURT: -- you're not going to get it. Although one of your clients managed to set up a GoFundMe page, pretty remarkable, but that's not an answer generally.

MR. GONZALEZ-PAGAN: It is remarkable, but I don't think everybody will have that opportunity, Your Honor, and we are just fortunate that Mr. Rothstein was able to.

Your Honor, my friend pointed to a few of the medical records of each of the plaintiffs. I will just note that it paints a very curated and cherry-picked picture. K.F. started working with the GEMS program in Boston when he was 7. He worked with them for over four years before he started puberty blockers, and his initial appointment included a two-hour psych evaluation, not a 25-minute visit.

August Dekker got diagnoses from a psychiatrist, a mental health counselor at Metro Inclusive Health, and then separately his psychiatrist.

Brit worked with several medical providers in order to access -- Brit Rothstein worked with several providers in order to access gender-affirming care, including Dr. Hart-Unger at Joe DiMaggio's Multidisciplinary Clinic.

The plaintiffs have provided what I think is mostly the norm in how this care is approached. It is also consistent

with Kim Hutton's own testimony about her son in another state.

And I would caution the Court on a point that I think my friend has raised multiple times, and that is this idea that there is this gender dysphoria exceptionalism or transgender exceptionalism, that because there may be a bad provider out there or a -- all of a sudden we need to so strictly regulate the provision of this care. Why? Why do we need to treat this care any different than any other care?

Of course it carries risks and benefits, and providers should provide all of the information that is known, as well as what they don't know, to parents and adolescent patients and to adult patients. That is what the standards of care and Clinical Practice Guidelines require and recommend, and just because a provider may not follow that -- which, again, there is no evidence of that occurring here in Florida in the record -- it's not a reason to ban care. And, in fact, there are already tools for that. There's medical malpractice; there's professional licensure and the like.

But just, lastly, for purposes of clarifying the record, Your Honor, we did approach opposing counsel with regards to the waiver for Mr. Rothstein following the preliminary injunction hearing, and, unfortunately, we did not get any answers as to how it would operate. I would note that Mr. Brackett's testimony at his deposition was that if the medical care --

THE COURT: Is this part of what you designated?

MR. GONZALEZ-PAGAN: This is correct, Your Honor, and this is page 80 of our trial brief.

That if the medical care for which it was -- one could seek an exception if the care was not experimental. But AHCA has determined this care to be experimental, so there is no exception to be had if one were to just follow his testimony.

So we did try to find this variance, but at the end of the day, Your Honor, the statute here supersedes, as Your Honor has noted, and it's categorical. And even if there was this variance process, I would argue that it is still discriminatory. Why the extra hoops is necessary here is part of the question, but those hoops are nonexistent.

THE COURT: And part of my question was: Why didn't you at least try?

MR. GONZALEZ-PAGAN: We did, Your Honor. That's what I was positing.

We did approach opposing counsel several instances between October and December to try to get information about how we could do that and what would be the best approach and to do it on an expedited timeline given his surgery date of December, and we were just unable to get that information.

And I believe that letter has been filed with the Court in some of our pleadings.

THE COURT: I would have thought the way to do that is

some kind of petition under Chapter 120, but I --

MR. GONZALEZ-PAGAN: If the Court has no further questions --

THE COURT: I do not.

Mr. Jazil, I do have a specific question, though. First, I take it if you wanted the exception, there would be some kind of 120 application?

MR. JAZIL: Yes, Your Honor, there would be. 120.54(2) is the statute. There is an accompanying rule of administrative procedure. No application was submitted.

THE COURT: Apparently, Mr. Brackett said when he was the 30(b)(6) designee that there wasn't any -- there wouldn't be an exception if the care was experimental.

Was he right about that, or is that one more thing that Mr. Brackett said that wasn't really in his area?

MR. JAZIL: No, Your Honor, he wasn't right about that, and the errata sheet goes to that issue. That clears that up.

Thank you, Your Honor.

THE COURT: All right. Very good.

I don't know if I mentioned this to you at the beginning -- I don't think I did. We talked some about telling the appellate court that there is another case -- both cases. My tentative plan, at least, is to rule on both cases at roughly the same time. The other decision impacts this decision, I

think. We can go back and work through all this standing and mootness and all those issues. It's the same kind of thing, so I'm probably going to rule on both close in time. I'm going to do it as soon as I can. It's not my only case. I've got a lot of work to do. So I'll -- I did go back and revisit some of the facts, and I note that it's -- well, it's the other case, I guess. But I know time is of the essence, so I'll get a ruling as quickly as I can.

MR. GONZALEZ-PAGAN: Your Honor, if I may, my co-counsel just informed me that the deposition designation regarding Mr. Brackett postdates his errata sheet to which my friend made. There were two depositions of Mr. Brackett.

THE COURT: Mr. Brackett is sometimes wrong but never in doubt. He's not a lawyer. He's been involved in rulemaking. If you wanted to know how to handle a matter under Chapter 120, you might ask any of these people sitting around here with their law degrees, but you probably would not ask Mr. Brackett.

MR. GONZALEZ-PAGAN: Yes, Your Honor.

THE COURT: So whatever he said about that, that's not the answer.

I don't mean to suggest that that makes a difference in the ruling. It made more difference when the rule was there. I don't think it matters under the statute. Mr. Jazil and I talked about that a little bit in his presentation. I'll take all that into account, and I'll try to get it right. I too am

sometimes wrong, but, frankly, I'm more often in doubt. The -- well, enough said.

We're adjourned.

Thank you, all.

MR. GONZALEZ-PAGAN: Thank you.

MR. JAZIL: Thank you.

(Proceedings concluded at 12:40 PM on Monday, May 22, 2023.)

* * * * * * * *

I certify that the foregoing is a correct transcript from the record of proceedings in the above-entitled matter. Any redaction of personal data identifiers pursuant to the Judicial Conference Policy on Privacy is noted within the transcript.

/s/ Megan A. Hague 5/22/2023

Megan A. Hague, RPR, FCRR, CSR Date
Official U.S. Court Reporter

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March 2, 2022

On October 1, 2022, the District Court for the Northern District of Texas issued a judgment vacating the March 2, 2022 document. HHS is evaluating its next steps in light of that judgment but is complying with it.

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

Office for Civil Rights

HHS Notice and Guidance on Gender Affirming Care, Civil Rights, and Patient Privacy

The Department of Health & Human Services (HHS) stands with transgender and gender nonconforming youth and their families—and the significant majority of expert medical associations—in unequivocally stating that gender affirming care for minors, when medically appropriate and necessary, improves their physical and mental health. Attempts to restrict, challenge, or falsely characterize this potentially lifesaving care as abuse is dangerous. Such attempts block parents from making critical health care decisions for their children, create a chilling effect on health care providers who are necessary to provide care for these youth, and ultimately negatively impact the health and well-being of transgender and gender nonconforming youth. The HHS Office for Civil Rights (OCR) will continue working to ensure that transgender and gender nonconforming youth are able to access health care free from the burden of discrimination. HHS understands that many families and health care providers are facing fear and concerns about attempts to portray gender affirming care as abuse. To help these families and providers navigate those concerns, HHS is providing additional information on federal civil rights protections and federal health privacy laws that apply to gender affirming care.

As a law enforcement agency, OCR is investigating and, where appropriate, enforcing Section 1557 of the Affordable Care Act[1] cases involving discrimination on the basis of sexual orientation and gender identity in accordance with all applicable law. This means that if people believe they have been discriminated against in a health program or activity that receives financial assistance from HHS, they can file a complaint.

Federal Civil Rights Laws:

Parents or caregivers who believe their child has been denied health care, including gender affirming care, on the basis of that child's gender identity, may file a complaint with OCR.

Health care providers who believe that they are or have been unlawfully restricted from providing health care to a patient on the basis of that patient's gender identity may file a complaint with OCR.

OCR enforces federal civil rights laws that prohibit discriminatory restrictions on access to health care. Among these laws is Section 1557, which prohibits discrimination on the basis of race, color, national origin, sex, age, and disability in covered health programs or activities. OCR

[1] 42 U.S.C. 18116; *see also* 45 C.F.R. part 92.

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also enforces Section 504 of the Rehabilitation Act,[2] which prohibits discrimination on the basis of disability in any program or activity receiving federal financial assistance.

Section 1557 protects the right of individuals to access the health programs and activities of recipients of federal financial assistance without facing discrimination on the basis of sex, which includes discrimination on the basis of gender identity. Categorically refusing to provide treatment to an individual based on their gender identity is prohibited discrimination. Similarly, federally-funded covered entities restricting an individual's ability to receive medically necessary care, including gender-affirming care, from their health care provider solely on the basis of their sex assigned at birth or gender identity likely violates Section 1557. For example, if a parent and their child visit a doctor for a consultation regarding or to receive gender affirming care, and the doctor or other staff at the facility reports the parent to state authorities for seeking such care, that reporting may constitute violation of Section 1557 if the doctor or facility receives federal financial assistance. Restricting a health care provider's ability to provide or prescribe such care may also violate Section 1557.

Section 504 protects qualified individuals with disabilities from discrimination in programs and activities receiving federal financial assistance. Title II of the Americans with Disabilities Act[3] (ADA) protects qualified individuals with disabilities from discrimination in state and local government programs. Gender dysphoria may, in some cases, qualify as a disability under these laws. Restrictions that prevent otherwise qualified individuals from receiving medically necessary care on the basis of their gender dysphoria, gender dysphoria diagnosis, or perception of gender dysphoria may, therefore, also violate Section 504 and Title II of the ADA.

If you believe that you or another party has been discriminated against on the basis of gender identity or disability in seeking to access gender affirming health care, visit the OCR complaint portal to file a complaint online. To read more about Section 1557 and other laws that OCR enforces, please visit our website at https:www.hhs.gov/ocr.

Federal Health Care Privacy Laws - Health Insurance Portability and Accountability Act of 1996 (HIPAA):

HIPAA, the cornerstone patient privacy law, limits the circumstances under which health care providers and other entities may disclose protected health information, such as gender affirming physical or mental health care administered by a licensed provider.

Providers who may be concerned about their obligations to disclose information concerning gender affirming care should seek additional legal guidance regarding their legal responsibilities and other laws.

[2] 29 U.S.C. 794; *see also* 45 C.F.R. part 84.
[3] 42 U.S.C. 12132.

OCR enforces the HIPAA Privacy, Security and Breach Notification Rules,[4] which establish requirements with respect to the use, disclosure, and protection of protected health information (PHI) by covered entities and business associates;[5] provide health information privacy and security protections; and establish rights for individuals with respect to their PHI.[6]

OCR reminds covered entities (health plans, health care providers, health care clearinghouses) and business associates that the HIPAA Privacy Rule permits, **but does not require,** covered entities and business associates to disclose PHI about an individual, without the individual's authorization,[7] when such disclosure is required by another law and the disclosure complies with the requirements of the other law.[8] This "required by law" exception to the authorization requirement is limited to "a mandate contained in law that compels an entity to make a use or disclosure of PHI and that is enforceable in a court of law."[9] Where a disclosure is required by law, the disclosure is limited to the relevant requirements of such law.[10] Disclosures of PHI that do not meet the "required by law definition" or exceed what is required by such law do not qualify as permissible disclosures under this exception.

HIPAA prohibits disclosure of gender affirming care that is PHI without an individuals' consent[11] except in limited circumstances.

If you believe that your (or someone else's) health privacy rights have been violated, visit the OCR complaint portal to file a complaint online.

DISCLAIMER: The contents of this document do not have the force and effect of law and are not meant to bind the public in any way. This document is intended only to provide clarity to the public regarding existing requirements under the law or the Departments' policies.

To obtain this information in an alternate format, contact the HHS Office for Civil Rights at (800) 368-1019, TDD toll-free: (800) 537-7697, or by emailing OCRMail@hhs.gov. Language assistance services for OCR matters are available and provided free of charge.

[4] 45 C.F.R. Parts 160 and 164, Subparts A, C, D, and E.
[5] *See* 45 C.F.R. 160.103 ("covered entity" and 'business associate" definitions).
[6] *See* 45 C.F.R. 160.103 ("protected health information" and "individually identifiable health information" definitions).
[7] *See* 45 C.F.R. 164.508(c) (HIPAA authorization required elements).
[8] 45 C.F.R. 164.512(a)(1).
[9] 45 C.F.R. 164.103 ("required by law" definition). Required by law includes, but is not limited to, court orders and court-ordered warrants; subpoenas or summons issued by a court, grand jury, a governmental or tribal inspector general, or an administrative body authorized to require the production of information; a civil or an authorized investigative demand; Medicare conditions of participation with respect to health care providers participating in the program; and statutes or regulations that require the production of information, including statutes or regulations that require such information if payment is sought under a government program providing public benefits.
[10] 45 C.F.R. 164.512(a)(1).
[11] For purposes of this guidance, "consent" refers to a valid HIPAA authorization. *See 45 C.F.R. 164.508.*

Doc. 193-2

OASH | Office of Population Affairs

Gender-Affirming Care and Young People

What is gender-affirming care?

Gender-affirming care is a supportive form of healthcare. It consists of an array of services that may include medical, surgical, mental health, and non-medical services for transgender and nonbinary people.

For transgender and nonbinary children and adolescents, early gender-affirming care is crucial to overall health and well-being as it allows the child or adolescent to focus on social transitions and can increase their confidence while navigating the healthcare system.

Why does it matter?

Research demonstrates that gender-affirming care improves the mental health and overall well-being of gender diverse children and adolescents.[1] Because gender-affirming care encompasses many facets of healthcare needs and support, it has been shown to increase positive outcomes for transgender and nonbinary children and adolescents. Gender-affirming care is patient-centered and treats individuals holistically, aligning their outward, physical traits with their gender identity.

Gender diverse adolescents, in particular, face significant health disparities compared to their cisgender peers. Transgender and gender nonbinary adolescents are at increased risk for mental health issues, substance use, and suicide.[2],[3] The Trevor Project's 2021 *National Survey on LGBTQ Youth Mental Health* found that 52 percent of LGBTQ youth seriously considered attempting suicide in the past year.[4]

A safe and affirming healthcare environment is critical in fostering better outcomes for transgender, nonbinary, and other gender expansive children and adolescents. Medical and psychosocial gender affirming healthcare practices have been demonstrated to yield lower rates of adverse mental health outcomes, build self-esteem, and improve overall quality of life for transgender and gender diverse youth.[5,6] Familial and peer support is also crucial in fostering similarly positive outcomes for these populations. Presence of affirming support networks is critical for facilitating and arranging gender affirming care for children and adolescents. Lack of such support can result in rejection, depression and suicide, homelessness, and other negative outcomes.[7,8,9]

Common Terms:
(in alphabetical order)

Cisgender: Describes a person whose gender identity aligns with their sex assigned at birth.

Gender diverse or expansive: An umbrella term for a person with a gender identity and/or expression broader than the male or female binary. Gender minority is also used interchangeably with this term.

Gender dysphoria: Clinically significant distress that a person may feel when sex or gender assigned at birth is not the same as their identity.

Gender identity: One's internal sense of self as man, woman, both or neither.

Nonbinary: Describes a person who does not identify with the man or woman gender binary.

Transgender: Describes a person whose gender identity and or expression is different from their sex assigned at birth, and societal and cultural expectations around sex.

Additional Information

- Endocrine Treatment of Gender-Dysphoric/Gender-Incongruent Persons: An Endocrine Society Clinical Practice Guideline
- Ensuring Comprehensive Care and Support for Transgender and Gender-Diverse Children and Adolescents | American Academy of Pediatrics
- Standards of Care (SOC) for the Health of Transsexual, Transgender, and Gender Nonconforming People | World Professional Association for Transgender Health

HHS Office of Population Affairs
Web: opa.hhs.gov | Email: opa@hhs.gov
Twitter: @HHSPopAffairs | YouTube: HHSOfficeofPopulationAffairs

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Gender-Affirming Care and Young People

Affirming Care	What is it?	When is it used?	Reversible or not
Social Affirmation	Adopting gender-affirming hairstyles, clothing, name, gender pronouns, and restrooms and other facilities	At any age or stage	Reversible
Puberty Blockers	Using certain types of hormones to pause pubertal development	During puberty	Reversible
Hormone Therapy	Testosterone hormones for those who were assigned female at birth Estrogen hormones for those who were assigned male at birth	Early adolescence onward	Partially reversible
Gender-Affirming Surgeries	"Top" surgery – to create male-typical chest shape or enhance breasts "Bottom" surgery – surgery on genitals or reproductive organs Facial feminization or other procedures	Typically used in adulthood or case-by-case in adolescence	Not reversible

Resources

- Discrimination on the Basis of Sex | HHS Office of Civil Rights
- Lesbian, Gay, Bisexual, and Transgender Health | Healthy People 2030
- Lesbian, Gay, Bisexual, and Transgender Health: Health Services | Centers for Disease Control and Prevention
- National Institutes of Health Sexual & Gender Minority Research Office
- Family Support: Resources for Families of Transgender & Gender Diverse Children | Movement Advancement Project
- Five Things to Know About Gender-Affirming Health Care | ACLU
- Gender-Affirming Care is Trauma-Informed Care | The National Child Traumatic Stress Network
- Gender-Affirming Care Saves Lives | Columbia University
- Gender Identity | The Trevor Project
- Genderspectrum.org
- Glossary of Terms | Human Rights Campaign
- Health Care for Transgender and Gender Diverse Individuals | ACOG
- Transgender and Gender Diverse Children and Adolescents | Endocrine Society

[1] Green, A. E., DeChants, J. P., Price, M. N., & Davis, C. K. (2021). Association of Gender-Affirming Hormone Therapy With Depression, Thoughts of Suicide, and Attempted Suicide Among Transgender and Nonbinary Youth. *Journal of Adolescent Health*, 70(4). https://doi.org/https://doi.org/10.1016/j.jadohealth.2021.10.036

[2] Rimes, K., Goodship N., Ussher, G., Baker, D. and West, E. (2019). Non-binary and binary transgender youth: Comparison of mental health, self-harm, suicidality, substance use and victimization experiences. *International Journal of Transgenderism*, 20 (2-3); 230-240.

[3] Price-Feeney, M., Green, A. E., & Dorison, S. (2020). Understanding the mental health of transgender and nonbinary youth. *Journal of Adolescent Health, 66*(6), 684–690. https://doi.org/10.1016/j.jadohealth.2019.11.314

[4] Trevor Project. (2021). *National Survey on LGBTQ Youth Mental Health 2021*. Trevor Project. https://www.thetrevorproject.org/survey-2021/.

[5] Wagner J, Sackett-Taylor AC, Hodax JK, Forcier M, Rafferty J. (2019). Psychosocial Overview of Gender-Affirmative Care. *Journal of pediatric and adolescent gynecology,* (6):567-573. doi: 10.1016/j.jpag.2019.05.004. Epub 2019 May 17. PMID: 31103711.

[6] Hughto JMW, Gunn HA, Rood BA, Pantalone DW. (2020). Social and Medical Gender Affirmation Experiences Are Inversely Associated with Mental Health Problems in a U.S. Non-Probability Sample of Transgender Adults. *Archives of sexual behavior*, 49(7):2635-2647. doi: 10.1007/s10508-020-01655-5. Epub 2020 Mar 25. PMID: 32215775; PMCID: PMC7494544.

[7] Brown, C., Porta, C. M., Eisenberg, M. E., McMorris, B. J., & Sieving, R. E. (2020). Family relationships and the health and well-being of transgender and gender-diverse youth: A critical review. *LGBT Health*, *7*, 407-419. https://doi.org/10.1089/lgbt.2019.0200

[8] Seibel BL, de Brito Silva B, Fontanari AMV, Catelan RF, Bercht AM, Stucky JL, DeSousa DA, Cerqueira-Santos E, Nardi HC, Koller SH, Costa AB. (2018). The Impact of the Parental Support on Risk Factors in the Process of Gender Affirmation of Transgender and Gender Diverse People. *Front Psychol*, 27;9:399. doi: 10.3389/fpsyg.2018.00399. Erratum in: Front Psychol. 2018 Oct 12;9:1969. PMID: 29651262; PMCID: PMC5885980.

[9] Sievert ED, Schweizer K, Barkmann C, Fahrenkrug S, Becker-Hebly I. (2021). Not social transition status, but peer relations and family functioning predict psychological functioning in a German clinical sample of children with Gender Dysphoria. *Clin Child Psychol Psychiatry*, 26(1):79-95. doi: 10.1177/1359104520964530. Epub 2020 Oct 20. PMID: 33081539.

Doc. 193-3

U.S. Department of Justice
Civil Rights Division

Assistant Attorney General
950 Pennsylvania Ave, NW - RFK
Washington, DC 20530

March 31, 2022

Dear State Attorneys General:

The U.S. Department of Justice (the Department) is committed to ensuring that transgender youth, like all youth, are treated fairly and with dignity in accordance with federal law. This includes ensuring that such youth are not subjected to unlawful discrimination based on their gender identity, including when seeking gender-affirming care. We write to remind you of several important federal constitutional and statutory obligations that flow from these fundamental principles.

People who are transgender are frequently vulnerable to discrimination in many aspects of their lives, and are often victims of targeted threats, legal restrictions, and anti-transgender violence.[1] The Department and the federal government more generally have a strong interest in protecting the constitutional rights of individuals who are lesbian, gay, bisexual, transgender, queer, intersex, nonbinary, or otherwise gender-nonconforming,[2] and in ensuring compliance with federal civil rights statutes. The Department is also charged with the coordination and enforcement of federal laws that protect individuals from discrimination in a wide range of federally-funded programs and activities.[3]

Intentionally erecting discriminatory barriers to prevent individuals from receiving gender-affirming care implicates a number of federal legal guarantees. State laws and policies that prevent parents or guardians from following the advice of a healthcare professional regarding what may be medically necessary or otherwise appropriate care for transgender minors may infringe on rights protected by both the Equal Protection and the Due Process Clauses of the Fourteenth Amendment. The Equal Protection Clause requires heightened scrutiny of laws that discriminate on the basis of sex[4] and prohibits such discrimination absent an "exceedingly

[1] *See, e.g.*, Michelle M. Johns et al., Ctrs. for Disease Control and Prevention, *Transgender Identity and Experiences of Violence Victimization, Substance Use, Suicide Risk, and Sexual Risk Behaviors Among High School Students—19 States and Large Urban School Districts, 2017*, Morbidity and Mortality Weekly Report 68: 67-71 (2019), https://www.cdc.gov/mmwr/volumes/68/wr/mm6803a3.htm?s_cid=mm6803a3_w (finding that transgender youth reported higher levels of violence victimization compared to their cisgender peers).
[2] *See, e.g.*, Exec. Order No. 13,988, § 1, 86 Fed. Reg. 7023 (Jan. 20, 2021); Pamela S. Karlan, Principal Deputy Assistant Attorney General, Civ. Rts. Div., U.S. Dep't of Justice, Memorandum, *Application of Bostock v. Clayton County to Title IX of the Education Amendments of 1972* (Mar. 26, 2021), https://www.justice.gov/crt/page/file/1383026/download.
[3] Exec. Order No. 12,250, § 1-201, 45 Fed. Reg. 72,995 (Nov. 2, 1980).
[4] *See*, *e.g.*, *Grimm v. Gloucester Cnty. Sch. Bd.*, 972 F.3d 586, 610-13 (4th Cir. 2020), *as amended* (Aug. 28, 2020), *reh'g en banc denied*, 976 F.3d 399 (4th Cir. 2020), *cert. denied*, 2021 WL 2637992 (June 28, 2021); *Whitaker* v.

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persuasive" justification.[5] Because a government cannot discriminate against a person for being transgender "without discriminating against that individual based on sex,"[6] state laws or policies that discriminate against transgender people must be "substantially related to a sufficiently important governmental interest."[7]

A law or policy need not specifically single out persons who are transgender to be subject to heightened scrutiny. When a state or recipient of federal funds criminalizes or even restricts a type of medical care predominantly sought by transgender persons, an intent to disfavor that class can "readily be presumed."[8] For instance, a ban on gender-affirming procedures, therapy, or medication may be a form of discrimination against transgender persons, which is impermissible unless it is "substantially related" to a sufficiently important governmental interest.[9] This burden of justification is "demanding."[10] Such a law or policy will not withstand heightened scrutiny when "the alleged objective" differs from the "actual purpose" underlying the classification.[11] In addition, the Due Process Clause protects the right of parents "to seek and follow medical advice" to safeguard the health of their children.[12] A state or local government must meet the heavy burden of justifying interference with that right since it is well established within the medical community that gender-affirming care for transgender youth is not only appropriate but often necessary for their physical and mental health.[13]

In addition to these constitutional guarantees, many federal statutes require recipients of federal financial assistance to comply with nondiscrimination requirements as a condition of receiving those funds. Relevant statutes include:

- **Section 1557 of the Affordable Care Act**[14] protects the civil rights of people—including transgender youth—seeking nondiscriminatory access to healthcare in a range of health

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Kenosha Unified Sch. Dist. No. 1 Bd. of Educ., 858 F.3d 1034, 1051 (7th Cir. 2017), *cert. dismissed*, 138 S. Ct. 1260 (2018); *see also* Brief for the United States as Amicus Curiae Supporting Plaintiffs-Appellees, *Brandt v. Rutledge*, No. 21-2875 (8th Cir. Jan. 21, 2022); En Banc Brief for the United States as Amicus Curiae Supporting Plaintiff-Appellee, *Adams v. School Board of St. John's County*, No. 18-13592 (11th Cir. Nov. 26, 2021); Brief for the United States as Amicus Curiae Supporting Plaintiffs-Appellees, *Corbitt v. Taylor*, No. 21-10486 (11th Cir. Aug. 2, 2021).

[5] *United States v. Virginia*, 518 U.S. 515, 531 (1996) ("Parties who seek to defend gender-based government action must demonstrate an 'exceedingly persuasive justification' for that action.") (quoting *Mississippi Univ. for Women v. Hogan*, 458 U.S. 718, 724 (1982)).

[6] *Bostock v. Clayton Cnty.*, 140 S. Ct. 1731, 1741 (2020).

[7] *Grimm*, 972 F.3d at 608 (quoting *City of Cleburne v. Cleburne Living Ctr.*, 473 U.S. 432, 441 (1985) (internal quotations omitted)).

[8] *Bray v. Alexandria Women's Health Clinic*, 506 U.S. 263, 270 (1993) ("Some activities may be such an irrational object of disfavor that, if they are targeted, and if they also happen to be engaged in exclusively or predominantly by a particular class of people, an intent to disfavor that class can readily be presumed.").

[9] *Virginia*, 518 U.S. at 533.

[10] *Id.*

[11] *Miss. Univ.*, 458 U.S. at 730.

[12] *Parham v. J.R.*, 442 U.S. 584, 602 (1979).

[13] *See, e.g.*, *Brandt v. Rutledge*, 551 F. Supp. 3d 882, 891, 893 (E.D. Ark. 2021).

[14] 42 U.S.C. § 18116.

programs and activities.[15] Categorically refusing to provide treatment to a person based on their gender identity, for example, may constitute prohibited discrimination under Section 1557. As the U.S. Department of Health and Human Services has stated, restricting an individual's ability to receive medically necessary care, including gender-affirming care, from their health care providers solely on the basis of their sex assigned at birth or their gender identity may also violate Section 1557.[16]

- **Title IX of the Education Amendments of 1972**[17] prohibits sex discrimination, including sex-based harassment, by recipients of federal financial assistance that operate education programs and activities.[18] Policies and practices that deny, limit, or interfere with access to the recipient's education program or activity because students are transgender minors receiving gender-affirming care may constitute discrimination on the basis of sex in violation of Title IX.

- The **Omnibus Crime Control and Safe Streets Act of 1968**[19] prohibits sex discrimination in certain law enforcement programs and activities receiving federal financial assistance.[20] If a law enforcement agency takes a transgender minor who is receiving gender-affirming care into custody or arrests the child's parents on suspicion of child abuse because the parents permitted such medical care, that agency may be violating the statute's nondiscrimination provision.

- **Section 504 of the Rehabilitation Act of 1973**[21] protects people with disabilities, which can include individuals who experience gender dysphoria.[22] Restrictions that prevent, limit, or interfere with otherwise qualified individuals' access to care due to their gender

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[15] *See, e.g.*, Notification of Interpretation and Enforcement of Section 1557 of the Affordable Care Act and Title IX of the Education Amendments of 1972, reprinted at 86 Fed. Reg. 27,984 (May 25, 2021).
[16] U.S. Dep't Health & Hum. Servs., *Notice and Guidance on Gender Affirming Care, Civil Rights, and Patient Privacy* (Mar. 2, 2022), https://www.hhs.gov/sites/default/files/hhs-ocr-notice-and-guidance-gender-affirming-care.pdf.
[17] 20 U.S.C. § 1681, *et seq*.
[18] *See* Karlan, *supra* note 2; *see also Doe v. Snyder*, --- F.4th ---, 2022 WL 711420, at *9 (9th Cir. Mar. 10, 2022); *Grimm*, 972 F.3d at 619.
[19] 34 U.S.C. § 10101, *et seq*.
[20] *See* 34 U.S.C. § 10228(c)(1); *see also* Kristen Clarke, Assistant Attorney General, Civ. Rts. Div., U.S. Dep't of Justice, Memorandum, *Interpretation of Bostock v. Clayton County regarding the nondiscrimination provisions of the Safe Streets Act, the Juvenile Justice and Delinquency Prevention Act, the Victims of Crime Act, and the Violence Against Women Act* (Mar. 10, 2022), https://www.justice.gov/crt/page/file/1481776/download.
[21] 29 U.S.C. § 794. Additionally, Title II of the Americans with Disabilities Act extends disability civil rights protections with respect to all programs, services and activities of state and local governments, regardless of the receipt of federal financial assistance. *See* 42 U.S.C. § 12132.
[22] *See, e.g.*, *Doe v. Penn. Dep't of Corrections*, No. 1:20-cv-00023-SPB-RAL, 2021 WL 1583556, at *12 (W.D. Pa. Feb. 19, 2021), report and recommendation adopted in relevant part, 2021 WL 1115373 (W.D. Pa. March 24, 2021); *Lange v. Houston Cnty.*, 499 F. Supp. 3d 1258, 1270 (M.D. Ga. 2020); *Doe v. Mass. Dep't of Correction*, No. 1:17-cv-12255-RGS, 2018 WL 2994403 at *6 (D. Mass. June 14, 2018); *Blatt v. Cabela's Retail, Inc.*, No. 5:14-CV-04822, 2017 WL 2178123 (E.D. Pa. May 18, 2017).

dysphoria, gender dysphoria diagnosis, or perception of gender dysphoria may violate Section 504.

All persons should be free to access the services, programs, and activities supported by federal financial assistance without fear that they might face unlawful discrimination for doing so. Courts have held that many nondiscrimination statutes contain an implied cause of action for retaliation based on the general prohibition against intentional discrimination, and agencies have made this clear in regulations.[23] Thus, any retaliatory conduct may give rise to an independent legal claim under the protections described above.

* * *

Thank you for your continued commitment to improving the well-being of children and their families. The Department is always available to help ensure that state and local governments, many of which are recipients of federal financial assistance, meet their obligations under federal law. Please feel free to contact the Department's Civil Rights Division for assistance if you have further questions.

Sincerely,

Kristen Clarke
Assistant Attorney General
Civil Rights Division
U.S. Department of Justice

[23] *See, e.g.*, *Jackson v. Birmingham Bd. of Ed.*, 544 U.S. 167, 173 (2005) ("Retaliation against a person because that person has complained of sex discrimination is another form of intentional sex discrimination…"). Examples of agency regulations that prohibit retaliation include 24 C.F.R. § 1.7(e) (Dep't of Housing and Urban Development); 34 C.F.R. § 100.7(e) (Dep't of Education); 38 C.F.R. § 18.7(e) (Dep't of Veterans Affairs); and 45 C.F.R. § 80.7(e) (Dep't of Health and Human Services). Other relevant regulations can be found in the Civil Rights Division's Title VI Legal Manual. Civ. Rts. Div., U.S. Dep't of Justice, *Title VI Legal Manual*, Section VIII, https://www.justice.gov/crt/book/file/1364106/download.

Doc. 193-8

Socialstyrelsen
THE NATIONAL BOARD OF HEALTH AND WELFARE

Care of children and adolescents with gender dysphoria

Summary of national guidelines
December 2022

DX
8

Summary

The National Board of Health and Welfare has been commissioned by the Swedish government to update the national guidelines entitled Good care of children and adolescents with gender dysphoria, published in 2015 [1]. The parts of the guidelines have been updated and published in stages. This is a summary of the final report published in December 2022, which contains the updated guidelines in its entirety, and thus replaces both previous interim reports and the guidelines from 2015.

For decision-makers

For several years, care for people with gender dysphoria has been characterised by accessibility problems and inadequate knowledge about the results of treatments. The National Board of Health and Welfare emphasises the importance of decision-makers in the health regions acting to promote improvement on both issues, and stresses that this needs to happen in the near future.

Young people suffering from gender dysphoria need to be promptly assessed and offered appropriate treatment measures, based on health care needs assessments. Good psychosocial care is essential. The patient group is heterogeneous and psychosocial care needs to clearly include young people with a non-binary gender identity. Gender-affirming treatments need to be offered when these are deemed indicated.

The 2015 guidelines stressed the importance of monitoring and evaluating the treatment interventions offered in the context of clinical work. The quality registry (gender dysphoria registry) that was planned at the time has so far not been able to meet existing needs. It is urgent that the health regions act to ensure that systematic documentation and monitoring of care at national level are realised. Longitudinal data are required to provide a coherent picture of this patient population, from referral to any diagnosis of gender dysphoria and with follow-ups of patients that are offered various treatment interventions.

The Swedish Agency for Health Technology Assessment and Assessment of Social Services (SBU) concludes that existing scientific evidence is insufficient for assessing the effects of puberty suppressing and gender-affirming hormone therapy on gender dysphoria, psychosocial health and quality of life of adolescents with gender dysphoria [2]. Knowledge gaps need to be addressed and the National Board of Health and Welfare recommends that these treatments be provided in the context of research. Here too, the health regions have a responsibility to provide support so that relevant research can begin in the near future. Research questions that need to be answered for the healthcare area are listed in the SBU's database of knowledge gaps. Priority needs to be given to studies that can answer the salient questions, as far as possible.

Caution in the use of hormonal and surgical treatment

At group level (i.e. for the group of adolescents with gender dysphoria, as a whole), the National Board of Health and Welfare currently assesses that the risks of puberty blockers and gender-affirming treatment are likely to outweigh the expected benefits of these treatments. The National Board of Health and Welfare therefore gives the following weak, negative recommendations as guidance to the healthcare system:

- Treatment with GnRH analogues, gender-affirming hormones, and mastectomy can be administered in exceptional cases.

Care must be provided on the basis of scientific evidence and proven experience and according to the principle of doing good and not harm. In revising its recommendations, the National Board of Health and Welfare has taken account of the fact that the efficacy and safety, benefits and risks of treatments are not proven [2] and that three factors have shifted the balance between benefit and risk in a negative direction:

- The uncertainty resulting from the lack of clarity about the causes, that the number of people diagnosed with gender dysphoria has continued to rise since the publication of the guidelines in 2015, particularly in the 13 to 17 age group and especially among people whose registered sex at birth is female.

- The documented prevalence among young adults of medical detransition, which is the process by which a person discontinues gender-affirming medical treatment for any reason or seeks to reverse the medical effects of completed gender-affirming treatment [3, 4]. According to the SBU, it is not possible to assess how common it is for young people to later change their perception of their gender identity or to discontinue a gender-affirming treatment [2].
- The experience-based knowledge of participating experts is less uniform than it was in 2015.

Decisions on treatment in an individual case

To guide the decision on puberty-suppressing treatment for an adolescent in Tanner Stage 3 and for gender-affirming hormone therapy, the National Board of Health and Welfare recommends the criteria whose use has been documented and monitored within the framework of the "Dutch protocol" [5-7]. The criteria include the existence of the incongruence since childhood, the stability of gender identity over time, clear distress caused by the onset of puberty, and the absence of factors that complicate the diagnostic assessment. According to the participating experts, puberty-suppressing treatment can in some cases be considered to be of great benefit even in Tanner stages 4 and 5, particularly for young people with a registered sex of male at birth whose masculinisation in later puberty makes it very difficult to pass as an adult.

The documented experience with the Dutch protocol includes only adolescents with binary gender identity, and among participating experts there is a lack of clinical experience with puberty-suppressing and gender-affirming hormone therapy for adolescents with non-binary gender identity. The National Board of Health and Welfare notes that there is a lack of knowledge to guide decisions on hormonal treatments for adolescents with non-binary gender identity, but still believes that gender dysphoria rather than gender identity should guide access to care and treatment. Urgent work that remains when updating the guidelines for adults with gender dysphoria [8] is to map the experience of assessment and gen-

der-affirming treatment for patients with non-binary gender identity in adult health care.

Other recommendations

Other recommendations include that health services should:

- Offer psychosocial support for unconditional exploration of gender identity during the diagnostic assessment. As in 2015, the National Board of Health and Welfare emphasises exploration as a prerequisite for good and safe care.
- Systematically search for signs of autism spectrum disorder (ASD) and ADHD/ADD before, or at an early stage of the assessment. In case of signs of ASD, neuropsychiatric assessment should be initiated.

The recommendations of the National Board of Health and Welfare remain as before, that the health care system should offer the following measures to adolescents with gender dysphoria:

- Sexology counselling and treatment
- Fertility preservation
- Voice and communication treatment
- Hair removal

The expected benefit to patients of the measures are considered high and the risks comparatively low. It is important that these measures are also documented for follow-up when they are offered, in order to enable increased and comprehensive knowledge regarding the patient group and care.

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Doc. 193-9

STM038:00/2020

Recommendation of the Council for Choices in Health Care in Finland (PALKO / COHERE Finland)

Medical Treatment Methods for Dysphoria Related to Gender Variance In Minors

Concepts

Suppression treatment	Pubertal suppression with GnRH analogues (drugs that inhibit gonadotropin-releasing hormone activity) to halt the development of secondary sex characteristics of the biological sex.
Cisgender/Cis person	A person whose gender identity matches the sex determined at birth (identifies, and is satisfied with, the sex determined at birth and generally expresses his/her gender accordingly).
Other gender identity	A person who does not identify as a man or a woman, but rather somewhere along the continuum or outside of it; genderless, nonbinary, or multigendered.
Transgender	A person whose gender identity differs from the legal and biological sex determined at birth but instead aligns with the opposite sex.

CERTIFICATE OF SERVICE

I certify that I e-filed this appendix on ECF, which will email everyone requiring notice.

Dated: October 13, 2023 /s/ Mohammad O. Jazil

No. 23-12155

UNITED STATES COURT OF APPEALS
FOR THE ELEVENTH CIRCUIT

August Dekker et al.,
Plaintiffs-Appellees,

v.

Secretary, Florida Agency for Health Care Administration et al.,
Defendants-Appellants.

U.S. District Court for the Northern District of Florida, No. 4:22-cv-325
(Hinkle, J.)

APPELLANTS' APPENDIX – VOLUME XIX OF XXI

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Dated: October 13, 2023

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1. Basis for Preparing These Recommendations

As the number of patients, including minors, referred to the Helsinki University Hospital (HUS) and the Tampere University Hospital (TAYS) multidisciplinary outpatient clinics for assessment and treatment of gender dysphoria has increased, PALKO (Council for Choices in Healthcare in Finland / COHERE Finland) decided to prepare recommendations for medical treatments of gender dysphoria, i.e., distress which is associated with a minor's gender variance and impairs function. Gender variance refers to a spectrum of gender experience anywhere on the male-female identity continuum or outside it, and is not exclusively confined to the dichotomized male/female conception of gender. Not all patients with gender variance experience significant suffering or functional impairments, and not all seek medical treatment.

These recommendations are based on the legislation in force at the time of the adoption of the recommendation, the available research evidence, and the clinical experience of multidisciplinary teams with expertise in gender dysphoria assessment and treatment at HUS and TAYS. The knowledge base supporting these recommendations is detailed in a separate Preparatory Memorandum and appendices and includes a description of planning and implementation of medical treatments, a literature review of medical treatments, an extensive ethical analysis, and feedback following meetings with patients and the advocacy groups who represent them.

Finnish legislation defines the requirements for the legal gender recognition of transsexuals (Act on Legal Recognition of the Gender of Transsexuals (Trans Act) 536/2002). The detailed requirements for providing the assessment and treatment to enable legal gender recognition are spelled out further in a Decree of the Ministry of Social Affairs and Health (1053/2002). The Trans Act and the related Decree apply to adults. For those who are not of legal age, there are no laws governing the provision and needs of transgender healthcare; however, these are subject to the Health Care Act of Finland (1326/2010), in particular section 7 (criteria for integrated care), section 7a (criteria for treatment options), section 8 (evidence-based, high quality, safe and appropriate care) and section 10 (rationale for centralization); and also to the Constitution of Finland (731/1999)'s section 6 on equality and section 19 on the right to adequate social and healthcare services. Finland's Act on the Status and Rights of Patients, (785/1992), and especially sections 5, 6, and 7, are also relevant.

2. Recommendations' Target Population

These recommendations apply to minors suffering from dysphoria related to gender variance who are seeking a consultation regarding an evaluation of medical examination and treatment needs; the children and adolescents may identify with the opposite sex (transgender), or may identify as genderless, non-binary, or anywhere along or outside the male/female gender identity continuum (other gender).

3. Procedures Assessed

These recommendations focus on medical treatment procedures that aim to decrease suffering and functional impairment of gender-dysphoric minors.

4. Current Care

Cross-sex identification in childhood, even in extreme cases, generally disappears during puberty. However, in some cases, it persists or even intensifies. Gender dysphoria may also emerge or intensify at the onset of puberty. There is considerable variation in the timing of the onset of puberty in both sexes. The first-line treatment for gender dysphoria is psychosocial support and, as necessary, psychotherapy and treatment of possible comorbid psychiatric disorders.

Consultation appointments (for parents / caregivers) regarding pre-pubescent children's cross-sex identification or gender dysphoria are provided by the research group on the gender identity of minors at TAYS or HUS. However, ongoing support or other treatment of psychiatric disorders are provided through the local municipal services.

In clear cases of pre-pubertal onset of gender dysphoria that intensified during puberty, a referral can be made for an assessment by the research group at TAYS or HUS regarding the appropriateness for puberty suppression. If no contraindications to early intervention are identified, pubertal suppression with GnRH analogues (to suppress the effect of gonadotropin-releasing hormone) may be considered to prevent further development of secondary sex characteristics of the biological sex.

Adolescents who have already undergone puberty, whose gender dysphoria occurs in the absence of co-occurring symptoms requiring psychiatric treatment, and whose experience of transgender identity failed to resolve following a period of reflection, can be referred for assessment by the research group on the gender identity of minors at TAYS or HUS. Hormone therapy (testosterone/estrogen and anti-androgen) can be started after the diagnostic evaluations, but no earlier than age 16. Additionally, patients under 18 receive three to six months of GnRH analogue treatment prior to the initiation of cross-sex hormones in order to suppress the hormonal activity of the gonads. No gender confirmation surgeries are performed on minors.

5. Risks, Benefits and Uncertainty

The literature review identified two studies with the total of 271 persons diagnosed with childhood-onset gender identity disorder and associated gender or body dysphoria that intensified after the onset of puberty (Preparatory Memorandum Appendix 1, Tables 15 and 16, pages 46-48).

In a smaller study of 70 adolescents, puberty was suppressed with the GnRH analogue at the average age of 14.8 (12-18 years) and puberty blockade continued for an average of 2 years. During the treatment period, the adolescents' mood improved, and the risk of behavioral disorders diminished, but gender dysphoria itself did not diminish, and there were no changes in body image. In a larger study consisting of 201 adolescents, 101 patients with the average age of 15.5 (12-18 years) started an 18-month psychological supportive intervention, and, additionally at six months, pubertal development was suppressed by starting GnRH analogue treatment. The other cohort of 100 only received psychological supportive intervention for 18 months. In both groups, statistically significant increases in global psychosocial functioning were found at 12 and 18 months; among those having received psychological intervention alone, the improvement in global functioning was already significant at the 6-month mark. Both studies lack long-term treatment follow-up into adulthood.

A recent Finnish study, published after the completion of this literature review, reported on the effect of initiating cross-sex hormone therapy on functioning, progression of developmental tasks of adolescence, and psychiatric symptoms. This study found that during cross-sex hormone therapy, problems in these areas did not decrease.

Potential risks of GnRH therapy include disruption in bone mineralization and the as yet unknown effects on the central nervous system. In trans girls, early pubertal suppression inhibits penile growth, requiring the use of alternative sources of tissue grafts for a potential future vaginoplasty. The effect of pubertal suppression and cross-sex hormones on fertility is not yet known.

6. Ethical Assessment

Although the ethics analysis did not systematically address the issues pertaining to children and adolescents, they have been discussed in several areas in the related documents (Preparatory Memorandum pages 52-62; Appendix 5).

According to the Health Care Act (section 8), healthcare services must be based on evidence and recognized treatment and operational practices. As far as minors are concerned, there are no medical treatment that can be considered evidence-based. At the same time, the numbers of minors developing gender dysphoria has increased. In this situation, it is vital to assure that children and young people are able to talk about their feelings, and that their feelings are acknowledged. The opportunity to reflect on one's experience should be easily accessible through the local health system (i.e., school or student health care, primary care). A young

person's feelings should not be interpreted as immediately requiring specialized medical examinations or treatments.

In cases of children and adolescents, ethical issues are concerned with the natural process of adolescent identity development, and the possibility that medical interventions may interfere with this process. It has been suggested that hormone therapy (e.g., pubertal suppression) alters the course of gender identity development; i.e., it may consolidate a gender identity that would have otherwise changed in some of the treated adolescents. The reliability of the existing studies with no control groups is highly uncertain, and because of this uncertainty, no decisions should be made that can permanently alter a still-maturing minor's mental and physical development.

From the point of view of patient advocacy groups, halting puberty is providing young people with a period of reflection, rather than consolidating their gender identity. This is based on the premise that halting the development of one's permanent sex characteristics will improve the minor's social interactions, while allowing more time for diagnostic evaluations. Additionally, patient advocacy groups assert that early intervention with hormonal treatments will lead to improved outcomes for the patients who do eventually pursue gender reassignment. Professionals, for their part, consider it important to ensure that irreversible interventions, which may also have significant adverse effects, both physical and mental, are only performed on individuals who are able to understand the permanence of the changes and the potential for harm, and who are unlikely to regret such interventions. It is not known how the hormonal suppression of puberty affects young people's judgement and decision-making.

The Act on the Status and Rights of Patients (1992/785) states that the patient shall be provided with information about his/her state of health, the significance of the treatment, various alternative forms of treatment and their effects, and about other factors concerning treatment that have an effect on treatment decision-making. In a situation where a minor's identification with the opposite sex causes long-term and severe dysphoria, it is important to make sure that he/she understands the realistic potential of gender reassignment treatments to alter secondary sex characteristics, the reality of a lifelong commitment to medical therapy, the permanence of the effects, and the possible physical and mental adverse effects of the treatments. Although patients may experience regret, after reassignment treatments, there is no going back to the non-reassigned body and its normal functions. Brain development continues until early adulthood – about age 25, which also affects young people's ability to assess the consequences of their decisions on their own future selves for rest of their lives.

A lack of recognition of comorbid psychiatric disorders common among gender-dysphoric adolescents can also be detrimental. Since reduction of psychiatric symptoms cannot be achieved with hormonal and surgical interventions, it is not a valid justification for gender reassignment. A young person's identity and personality development must be stable so that they can genuinely face and discuss their gender dysphoria, the significance of their own feelings, and the need for various treatment options.

For children and adolescents, these factors are key reasons for postponing any interventions until adulthood.

7. Conclusions

The first-line intervention for gender variance during childhood and adolescent years is psychosocial support and, as necessary, gender-explorative therapy and treatment for comorbid psychiatric disorders. Uncertainty related to gender identity should be dealt with according to the severity of symptoms and the need for treatment and should be handled at the school / student health care, primary health care at the local level, or in specialty care.

In adolescents, psychiatric disorders and developmental difficulties may predispose a young person to the onset of gender dysphoria. These young people should receive treatment for their mental and behavioral health issues, and their mental health must be stable prior to the determination of their gender identity.

Clinical experience reveals that autistic spectrum disorders (ASD) are overrepresented among adolescents suffering from gender dysphoria; even if such adolescents are presenting with gender dysphoria, rehabilitative interventions for ASD must be properly addressed.

In light of available evidence, gender reassignment of minors is an experimental practice. Based on studies examining gender identity in minors, hormonal interventions may be considered before reaching adulthood in those with firmly established transgender identities, but it must be done with a great deal of caution, and no irreversible treatment should be initiated. Information about the potential harms of hormone therapies is accumulating slowly and is not systematically reported. It is critical to obtain information on the benefits and risks of these treatments in rigorous research settings.

At a minimum, a consultation for a pre- pubescent child at the specialist setting at the TAYS includes an extensive assessment appointment costing EUR 369. If necessary, a day-long outpatient consultation can be arranged, costing EUR 1,408.

The consultation and assessment process for minors at the specialist settings of TAYS or HUS costs EUR 4,300. If it is determined that this process would be untimely, the minimum cost is EUR 640. An initial assessment / consultation by phone costs EUR 100.

The planning and monitoring costs for pubertal suppression are EUR 2,000 for the first year, and EUR 1,200 for subsequent years. The costs for the planning and monitoring of hormone treatments are a minimum of EUR 400 per year.

These costs do not take into account the additional costs of psychosocial support provided in the local level, the possible need for psychiatric treatment, or hormone treatment medication costs.

8. Summary of the Recommendations

PALKO / COHERE maintains the following:

1. For the treatment of gender dysphoria due to variations in gender identity in minors, psychosocial support should be provided in school and student healthcare and in primary healthcare, and there must be sufficient competency to provide such support.
2. Consultation with a child or youth psychiatrist and the necessary psychiatric treatment and psychotherapy should be arranged locally according to the level of treatment needed.
3. If a child or young person experiencing gender-related anxiety has other simultaneous psychiatric symptoms requiring specialised medical care, treatment according to the nature and severity of the disorder must be arranged within the services of their own region, as no conclusions can be drawn on the stability of gender identity during the period of disorder caused by a psychiatric illness with symptoms that hamper development.

PALKO / COHERE considers that the consultation, periods of assessment, and treatments by the research group on the gender identity of minors at TAYS or HUS must be carried out according to the following principles:

1. Children who have not started puberty and are experiencing persistent, severe anxiety related to gender conflict and/or identification as the other sex may be sent for a consultation visit to the research group on the gender identity of minors at TAYS or HUS. Any need for support beyond the consultation visit or need for other psychiatric treatment should be addressed by local services according to the nature and severity of the problem.

2. If a child is diagnosed prior to the onset of puberty with a persistent experience of identifying as the other sex and shows symptoms of gender-related anxiety, which increases in severity in puberty, the child can be guided at the onset of puberty to the research group on the gender identity of minors at TAYS or HUS for an assessment of the need for treatment to suppress puberty. Based on these assessments, puberty suppression treatment may be initiated on a case-by-case basis after careful consideration and appropriate diagnostic examinations if the medical indications for the treatment are present and there are no contraindications. Therapeutic amenorrhea, i.e. prevention of menstruation, is also medically possible.

3. A young person who has already undergone puberty can be sent to the research clinic on the gender identity of minors at TAYS or HUS for extensive gender identity studies if the variation in gender identity and related dysphoria do not reflect the temporary search for identity typical of the development stage of adolescence and do not subside once the young person has had the opportunity to reflect on their identity but rather their identity and personality development appear to be stable.

4. Based on thorough, case-by-case consideration, the initiation of hormonal interventions that alter sex characteristics may be considered before the person is 18 years of age only if it can be ascertained that their identity as the other sex is of a permanent nature and causes severe dysphoria. In addition, it must be confirmed that the young person is able to understand the significance of irreversible treatments and the

benefits and disadvantages associated with lifelong hormone therapy, and that no contraindications are present.

5. If a young person experiencing gender-related anxiety has experienced or is simultaneously experiencing psychiatric symptoms requiring specialized medical care, a gender identity assessment may be considered if the need for it continues after the other psychiatric symptoms have ceased and adolescent development is progressing normally. In this case, a young person can be sent by the specialized youth psychiatric care in their region for an extensive gender identity study by the TAYS or HUS research group on the gender identity of minors, which will begin the diagnostic studies. Based on the results of the studies, the need for and timeliness of medically justified treatments will be assessed individually.

Surgical treatments are not part of the treatment methods for dysphoria caused by gender-related conflicts in minors. The initiation and monitoring of hormonal treatments must be centralized at the research clinics on gender identity at HUS and TAYS.

9. Additional Evidence Gathering and Monitoring the Effectiveness of Recommendations

Moving forward, the following information must be obtained about the patients diagnosed and receiving treatments in Finland before re-evaluating these recommendations:

- Number of new patient referrals
- Number of patients starting the assessment period, and numbers of new transgender (F64.0) vs “other gender” (F64.8) diagnoses
- Whether the diagnosis remains stable or changes during the assessment phase
- Number of patients discontinuing the assessment period and the reasons for the discontinuation
- Adverse effects of treatments (especially long-term effects and effect on fertility)
- Number of patients regretting hormone therapy
- Analysis of the effects of the assessment and the treatment period on gender dysphoria outcomes, as measured by the Gender Congruence and Life Satisfaction Scale (GCLS)
- Analysis of the effects of the assessment and the treatment period on functional capacity and quality of life
- The prevalence of co-occurring psychiatric diagnoses (especially neurodevelopmental diagnoses F80-F90) among those diagnosed with / seeking treatment for gender dysphoria, and whether the presence of these co-occurring diagnoses impacts the ability to achieve the desired outcome (e.g. decreased dysphoria) in the assessment or the treatment phase.
- Whether the assessment and treatment periods lead to a reduction of suicide attempts
- Whether the assessment and treatment periods lead to a reduction in depression and distress

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10. Appendices

Preparatory Memorandum, with Appendices 1-5.

Doc. 193-10

The Cass Review

Independent review of gender identity services for children and young people: Interim report

February 2022

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About this report

This interim report represents the work of the independent review of gender identity services for children and young people to date. It reflects a point in time. It does not set out final recommendations; these will be developed over the coming months, informed by our formal research programme.

This Review is forward looking. Its role is to consider how to improve and develop the future clinical approach and service model. However, in order to do this, it is first necessary to understand the current landscape and the reasons why change is needed, so that any future model addresses existing challenges, whilst retaining those features that service users and the professionals supporting them most value.

This report is primarily for the commissioners and providers of services for children and young people needing support around their gender. However, because of the wide interest in this topic, we have included some explanations about how clinical service development routinely takes place in the NHS, which sets the context for some of our interim advice.

The care of this group of children and young people is everyone's business. We therefore encourage the wider clinical community to take note of our work and consider their own roles in providing the best holistic support to this population.

Since the Review began, it has focused on hearing a wide range of perspectives to better understand the challenges within the current system and aspirations for how these could be addressed. This report does not contain all that we have heard during our listening sessions but summarises consistent themes. These conversations will continue throughout the course of the Review and there will be further opportunities for stakeholders to engage and contribute.

It is important to note that the references cited in this report do not constitute a comprehensive literature review and are included only to clarify why specific lines of enquiry are being pursued, and where there are unanswered questions that will be addressed more fully during the life of the Review. A formal literature review is one strand of the Review's commissioned work, and this will be reported in full when complete.

A note about language

There is sometimes no consensus on the best language to use relating to this subject. The language surrounding this area has also changed rapidly and young people have developed varied ways of describing their experiences using different terms and constructs that are relevant to them.

The Review tries as far as possible to use language and terms that are respectful and acknowledge diversity, but that also accurately illustrate the complexity of what we are trying to describe and articulate.

The terms we have used may not always feel right to some; nevertheless, it is important to emphasise that the language used is not an indication of a position being taken by the Review. A glossary of terms is included.

The Review is cognisant of the broader cultural and societal debates relating to the rights of transgender adults. It is not the role of the Review to take any position on the beliefs that underpin these debates. Rather, this Review is strictly focused on the clinical services provided to children and young people who seek help from the NHS to resolve their gender-related distress.

A letter to children and young people

Children and young people accessing the NHS deserve safe, timely and supportive services, and clinical staff with the training and expertise to meet their healthcare needs.

Dr Hilary Cass

I understand that as you read this letter some of you may be anxious because you are waiting to access support from the NHS around your gender identity. Maybe you have tried to get help from your local services, or from the Gender Identity Development Service (GIDS), and because of the long waiting lists they have not yet been able to see you. I hope that some of you have had help – maybe from a supportive GP, a local Child and Adolescent Mental Health Service (CAMHS), or from GIDS.

I have heard that young service users are particularly worried that I will suggest that services should be reduced or stopped. I want to assure you that this is absolutely not the case – the reverse is true. I think that more services are needed for you, closer to where you live. The GIDS staff are working incredibly hard and doing their very best to see you as quickly as possible but providing supportive care is not something that can be rushed – each young person needs enough time and space for their personal needs to be met. So, with the best will in the world, one service is not going to be able to respond to the growing demand in a timely way.

I am advising that more services are made available to support you. But I must be honest; this is not something that can happen overnight, and I can't come up with a solution that will fix the problems immediately. However, we do need to start now.

The other topic that I know is worrying some of you is whether I will suggest that hormone treatments should be stopped. On this issue, I have to share my thoughts as a doctor. We know quite a bit about hormone treatments, but there is still a lot we don't know about the long-term effects.

Whenever doctors prescribe a treatment, they want to be as certain as possible that the benefits will outweigh any adverse effects so that when you are older you don't end up saying 'Why did no-one tell me that that might happen?' This includes understanding both the risks and benefits of having treatment and not having treatment.

Therefore, what we will be doing over the next few months is trying to make sense of all the information that is available, as well as seeing if we can plug any of the gaps in the research. I am currently emphasising the importance of making decisions about prescribing as safe as possible. This means making sure you have all the information you need – about what we do know and what we don't know.

Finally, some of you may want the chance to talk to me and share your thoughts about how services should look in the future. Over the coming months we will need your help and there will be opportunities to get involved with the Review, so please keep an eye on our website (www.cass.independent-review.uk), where we will provide updates on our work.

Dr Hilary Cass, OBE

Introduction from the Chair

Anyone with an interest in the care of gender-questioning children and young people, as well as those with lived experience, may have wondered what qualifies me to take on this Review, and whether I have a pre-existing position on this subject.

I am a paediatrician who was in clinical practice until 2018, my area of specialism being children and young people with disability. I have also held many management and policy roles throughout my career, most notably as President of the Royal College of Paediatrics and Child Health (RCPCH) from 2012-15.

Children's services are often at a disadvantage in healthcare because health services are usually designed around the needs of adults. As President of RCPCH, a key part of my role was to advocate for services to be planned with children and families at their heart.

I have not worked in gender services during my career, but my strong focus on hearing the voice of service users, supporting vulnerable young people, equity of access, and strong clinical standards applies in this area as much as in my other work.

With this in mind, the aim of the Review is to ensure that children and young people who are experiencing gender incongruence or gender-related distress receive a high standard of NHS care that meets their needs and is safe, holistic and effective.

I have previously set out the principles governing this Review process, namely that:

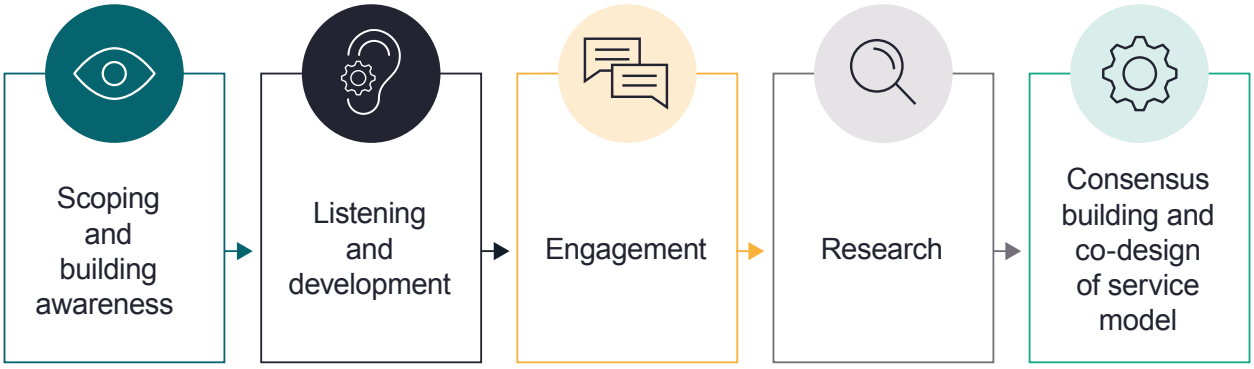
- The welfare of the child and young person will be paramount in all considerations.
- Children and young people must receive a high standard of care that meets their needs.
- There will be extensive and purposeful stakeholder engagement, including ensuring that children and young people can express their own views through a supportive process.
- The Review will be underpinned by research and evidence, including international models of good practice where available.
- There will be transparency in how the Review is conducted and how recommendations are made.
- There are no pre-determined outcomes with regards to the recommendations the Review will make.

The Review's terms of reference (**Appendix 1**) are wide ranging in scope, looking at different aspects of gender identity services across the whole pathway through primary, secondary and specialist services, up to the point of transition to adult services. This includes consideration of referral pathways, assessment, appropriate clinical management and workforce recommendations.

I have also been asked to explore the reasons for the considerable increase in the number of referrals, which have had a significant impact on waiting times, as well as the changing case-mix of gender-questioning children and young people presenting to clinical services.

The Review is taking an investigative approach to understanding what the future service model should look like for children and young people. This means that its outcomes are not being developed in isolation or by committee but rather through an ongoing dialogue aimed at building a shared understanding of the current situation and how it can and should be improved.

The key aspects of the approach to the Review are:



My starting point has been to hear from a variety of experts with relevant expertise and those with lived experience to understand as many perspectives as possible. To date, this has included hearing directly from those with lived experience, from professionals and support and advocacy groups. This listening process will continue.

We have been very fortunate in the generosity of all those who have been prepared to talk to the Review and share their experiences. In addition to some divergent opinions, there are also some themes and views which seem to be widely shared. The commitment of professionals at all levels is striking and I genuinely believe that with collective effort we can improve services for the children and young people who are at the heart of this Review.

These discussions have been valuable to get an in-depth sense of the current situation and different viewpoints on how it may be improved. However, it is essential that this initial understanding is underpinned by more detailed data and an enhanced evidence base, which is being delivered through the Review's academic research programme.

Providing this evidence base for the Review is going to take some time. I recognise there is a pressing need to enhance the services currently available for children, young people, their

parents and carers, some of whom are experiencing considerable distress. Clinicians providing their treatment and care are also under pressure and cannot sustain the current workload. As such, I know the time I am taking to complete this Review and make recommendations will be difficult for some, but it is necessary.

I wrote to NHS England in May 2021 (**Appendix 2**) setting out some more immediate considerations whilst awaiting my full recommendations. This report builds on that letter and looks to provide some further interim advice.

Through our research programme, the Review team will continue to examine the literature and, where possible, will fill gaps in the existing evidence base. However, there will be persisting evidence gaps and areas of uncertainty. We need the engagement of service users, support and advocacy groups, and professionals across the wider workforce to work with us in the coming months in a collaborative and open-minded manner in order to reach a shared understanding of the problems and an agreed way forward that is in the best interests of children and young people.

My measure of success for this Review will be that this group of children and young people receive timely, appropriate and excellent care, not just from specialists but from every healthcare professional they encounter as they take the difficult journey from childhood to adulthood.

1. Summary and interim advice

Summary

1.1. In recent years, there has been a significant increase in the number of referrals to the Gender Identity Development Service (GIDS) at the Tavistock and Portman NHS Foundation Trust. This has contributed to long waiting lists and growing concern about how the NHS should most appropriately assess, diagnose and care for this population of children and young people.

1.2. Within the UK, the single specialist service has developed organically, and the clinical approach has not been subjected to some of the usual control measures that are typically applied when new or innovative treatments are introduced. Many of the challenges and knowledge gaps that we face in the UK are echoed internationally,[1] and there are significant gaps in the research and evidence base.

1.3. This Review was commissioned by NHS England to make recommendations on how to improve services provided by the NHS to children and young people who are questioning their gender identity or experiencing gender incongruence and ensure that the best model for safe and effective services is commissioned (**Appendix 1**).

1.4. This interim report represents the Review's work to date. It sets out what we have heard so far and the approach we are taking moving forward. There is still much evidence to be gathered, questions to be answered, and voices to be heard, and our perspective will evolve as more evidence comes to light. However, there is sufficient clarity on several areas for the Review to be able to offer advice at this stage so that action can be taken more quickly.

1.5. The Review is not able to provide definitive advice on the use of puberty blockers and feminising/masculinising hormones at this stage, due to gaps in the evidence base; however, recommendations will be developed as our research programme progresses.

Every gender-questioning child or young person who seeks help from the NHS must receive the support they need to get on the appropriate pathway for them as an individual.

Children and young people with gender incongruence or dysphoria must receive the same standards of clinical care, assessment and treatment as every other child or young person accessing health services.

[1] Vrouenraets LJ, Fredriks AM, Hannema SE, Cohen-Kettenis PT, de Vries MC (2015). Early medical treatment of children and adolescents with gender dysphoria: an empirical ethical study. J Adolesc Health 57(4): 367-73. DOI: 10.1016/.2015.04.004.

Conceptual understanding and consensus about the meaning of gender dysphoria

1.6. In clinical practice, a diagnosis of gender dysphoria is currently based on an operational definition, using the criteria set out in DSM-5 (**Appendix 3**). Some of these criteria are seen by some as outdated in the context of current understanding about the flexibility of gender expression.

1.7. At primary, secondary and specialist level, there is a lack of agreement, and in many instances a lack of open discussion, about the extent to which gender incongruence in childhood and adolescence can be an inherent and immutable phenomenon for which transition is the best option for the individual, or a more fluid and temporal response to a range of developmental, social, and psychological factors. Professionals' experience and position on this spectrum may determine their clinical approach.

1.8. Children and young people can experience this as a 'clinician lottery', and failure to have an open discussion about this issue is impeding the development of clear guidelines about their care.

Service capacity and delivery

1.9. A rapid change in epidemiology and an increase in referrals means that the number of children seeking help from the NHS is now outstripping the capacity of the single national specialist service, the Gender Identity Development Service (GIDS) at The Tavistock and Portman NHS Foundation Trust.

1.10. The mix of young people presenting to the service is more complex than seen previously, with many being neurodiverse and/or having a wide range of psychosocial and mental health needs. The largest group currently comprises birth-registered females first presenting in adolescence with gender-related distress.

1.11. Until very recently, any local professional, including non-health professionals, could refer to GIDS, which has meant that the quality and appropriateness of referrals lacks consistency, and local service provision has remained patchy and scarce.

1.12. The staff working within the specialist service demonstrate a high level of commitment to the population they serve. However, the waiting list pressure and lack of consensus development on the clinical approach, combined with criticism of the service, have all resulted in rapid turnover of staff and inadequate capacity to deal with the increasing workload. Capacity constraints cannot be addressed through financial investment alone; there are some complex workforce (recruitment; retention; and training) and cultural issues to address.

1.13. Our initial work has indicated that many professionals working at primary and secondary level feel that they have the transferable skills and the commitment to offer more robust support to this group of children and young people, but are nervous about doing so, partly because of the lack of formal clinical guidance, and partly due to the broader societal context.

1.14. Primary and secondary care staff have told us that they feel under pressure to adopt an unquestioning affirmative approach and that this is at odds with the standard process of clinical assessment and diagnosis that they have been trained to undertake in all other clinical encounters.

1.15. Children and young people are waiting lengthy periods to access GIDS, during which time some may be at considerable risk. By the time they are seen, their distress may have worsened, and their mental health may have deteriorated.

1.16. Another significant issue raised with us is one of diagnostic overshadowing – many of the children and young people presenting have complex needs, but once they are identified as having gender-related distress, other important healthcare issues that would normally be managed by local services can sometimes be overlooked.

1.17. The current move to adult services at age 17-18 may fall at a critical time in the young person's gender management. In contrast, young people with neurodiversity often remain under children's services until age 19 and some other clinical services continue to mid-20s. Further consideration will be needed regarding the age of transfer to adult services.

Service standards

1.18. The Multi-Professional Review Group (MPRG), set up by NHS England to ensure that procedures for assessment and for informed consent have been properly followed, has stated that the following areas require consideration:

- From the point of entry to GIDS there appears to be predominantly an affirmative, non-exploratory approach, often driven by child and parent expectations and the extent of social transition that has developed due to the delay in service provision.
- From documentation provided to the MPRG, there does not appear to be a standardised approach to assessment or progression through the process, which leads to potential gaps in necessary evidence and a lack of clarity.
- There is limited evidence of mental health or neurodevelopmental assessments being routinely documented, or of a discipline of formal diagnostic or psychological formulation.
- Of 44 submissions received by the MPRG, 31% were not initially assured due to lack of safeguarding information. And in a number of cases there were specific safeguarding concerns. There do not appear to be consistent processes in place to work with other agencies to identify children and young people and families who may be vulnerable, at risk and require safeguarding.

- Appropriate clinical experts need to be involved in informing decision making.

1.19. Many of these issues were also highlighted by the Care Quality Commission (CQC) in 2020.[2]

International comparisons

1.20. The Netherlands was the first country to provide early endocrine interventions (now known internationally as the Dutch Approach). Although GIDS initially reported its approach to early endocrine intervention as being based on the Dutch Approach,[3] there are significant differences in the NHS approach. Within the Dutch Approach, children and young people with neurodiversity and/or complex mental health problems are routinely given therapeutic support in advance of, or when considered appropriate, instead of early hormone intervention. Whereas criteria to have accessed therapeutic support prior to starting hormone blocking treatment do not appear to be integral to the current NHS process.

1.21. NHS endocrinologists do not systematically attend the multi-disciplinary meetings where the complex cases that may be referred to them are discussed, and until very recently did not routinely have direct contact with the clinical staff member who had assessed the child or young person. This is not consistent with some international approaches for this group of children and young people, or in other multi-disciplinary models of care across paediatrics and adult medicine where challenging decisions about life-changing interventions are made.[4,5]

1.22. In the NHS, once young people are started on hormone treatment, the frequency of appointments drops off rather than intensifies, and review usually takes place quarterly. Again, this is different to the Dutch Approach.[6] GIDS staff would recommend more frequent contact during this period, but the fall-off in appointments reflects a lack of service capacity, with the aspiration being for more staff time to remedy this situation.

Existing evidence base

1.23. Evidence on the appropriate management of children and young people with gender incongruence and dysphoria is inconclusive both nationally and internationally.

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[2] Care Quality Commission (2021). The Tavistock and Portman NHS Foundation Trust Gender Identity Service Inspection Report. London: CQC.
[3] de Vries ALC, Cohen-Kettenis PT (2012). Clinical management of gender dysphoria in children and adolescents: the Dutch approach. J Homosex 59: 301–320. DOI: 10.1080/00918369.2012.653300.
[4] Ibid.
[5] Kyriakou A, Nicolaides NC, Skordis N (2020). Current approach to the clinical care of adolescents with gender dysphoria. Acta Biomed 91(1): 165–75. DOI: 10.23750/abm.v91i1.9244.
[6] de Vries ALC, Cohen-Kettenis PT (2012). Clinical management of gender dysphoria in children and adolescents: the Dutch approach. J Homosex 59: 301–320. DOI: 10.1080/00918369.2012.653300.

1.24. A lack of a conceptual agreement about the meaning of gender dysphoria hampers research, as well as NHS clinical service provision.

1.25. There has not been routine and consistent data collection within GIDS, which means it is not possible to accurately track the outcomes and pathways that children and young people take through the service.

1.26. Internationally as well as nationally, longer-term follow-up data on children and young people who have been seen by gender identity services is limited, including for those who have received physical interventions; who were transferred to adult services and/or accessed private services; or who desisted, experienced regret or detransitioned.

1.27. There has been research on the short-term mental health outcomes and physical side effects of puberty blockers for this cohort, but very limited research on the sexual, cognitive or broader developmental outcomes.[7]

1.28. Much of the existing literature about natural history and treatment outcomes for gender dysphoria in childhood is based on a case-mix of predominantly birth-registered males presenting in early childhood. There is much less data on the more recent case-mix of predominantly birth-registered females presenting in early teens, particularly in relation to treatment and outcomes.

1.29. Aspects of the literature are open to interpretation in multiple ways, and there is a risk that some authors interpret their data from a particular ideological and/or theoretical standpoint.

The mismatch between service user expectations and clinical standards

1.30. By the time children and young people reach GIDS, they have usually had to experience increasingly long, challenging waits to be seen.[8] Consequently, some feel they want rapid access to physical interventions and find having a detailed assessment distressing.

1.31. Clinical staff are governed by professional, legal and ethical guidance which demands that certain standards are met before a treatment can be provided. Clinicians carry responsibility for their assessment and recommendations, and any harm that might be caused to a patient under their care. This can create a tension between the aspirations of the young person and the responsibilities of the clinician.

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[7] National Institute for Health and Care Excellence (2020). Evidence Review: Gonadotrophin Releasing Hormone Analogues for Children and Adolescents with Gender Dysphoria.
[8] Care Quality Commission (2021). The Tavistock and Portman NHS Foundation Trust Gender Identity Service Inspection Report. London: CQC.

Interim advice

1.32. The Review considers that there are some areas where there is sufficient clarity about the way forward and we are therefore offering some specific observations and interim advice. The Review will work with NHS England, providers and the broader stakeholder community to progress action in these areas.

Service model

1.33. It has become increasingly clear that a single specialist provider model is not a safe or viable long-term option in view of concerns about lack of peer review and the ability to respond to the increasing demand.

1.34. Additionally, children and young people with gender-related distress have been inadvertently disadvantaged because local services have not felt adequately equipped to see them. It is essential that they can access the same level of psychological and social support as any other child or young person in distress, from their first encounter with the NHS and at every level within the service.

1.35. A fundamentally different service model is needed which is more in line with other paediatric provision, to provide timely and appropriate care for children and young people needing support around their gender identity. This must include support for any other clinical presentations that they may have.

1.36. The Review supports NHS England's plan to establish regional services, and welcomes the move from a single highly specialist service to regional hubs.

1.37. Expanding the number of providers will have the advantages of:

- creating networks within each area to improve early access and support;
- reducing waiting times for specialist care;
- building capacity and training opportunities within the workforce;
- developing a specialist network to ensure peer review and shared standards of care; and
- providing opportunities to establish a more formalised service improvement strategy.

Service provision

1.38. The primary remit of NHS England's proposed model is for the regional hubs to provide support and advice to referrers and professionals. However, it includes limited provision for direct contact with children and young people and their families.

1: The Review advises that the regional centres should be developed, as soon as feasibly possible, to become direct service providers, assessing and treating children and young people who may need specialist care, as part of a wider pathway. The Review team will work with NHS England and stakeholders to further define the proposed model and workforce implications.

2: Each regional centre will need to develop links and work collaboratively with a range of local services within their geography to ensure that appropriate clinical, psychological and social support is made available to children and young people who are in early stages of experiencing gender distress.

3: Clear criteria will be needed for referral to services along the pathway from primary to tertiary care so that gender-questioning children and young people who seek help from the NHS have equitable access to services.

4: Regional training programmes should be run for clinical practitioners at all levels, alongside the online training modules developed by Health Education England (HEE). In the longer-term, clearer mapping of the required workforce, and a series of competency frameworks will need to be developed in collaboration with relevant professional organisations.

Data, audit and research

1.39. A lack of routine and consistent data collection means that it is not possible to accurately track the outcomes and pathways children and young people take through the service. Standardised data collection is required in order to audit service standards and inform understanding of the epidemiology, assessment and treatment of this group. This, alongside a national network which brings providers together, will help build knowledge and improve outcomes through shared clinical standards and systematic data collection. In the longer-term, formalisation of such a network into a learning health system[9] with an academic host would mean that there was systematised use of data to produce a continuing research programme with rapid translation into clinical practice and a focus on training.

[9] Scobie S, Castle-Clarke S (2019). Implementing learning health systems in the UK NHS: Policy actions to improve collaboration and transparency and support innovation and better use of analytics. Learning Health Systems 4(1): e10209. DOI:10.1002/lrh2.10209.

5: The regional services should have regular co-ordinated national provider meetings and operate to shared standards and operating procedures with a view to establishing a formal learning health system.

6: Existing and future services should have standardised data collection in order to audit standards and inform understanding of the epidemiology, assessment and treatment of this group of children and young people.

7: Prospective consent of children and young people should be sought for their data to be used for continuous service development, to track outcomes, and for research purposes. Within this model, children and young people put on hormone treatment should be formally followed up into adult services, ideally as part of an agreed research protocol, to improve outcome data.

Clinical approach

Assessment processes

1.40. We have heard that there are inconsistencies and gaps in the assessment process. Our work to date has also demonstrated that clinical staff have different views about the purpose of assessment and where responsibility lies for different components of the process within the pathway of care. The Review team has commenced discussions with clinical staff across primary, secondary and tertiary care to develop a framework for these processes.

8: There needs to be agreement and guidance about the appropriate clinical assessment processes that should take place at primary, secondary and tertiary level.

9: Assessments should be respectful of the experience of the child or young person and be developmentally informed. Clinicians should remain open and explore the patient's experience and the range of support and treatment options that may best address their needs, including any specific needs of neurodiverse children and young people.

Hormone treatment

1.41. The issues raised by the Multi-Professional Review Group echo several of the problems highlighted by the CQC. It is essential that principles of the General Medical Council's Good Practice in Prescribing and Managing Medicine's and Devices[10] are closely followed, particularly given the gaps in the evidence base regarding hormone treatment. Standards for decision making regarding endocrine treatment should also be consistent with international best practice.[11,12,13]

10: Any child or young person being considered for hormone treatment should have a formal diagnosis and formulation, which addresses the full range of factors affecting their physical, mental, developmental and psychosocial wellbeing. This formulation should then inform what options for support and intervention might be helpful for that child or young person.

11: Currently paediatric endocrinologists have sole responsibility for treatment, but where a life-changing intervention is given there should also be additional medical responsibility for the differential diagnosis leading up to the treatment decision.

1.42. Paediatric endocrinologists develop a wide range of knowledge within their paediatric training, including safeguarding, child mental health, and adolescent development. Being party to the discussions and deliberations that have led up to the decision for medical intervention supports them in carrying out their legal responsibility for consent to treatment and the prescription of hormones.

12: Paediatric endocrinologists should become active partners in the decision making process leading up to referral for hormone treatment by participating in the multidisciplinary team meeting where children being considered for hormone treatment are discussed.

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[10] General Medical Council (2021). Good practice in prescribing and managing medicines and devices (76-78).
[11] Hembree WC, Cohen-Kettenis PT, Gooren L, Hannema SE, Meyer WJ, Murad MH, et al (2017). Endocrine treatment of gender-dysphoric/gender-incongruent persons: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 102(11): 3869–903. DOI: 10.1210/jc.2017-01658.
[12] Cohen-Kettenis PT, Steensma TD, de Vries ALC (2001). Treatment of adolescents with gender dysphoria in the Netherlands. Child Adolesc Psychiatr Clin N Am 20: 689–700. DOI: 10.1016/j.chc.2011.08.001.
[13] Kyriakou A, Nicolaides NC, Skordis N (2020). Current approach to the clinical care of adolescents with gender dysphoria. Acta Biomed 91(1): 165–75. DOI: 10.23750/abm.v91i1.9244.

1.43. Given the uncertainties regarding puberty blockers, it is particularly important to demonstrate that consent under this circumstance has been fully informed and to follow GMC guidance[14] by keeping an accurate record of the exchange of information leading to a decision in order to inform their future care and to help explain and justify the clinician's decisions and actions.

13: Within clinical notes, the stated purpose of puberty blockers as explained to the child or young person and parent should be made clear. There should be clear documentation of what information has been provided to each child or young person on likely outcomes and side effects of all hormone treatment, as well as uncertainties about longer-term outcomes.

14: In the immediate term the Multi-Professional Review Group (MPRG) established by NHS England should continue to review cases being referred by GIDS to endocrine services.

[14] General Medical Council (2020). Decision making and consent.

2. Context

Transgender, non-binary and gender fluid adults

2.1. NHS clinical services to support transgender adults with hormone treatment and subsequent surgery began in 1966.

2.2. Services were initially established within a mental health model, in conjunction with endocrinology and surgical services.

2.3. Currently, NHS services for transgender adults do not have adequate capacity to cope with demand.[15] In addition, the broader healthcare needs of this group are not well met. This is important in the context of the current generation of gender-questioning children and young people in that there are now two inflows into adult services – individuals transitioning in adulthood, and those moving through from children's services.

2.4. Legal rights and protections for transgender people lagged behind the provision of medical services, with the Gender Recognition Act 2004 coming into force in April 2005. Over the last few years, broader discussions about transgender issues have been played out in public, with discussions becoming increasingly polarised and adversarial. This polarisation is such that it undermines safe debate and creates difficulties in building consensus.

2.5. It is not the role of this Review to take any position on the cultural and societal debates relating to transgender adults. However, in achieving its objectives there is a need to consider the information and support that children and young people access from whatever source, as well as any pressures that they are subject to, before they access clinical services.

Terminology and diagnostic frameworks

2.6. The Office for National Statistics defines sex as "referring to the biological aspects of an individual as determined by their anatomy, which is produced by their chromosomes, hormones and their interactions; generally male or female; something that is assigned at birth".[16]

2.7. The Office for National Statistics defines gender as "a social construction relating to behaviours and attributes based on labels of masculinity and femininity; gender identity is a personal, internal perception of oneself and so the gender category someone identifies with may not match the sex they were assigned at birth".[17]

2.8. Societal attitudes towards gender roles and gender expression are changing. Children, teenagers and younger adults may more commonly see gender as a fluid, multi-faceted phenomenon which

[15] Gender Identity Clinic, The Tavistock and Portman NHS Foundation Trust. Waiting times.
[16] Office for National Statistics (2019). What is the difference between sex and gender?
[17] Ibid.

does not have to be binary, whereas older generations have tended to see gender as binary and fixed. It is not unusual for young people to explore both their sexuality and gender as they go through adolescence and early adulthood before developing a more settled identity. Many achieve this without experiencing significant distress or requiring support from the NHS, but this is not the case for all.

2.9. For those who require support from the NHS, there are two widely used frameworks which provide diagnostic criteria. The International Classification of Diseases (ICD), which is the World Health Organization (WHO) mandated health data standard, and the Diagnostic and Statistical Manual of Mental Disorders (DSM), which is the classification system for mental health disorders produced by the American Psychiatric Association. The current editions of these manuals – ICD-11 and DSM-5 – came into effect in January 2022 and 2013 respectively.

2.10. ICD-11[18] has attempted to depathologise gender diversity, removing the term 'gender identity disorders' from its mental health section and creating a new section for gender incongruence and transgender identities in a chapter on sexual health. These changes are part of a much broader societal drive to remove the stigma previously associated with transgender healthcare. ICD-11 defines gender incongruence as being "characterised by a marked incongruence between an individual's experienced/ expressed gender and the assigned sex." Gender variant behaviour and preferences alone are not a basis for assigning the diagnosis. The full criteria for gender incongruence of childhood and gender incongruence of adolescence or adulthood are listed in **Appendix 3**.

2.11. DSM-5[19] is currently the framework used to diagnose gender dysphoria. This diagnostic category describes gender dysphoria as "the distress that may accompany the incongruence between one's experienced or expressed gender and one's assigned gender". A diagnosis of gender dysphoria is usually deemed necessary before a young person can access hormone treatment, and criteria are listed in **Appendix 3**.

Conceptual understanding of gender incongruence in children and young people

2.12. Children and young people presenting to gender identity services are not a homogeneous group. They vary in their age at presentation, their cultural background, whether they identify as binary, non-binary, or gender fluid, whether they are neurodiverse and in a host of other ways.

[18] World Health Organization (2022). International Classification of Diseases Eleventh Revision.
[19] American Psychiatric Association (2013). Diagnostic and Statistical Manual of Mental Health Disorders: DSM-5™, 5th ed.

2.13. Some children and young people may thrive during a period of gender-questioning whilst for others it can be accompanied with a level of distress that can have a significant impact on their functioning and development.

2.14. Alongside these very varied presentations, it is highly unlikely that a single cause for gender incongruence will be found. Many authors view gender expression as a result of a complex interaction between biological, cultural, social and psychological factors.

2.15. Despite a high level of agreement about these points, there are widely divergent and, in some instances, quite polarised views among service users, parents, clinical staff and the wider public about how gender incongruence and gender-related distress in children and young people should be interpreted, and this has a bearing on expectations about clinical management.

2.16. These views will be influenced by how each individual weighs the balance of factors that may lead to gender incongruence, and the distress that may accompany it. Beliefs about whether it might be inherent and/or immutable, whether it might be a transient response to adverse experiences, whether it might be highly fluid and/or likely to change in later adolescence/early adulthood, etc will have a profound influence on expectations about treatment options.[20]

2.17. All of these views may be overlaid with strongly held concerns about children's and young people's rights, autonomy, and/or protection.

2.18. The disagreement and polarisation is heightened when potentially irreversible treatments are given to children and young people, when the evidence base underlying the treatments is inconclusive, and when there is uncertainty about whether, for any particular child or young person, medical intervention is the best way of resolving gender-related distress.

2.19. As with many other contemporary polarised disagreements, the situation is exacerbated when there is no space to have open, non-judgemental discussions about these differing perspectives. A key aim of this review process will be to encourage such discussions in a safe and respectful manner so that progress can be made in finding solutions.

[20] Wren B (2019). Notes on a crisis of meaning in the care of gender-diverse children. In: Hertzmann L, Newbigin J (eds) Sexuality and Gender Now: Moving Beyond Heteronormativity. Routledge.

3. Current services

Current service model for gender-questioning children and young people

3.1. Currently there are no locally or regionally commissioned services for children and young people who seek help from the NHS in managing their gender-related distress. Within primary and secondary care, some clinical staff have more interest and expertise in initial management of this group of young people, but such individuals are few and far between.

3.2. The pathway for NHS support around gender identity for children and young people is designated as a highly specialised service.[21] The Gender Identity Development Service (GIDS) at the Tavistock and Portman NHS Foundation Trust is commissioned by NHS England to provide specialist assessment, support and, where appropriate, hormone intervention for children and young people with gender dysphoria. It is the only NHS provider of specialist gender services for children and young people in England. The Trust runs satellite bases in Leeds and Bristol. Until recently GIDS accepted referrals from multiple sources, for example, GPs, secondary care, social care, schools, and support and advocacy groups, which is unusual for a specialist service.

3.3. Children and young people are assessed by two members of the GIDS team who may be any combination of psychologists, psychotherapists, family therapists, or social workers. If there is uncertainty about the right approach, individual cases may be discussed in a complex case meeting. Those deemed appropriate for physical interventions are referred on to the endocrine team; under the current Standard Operating Procedure (SOP), this decision requires a multi-disciplinary team (MDT) discussion within GIDS. A member of the GIDS team attends new appointments in the endocrine clinic, but they will not routinely be the member of staff who saw the young person for assessment. However, very recently a triage meeting has been piloted to enable endocrinologists to discuss upcoming appointments with the clinician who saw the young person for assessment. The young person then attends an education session prior to their endocrine appointment. The endocrinologist will assess any medical contraindications prior to seeking consent from the patient for any hormone treatments.

3.4. For many years, the GIDS approach was to offer assessment and support, and to only start puberty blockers when children reached sexual maturity at about age 15 (Tanner Stage 5) as the first step in the treatment process to feminise or masculinise the young person, with

[21] National Health Service Commissioning Board and Clinical Commissioning Groups (Responsibilities and Standing Rules) Regulations 2012.

oestrogen or testosterone given from age 16. Feminising/masculinising hormones are not given at an earlier stage because of the irreversibility of some of their actions in developing secondary sex characteristics of the acquired gender.[22,23]

3.5. In 1998, a new protocol was published by the Amsterdam gender identity clinic.[24] It was subsequently named the Dutch Approach.[25] This involved giving puberty blockers much earlier, from the time that children showed the early signs of puberty (Tanner Stage 2), to pause further pubertal changes of the sex at birth. This stage of pubertal development was chosen because it was felt that although many younger children experienced gender incongruence as a transient developmental phenomenon, those who expressed early gender incongruence which continued into puberty were unlikely to desist at that stage.

3.6. It was felt that blocking puberty would buy time for children and young people to fully explore their gender identity and help with the distress caused by the development of their secondary sexual characteristics. The Dutch criteria for treating children with early puberty blockers were: (i) a presence of gender dysphoria from early childhood; (ii) an increase of the gender dysphoria after the first pubertal changes; (iii) an absence of psychiatric comorbidity that interferes with the diagnostic work-up or treatment; (iv) adequate psychological and social support during treatment; and (v) a demonstration of knowledge and understanding of the effects of gonadotropin-releasing hormones (puberty blockers), feminising/masculinising hormones, surgery, and the social consequences of sex reassignment.[26]

3.7. Under the Dutch Approach, feminising/masculinising hormones were started at age 16 and surgery was permitted to be undertaken from age 18, as in England.

3.8. From 2011, early administration of puberty blockers was started in England under a research protocol, which partially paralleled the Dutch Approach (the Early Intervention Study). From 2014, this protocol was adopted by GIDS as routine clinical practice. Results of the Early Intervention Study were published in December 2021.[27]

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[22] Delemarre-van de Wall HA, Cohen-Kettinis PT (2006). Clinical management of gender identity disorder in adolescents: a protocol on psychological and paediatric endocrinology aspects. Eur J Endocrinol 155 (Suppl 1): S131–7. DOI: 10.1530/eje.1.02231.
[23] de Vries ALC, Cohen-Kettenis PT (2012). Clinical management of gender dysphoria in children and adolescents: the Dutch approach. J Homosex 59: 301–320. DOI: 10.1080/00918369.2012.653300.
[24] Cohen-Kettenis PT, Van Goozen S (1998). Pubertal delay as an aid in diagnosis and treatment of a transsexual adolescent. Eur Child Adolesc Psychiatry 7: 246–8. DOI: 10.1007/s007870050073.
[25] de Vries ALC, Cohen-Kettenis PT (2012). Clinical management of gender dysphoria in children and adolescents: the Dutch approach. J Homosex 59: 301–320. DOI: 10.1080/00918369.2012.653300.
[26] Ibid.
[27] Carmichael P, Butler G, Masic U, Cole TJ, De Stavola BL, Davidson S, et al (2021). Short-term outcomes of pubertal suppression in a selected cohort of 12 to 15 year old young people with persistent gender dysphoria in the UK. PLoS One. 16(2):e0243894. DOI:10.1371/journal.pone.0243894.

3.9. However, the Dutch Approach differs from the GIDS approach in having stricter requirements about provision of psychological interventions. For example, under the Dutch Approach, if young people have gender confusion, aversion towards their sexed body parts, psychiatric comorbidities or Autism Spectrum Disorder (ASD) related diagnostic difficulties, they may receive psychological interventions only, or before, or in combination with medical intervention. Of note, in 2011, the Amsterdam team were reporting that up to 10% of their referral base were young people with ASD.[28]

Changing epidemiology

3.10. In the last few years, there has been a significant change in the numbers and case-mix of children and young people being referred to GIDS.[29] From a baseline of approximately 50 referrals per annum in 2009, there was a steep increase from 2014-15, and at the time of the CQC inspection of the Tavistock and Portman NHS Foundation Trust in October 2020 there were 2,500 children and young people being referred per annum, 4,600 children and young people on the waiting list, and a waiting time of over two years to first appointment.[30] This has severely impacted on the capacity of the existing service to manage referrals in the safe and responsive way that they aspire to and has led to considerable distress for those on the waiting list.

3.11. This increase in referrals has been accompanied by a change in the case-mix from predominantly birth-registered males presenting with gender incongruence from an early age, to predominantly birth-registered females presenting with later onset of reported gender incongruence in early teen years. In addition, approximately one third of children and young people referred to GIDS have autism or other types of neurodiversity. There is also an over-representation percentage wise (compared to the national percentage) of looked after children.[31]

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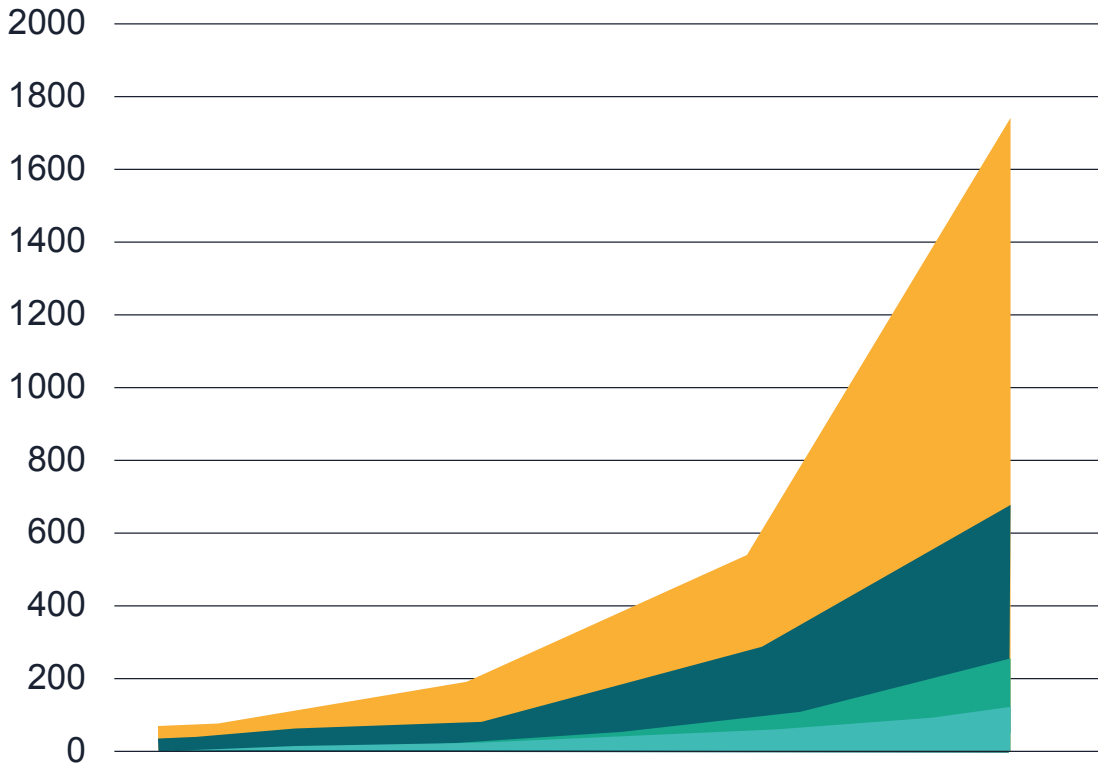
[28] Cohen-Kettenis PT, Steensma TD, de Vries ALC (2001). Treatment of adolescents with gender dysphoria in the Netherlands. Child Adolesc Psychiatr Clin N Am 20: 689–700. DOI: 10.1016/j.chc.2011.08.001.
[29] de Graaf NM, Giovanardi G, Zitz C, Carmichael P (2018). Sex ratio in children and adolescents referred to the gender identity development service in the UK (2009-2016). Arch Sex Behav 47(5): 1301–4.
[30] Care Quality Commission (2021). The Tavistock and Portman NHS Foundation Trust Gender Identity Service Inspection Report. London: CQC.
[31] Matthews T, Holt V, Sahin S, Taylor A, Griksaitis (2019). Gender Dysphoria in looked-after and adopted young people in a gender identity development service. Clinical Child Psychol Psychiatry 24: 112-128. DOI: 10.1177/1359104518791657.

Figure 1: Sex ratio in children and adolescents referred to GIDS in the UK (2009-16)



	2009	2010	2011	2012	2013	2014	2015	2016
Adolescents F	15	48*	78*	141*	221*	314*	689*	1071*
Adolescents M	24	44*	41	77*	120*	185*	293*	426*
Children F	2	7	12	17	22	36	77*	138*
Children M	10	19	29	30	31	55*	103*	131

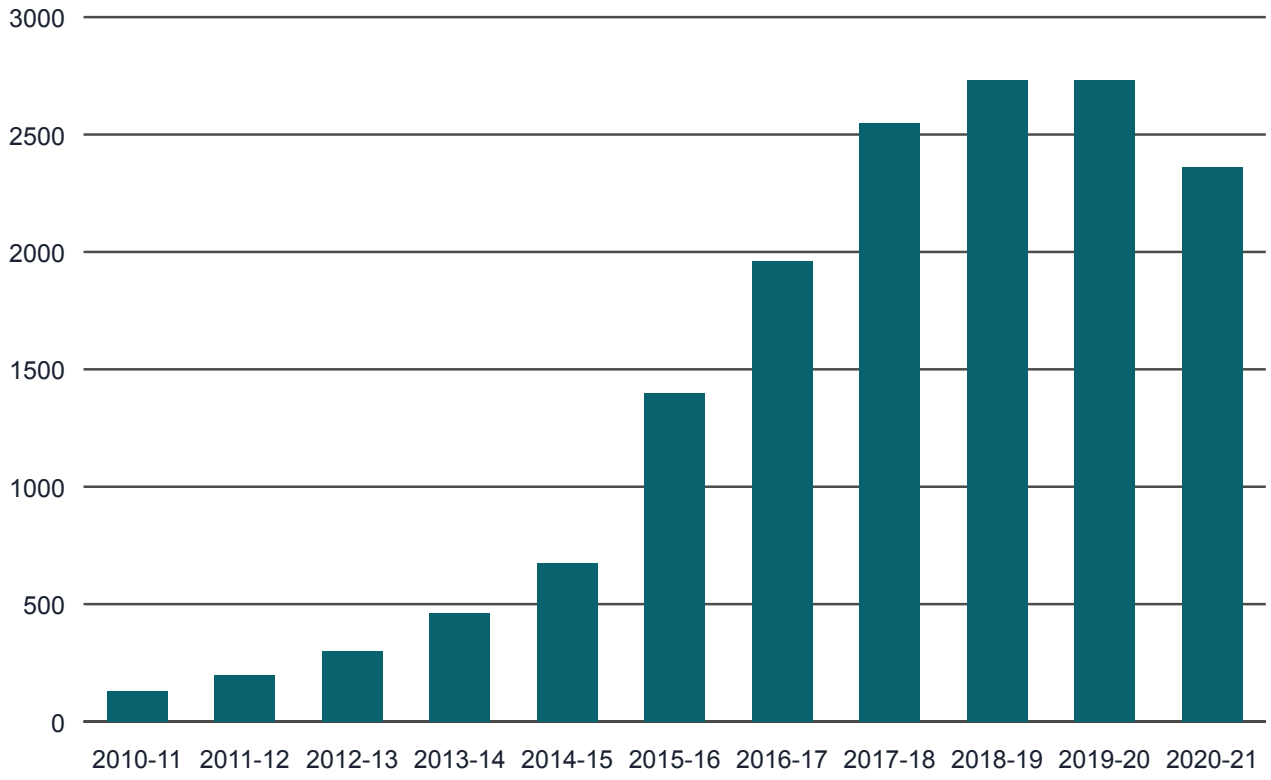
AFAB = assigned female at birth; AMAB = assigned male at birth

***Indicates** p<.05 which shows a significant increase of referrals compared to the previous year

Source: de Graaf NM, Giovanardi G, Zitz C, Carmichael P (2018).[32]

[32] de Graaf NM, Giovanardi G, Zitz C, Carmichael P (2018). Sex ratio in children and adolescents referred to the gender identity development service in the UK (2009-2016). Arch Sex Behav 47(5): 1301–4.

Figure 2: Referrals to GIDS, 2010-11 to 2020-21



Source: Gender Identity Development Service.[33]

3.12. In 2019, GIDS reported that about 200 children and young people from a referral base of 2,500 were referred on to the endocrine pathway. There is no published data on how the other children and young people from this referral baseline were managed, for example if: their gender dysphoria was resolved; they were still being assessed or receiving ongoing psychological support and input; they were not eligible for puberty blockers due to age; they were referred to endocrine services at a later stage; they were transferred to adult services; or they accessed private services.

Challenges to the service model and clinical approach

3.13. Over a number of years, in parallel with the increasing numbers of referrals, GIDS faced increasing challenges, both internally and externally. There were different views held within the staff group about the appropriate clinical approach, with some more strongly affirmative and some more cautious and concerned about the use of physical intervention. The complexity of the cases had also increased, so clinical decision making had become more difficult. There was also a high staff

[33] Gender Identity Development Service. Referrals to GIDS, financial years 2010-11 to 2020-21.

turnover, and accounts from staff concerned about the clinical care, which were picked up in both mainstream and social media. This culminated in 2018 with an internal report by a staff governor.

3.14. Following that report, a review was carried out in 2019 by the Trust's medical director. This set out the need for clearer processes for the service's referral management, safeguarding, consent, and clinical approach, and an examination of staff workload and support, and a new Standard Operating Procedure (SOP) was put in place.

NHS England Policy Working Group

3.15. In January 2020, a Policy Working Group (PWG) was established by NHS England to undertake a review of the published evidence on the use of puberty blockers and feminising/masculinising hormones in children and young people with gender dysphoria to inform a policy position on their future use. Given the increasingly evident polarisation among clinical professionals, Dr Cass was asked to chair the group as a senior clinician with no prior involvement or fixed views in this area. The PWG comprised an expert group including endocrinologists, child and adolescent psychiatrists and paediatricians representing their respective Royal Colleges, an ethicist, a GP, senior clinicians from the NHS GIDS, a transgender adult and parents of gender-questioning young people. The process was supported by a public health consultant and policy, pharmacy and safeguarding staff from NHS England.

3.16. NHS England uses a standardised protocol for developing clinical policies. The first step of this involves defining the PICO (the Population being treated, the Intervention, a Comparator treatment, and the intended Outcomes). This of itself was challenging, with a particular difficulty being definition of the intended outcomes of puberty blockers, and suitable comparators for both hormone interventions. However, agreement was reached on what should be included in the PICO and subsequently the National Institute for Health and Care Excellence (NICE) was commissioned to review the published evidence,[34,35] again following a standardised protocol which has strict criteria about the quality of studies that can be included.

3.17. Unfortunately, the available evidence was not strong enough to form the basis of a policy position. Some of the challenges and outstanding uncertainties are summarised as follows.

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[34] National Institute for Health and Care Excellence (2020). Evidence Review: Gonadotrophin Releasing Hormone Analogues for Children and Adolescents with Gender Dysphoria.
[35] National Institute for Health and Care Excellence (2020). Evidence review: gender-affirming hormones for children and adolescents with gender dysphoria.

Feminising/masculinising hormones

3.18. Sex hormones have been prescribed for transgender adults for several decades, and the long-term risks and side effects are well understood. These include increased cardiovascular risk, osteoporosis, and hormone-dependent cancers.

3.19. In young people, consideration also needs to be given to the impact on fertility, with the need for fertility counselling and preservation.

3.20. The additional physical risk of starting these treatments at age 16+ rather than age 18+ is unlikely to add significantly to the total lifetime risk, although data on this will not be available for many years. However, as evidenced by take-up of treatment with feminising/masculinising hormones, where there is a high level of certainty that physical transition is the right option, the child or young person may be more accepting of these risks, which can seem remote from the immediate gender distress.

3.21. The most difficult question in relation to feminising/masculinising hormones therefore is not about long-term physical risk which is tangible and easier to understand. Rather, given the irreversible nature of many of the changes, the greatest difficulty centres on the decision to proceed to physical transition; this relies on the effectiveness of the assessment, support and counselling processes, and ultimately the shared decision making between clinicians and patients. Decisions need to be informed by long-term data on the range of outcomes, from satisfaction with transition, through a range of positive and negative mental health outcomes, through to regret and/or a decision to detransition. The NICE evidence review demonstrates the poor quality of these data, both nationally and internationally.

3.22. Regardless of the nature of the assessment process, some children and young people will remain fluid in their gender identity up to early to mid-20s, so there is a limit as to how much certainty one can achieve in late teens. This is a risk that needs to be understood during the shared decision making process with the young person.

3.23. It is also important to note that any data that are available do not relate to the current predominant cohort of later-presenting birth-registered female teenagers. This is because the rapid increase in this subgroup only began from around 2014-15. Since young people may not reach a settled gender expression until their mid-20s, it is too early to assess the longer-term outcomes of this group.

Puberty blockers

3.24. The administration of puberty blockers is arguably more controversial than administration of the feminising/ masculinising hormones, because there are more uncertainties associated with their use.

3.25. There has been considerable discussion about whether the treatment is 'experimental'; strictly speaking an experimental treatment is one that is being given as part of a research protocol, and this is not the case with puberty blockers, because the GIDS research protocol was stopped in 2014. At that time, the treatment was experimental and innovative, because the drug was licensed for use in children, but specifically for children with precocious puberty. This was therefore the first time it was used 'off-label' in the UK for children with gender dysphoria. If a drug is used 'off-label' it means it is being used for a condition that is different from the one for which it was licensed. The many uncertainties around the 'off-label' use were recognised, but given that this was not a new drug, it did not need Medicines and Healthcare products Regulatory Agency (MHRA) approval at that time.

3.26. The important question now, as with any treatment, is whether the evidence for the use and safety of the medication is strong enough as judged by reasonable clinical standards.

3.27. One of the challenges that NHS England's PWG faced in considering this question was the lack of clarity about intended outcomes, several of which have been proposed including:

- providing time/space for the young person to make a decision about continuing with transition;
- reducing or preventing worsening of distress;
- improving mental health; and
- stopping potentially irreversible pubertal changes which might later make it difficult for the young person to 'pass' in their intended gender role.

3.28. Proponents for the use of puberty blockers highlight the distress that young people experience through puberty and the risk of self-harm or suicide.[36] However, some clinicians do not feel that distress is actually alleviated until children and young people are able to start feminising/ masculinising hormones. The Review will seek to gain a better understanding of suicide data and the impact of puberty blockers through its research programme.

3.29. On the other hand, it has been asserted that starting puberty blockers at an older age provides children and young people with more time to achieve fertility preservation. In the case of birth-registered males, there is an argument that it also

[36] Turban JL, King D, Carswell JM, et al (2020). Pubertal suppression for transgender youth and risk of suicidal ideation. Pediatrics 145 (2): e20191725. DOI: 10.1542/peds.2019-1725.

allows more time to achieve adequate penile growth for successful vaginoplasty.

3.30. In the short-term, puberty blockers may have a range of side effects such as headaches, hot flushes, weight gain, tiredness, low mood and anxiety, all of which may make day-to-day functioning more difficult for a child or young person who is already experiencing distress. Short-term reduction in bone density is a well-recognised side effect, but data is weak and inconclusive regarding the long-term musculoskeletal impact.[37]

3.31. The most difficult question is whether puberty blockers do indeed provide valuable time for children and young people to consider their options, or whether they effectively 'lock in' children and young people to a treatment pathway which culminates in progression to feminising/masculinising hormones by impeding the usual process of sexual orientation and gender identity development. Data from both the Netherlands[38] and the study conducted by GIDS[39] demonstrated that almost all children and young people who are put on puberty blockers go on to sex hormone treatment (96.5% and 98% respectively). The reasons for this need to be better understood.

3.32. A closely linked concern is the unknown impacts on development, maturation and cognition if a child or young person is not exposed to the physical, psychological, physiological, neurochemical and sexual changes that accompany adolescent hormone surges. It is known that adolescence is a period of significant changes in brain structure, function and connectivity.[40] During this period, the brain strengthens some connections (myelination) and cuts back on others (synaptic pruning). There is maturation and development of frontal lobe functions which control decision making, emotional regulation, judgement and planning ability. Animal research suggests that this development is partially driven by the pubertal sex hormones, but it is unclear whether the same is true in humans.[41] If pubertal sex hormones are essential to these brain maturation processes, this raises a secondary question of whether there is a critical time window for the processes to take place, or whether catch up is possible when oestrogen or testosterone is introduced later.

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[37] National Institute for Health and Care Excellence (2020). Evidence Review: Gonadotrophin Releasing Hormone Analogues for Children and Adolescents with Gender Dysphoria.
[38] Brik T, Vrouenraets LJJJ, de Vries MC, Hannema SE (2020). Trajectories of adolescents treated with gonadotropin-releasing hormone analogues for gender dysphoria. Arch Sex Behav 49: 2611–8. DOI: 10.1007/s10508-020-01660-8.
[39] Carmichael P, Butler G, Masic U, Cole TJ, De Stavola BL, Davidson S, et al (2021). Short-term outcomes of pubertal suppression in a selected cohort of 12 to 15 year old young people with persistent gender dysphoria in the UK. PLoS One. 16(2):e0243894. DOI:10.1371/journal.pone.0243894.
[40] Delevichab K, Klinger M, Nana OJ, Wilbrecht L (2021). Coming of age in the frontal cortex: The role of puberty in cortical maturation. Semin Cell Dev Biol 118: 64–72. DOI: 10.1016/j.semcdb.2021.04.021.
[41] Goddings A-L, Beltz A, Jiska S, Crone EA, Braams BR (2019). Understanding the role of puberty in structural and functional development of the adolescent brain. J Res Adolesc 29(1): 32–53. DOI: 10.1111/jora.12408.

3.33. An international interdisciplinary panel[42] has highlighted the importance of understanding the neurodevelopmental outcomes of pubertal suppression and defined an appropriate approach for investigating this further. However, this work has not yet been undertaken.

Initiation of Cass Review

3.34. Dr Cass' own reflections on the PWG process, the available literature, and the issues it highlighted were as follows:

- Firstly, that hormone treatment is just one possible outcome for gender-questioning children and young people. A much better understanding is needed about: the increasing numbers of children and young people with gender-related distress presenting for help; the appropriate clinical pathway for each individual; their support needs; and the full range of potential treatment options.
- Secondly, there is very limited follow-up of the subset of children and young people who receive hormone treatment, which limits our understanding about the long-term outcomes of these treatments and this lack of follow up data should be corrected.
- Thirdly, the assessment process is inconsistent across the published literature. The outcome of hormone treatment is highly influenced by whether the assessment process accurately selects those children and young people most likely to benefit from medical treatment. This makes it difficult to draw conclusions from published studies.

3.35. In light of the above, NHS England commissioned this independent review to make recommendations on how the clinical management and service provision for children and young people who are experiencing gender incongruence or gender-related distress can be improved.

CQC inspection

3.36. In October and November 2020, the Care Quality Commission (CQC) inspectors carried out an announced, focused inspection of GIDS due to concerns reported to them by healthcare professionals and the Children's Commissioner for England. Concerns related to clinical practice, safeguarding procedures, and assessments of capacity and consent to treatment.

[42] Chen D, Strang JF, Kolbuck VD, Rosenthal SM, Wallen K, Waber DP, et al (2020). Consensus parameter: research methodologies to evaluate neurodevelopmental effects of pubertal suppression in transgender youth. Transgender Health 5(4). DOI: 10.1089/trgh.2020.0006.

3.37. The CQC report, published in January 2021,[43] gave the service an overall rating of inadequate. The report noted the high level of commitment and caring approach of the staff but identified a series of issues that needed improvement. In addition to the growing waiting list pressures, the CQC identified problems in several other areas including: the assessment and management of risk; the variations in clinical approach; the lack of clarity and consistency of care plans; the lack of any clear written rationale for decision making in individual cases; and shortfalls in the multidisciplinary mix required for some patient groups. Recording of capacity, competency and consent had improved since the new SOP in January 2020; however, there remained a culture in which staff reported feeling unable to raise concerns.

3.38. The CQC reported that when it inspected GIDS, there did not appear to be a formalised assessment process, or standard questions to explore at each session, and it was not possible to tell from the notes why an individual child might have been referred to endocrinology whilst another had not. Current GIDS data demonstrate that a majority of children and young people seen by the service do not get referred for endocrine treatment, but there is no clear information about what other diagnoses they receive, and what help or support they might need.

3.39. Since the CQC report, NHS England and The Tavistock and Portman NHS Foundation Trust management team have been working to address the issues raised. However, whilst some problems require a focused Trust response, the waiting list requires a system-wide response. This was noted in the letter from the Review to NHS England in May 2021 (**Appendix 2**).

Legal background

3.40. This section sets out the chronology of recent case law. In October 2019, a claim for Judicial Review was brought against The Tavistock and Portman NHS Foundation Trust. The claimants' case was summarised by the High Court as follows: "The claimants' case is that children and young persons under 18 are not competent to give consent to the administration of puberty blocking drugs. Further, they contend that the information given to those under 18 by the defendant [GIDS] is misleading and insufficient to ensure such children or young persons are able to give informed consent. They further contend that the absence of procedural safeguards, and the inadequacy of the information provided, results in an infringement of the rights of such children and young persons under Article 8 of the European Convention

[43] Care Quality Commission (2021). The Tavistock and Portman NHS Foundation Trust Gender Identity Service Inspection Report. London: CQC.

for the Protection of Human Rights and Fundamental Freedoms."[44]

3.41. In December 2020, three judges in the High Court of England and Wales handed down judgment in *Bell v Tavistock.*[45] (Most cases in the High Court are heard by a single judge sitting alone, and when a case is heard by more than one judge in the High Court, it is described as the Divisional Court.) The Divisional Court recognised that the Tavistock's policies and practices as set out in the service specification were not unlawful. However, the Court made a declaration that set out in detail a series of implications of treatment that a child would need to understand to be *Gillick* competent[46] to consent to puberty blockers. Specifically, because most children put on puberty blockers go on to have feminising/masculinising hormones, the judgment said a child would need to understand not only the full implications of puberty blocking drugs, but also the implications of the full pathway of medical and surgical transition. The judges concluded that it will be "very doubtful" that 14-15 year-olds have such competence, and "highly unlikely" that children aged 13 or under have competence for that decision. Under the Mental Capacity Act 2005, 16-17 year-olds are presumed to have capacity, and they are effectively treated as adults for consent to medical treatment under the Family Law Reform Act 1969 section 8, but the judges suggested that it would be appropriate for clinicians to involve the court in any case where there were doubts as to whether the proposed treatment would be in the long term best interests of a 16-17 year-old.

3.42. Following the Divisional Court judgment in *Bell v Tavistock*, a claim was brought against the Tavistock in the High Court Family Division by the mother of a child for a declaration that she and the child's father had the ability in law to consent on behalf of their child to the administration of puberty blockers *(AB v CD)*.[47] The Court concluded that "the parents' right to consent to treatment on behalf of the child continues even when the child is *Gillick* competent to make the decision, save where the parents are seeking to override the decision of the child" [para 114] and that there is no "general rule that puberty blockers should be placed in a special category by which parents are unable in law to give consent" [para 128].

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[44] Bell v Tavistock. [2020] EWHC 3274 (Admin).
[45] Ibid.
[46] Gillick v West Norfolk and Wisbech AHA [1986] AC 112.
[47] AB v CD & Ors [2021] EWHC 741.

3.43. Subsequently, the Tavistock appealed the Divisional Court's earlier decision in *Bell v Tavistock* and was successful.[48] The Court of Appeal held that it was not appropriate for the Divisional Court to provide the guidance about the likelihood of having *Gillick* competence at particular ages, or about the need for court approval [para 91]. The Court of Appeal went on to say "The Divisional Court concluded that Tavistock's policies and practices (as expressed in the service specification and the SOP) were not unlawful and rejected the legal criticism of its materials. In those circumstances, the claim for judicial review is dismissed." [para 91]. However, clinicians should "take great care before recommending treatment to a child and be astute to ensure that the consent obtained from both child and parents is properly informed" [para 92].

3.44. The Court of Appeal in *Bell v Tavistock* recognised the lawfulness of treating children for gender dysphoria in this jurisdiction. Recognising the divergences in medical opinion, morality and ethics, it indicated that the question of whether treatment should be made available is a matter of policy "for the National Health Service, the medical profession and its regulators and Government and Parliament" [para 3].

3.45. Following the Divisional Court decision in *Bell v Tavistock*, new referrals for puberty blockers were suspended and a requirement was put in place that children currently on puberty blockers were reviewed with a view to court proceedings for a judge to determine the best interests for children in whom these medications were considered essential. This requirement was changed following *AB v CD*, with the reinstatement of the hormone pathway in March 2021. However, an external panel, the Multi Professional Review Group (MPRG), was established to ensure that procedures for assessment and for informed consent had been properly followed. The outcome of the *Bell* appeal has not changed this requirement, which is contingent not just on the legal processes but on the concerns raised by CQC regarding consent, documentation and clarity about decision making within the service.[49]

[48] EWCA [2021] Civ 1363.
[49] Care Quality Commission (2021). The Tavistock and Portman NHS Foundation Trust Gender Identity Service Inspection Report. London: CQC.

The Multi-Professional Review Group

3.46. NHS England has established a Multi-Professional Review Group (MPRG) to review whether the agreed process has been followed for a child to be referred into the endocrinology clinic and to be prescribed treatment. The Review has spoken directly to the MPRG, which has reported its observations of current practice.

3.47. The MPRG has stated that its work has been impeded by delays in the provision of clinical information, the lack of structure in the documentation received, and gaps in the necessary evidence. This means that when reviewing the documents provided it is not always easy to determine if the process for referral for endocrine treatment has been fully or safely followed for a particular child or young person.

3.48. The MPRG indicates that there does not appear to be a standardised approach to assessment. They are particularly concerned about safeguarding shortfalls within the assessment process. There is also limited evidence of systematic, formal mental health or neurodevelopmental assessments being routinely documented, or of a discipline of formal diagnostic formulation in relation to co-occurring mental health difficulties. This issue was also highlighted by the Care Quality Commission (CQC).[50]

3.49. Additionally, there is concern that communications to GPs and parents regarding prescribed treatment with puberty blockers sometimes come from non-medical staff.

[50] Care Quality Commission (2021). The Tavistock and Portman NHS Foundation Trust Gender Identity Service Inspection Report. London: CQC.

4. What the review has heard so far

Listening sessions

4.1. Since its establishment, the Review has met with an extensive range of stakeholders, including professionals, their respective governing organisations and those with lived experience, both directly and through support and advocacy groups, to understand the broad range of views and experiences surrounding the delivery of gender identity services.

What we have heard from service users, their families and support and advocacy groups

Issues for children and young people

4.2. What we understand most clearly from all we have heard is that at the centre of a difficult and complex debate are children, young people and families in great distress. We have heard concerns about children and young people facing the stress of being on a prolonged waiting list with limited support available from statutory services, lack of certainty about when and if they might reach the top of that list and subsequent impacts on mental health. Also, the particular issues that have followed the *Bell v Tavistock* litigation.

4.3. We have heard about the anxiety that birth-registered males face as they come closer to the point where they will grow facial hair and their voice drops, and the fear that it will make it harder for them to pass as a transgender woman in later life. We have also heard about the distress experienced by birth-registered females as they reach puberty, including the use of painful, and potentially harmful, binding processes to conceal their breasts.

4.4. When children and young people are able to access the service, there is often a sense of frustration with what several describe as the “gatekeeping” medical model and a “clinician lottery”. This can feel like a series of barriers and hurdles designed to add to, rather than alleviate, distress. Most children and young people seeking help do not see themselves as having a medical condition; yet to achieve their desired intervention they need to engage with clinical services and receive a medical diagnosis of gender dysphoria. By the time they are seen in the GIDS clinic, they may feel very certain of their gender identity and be anxious to start hormone treatment as quickly as possible. However, they can then face a period of what can seem like intrusive, repetitive and unnecessary questioning. Some feel that this undermines their autonomy and right to self-determination.

4.5. We have heard that some young people learn through peers and social media what they should and should not say to therapy staff in order to access hormone treatment; for example, that they are advised not to admit to previous abuse or trauma, or uncertainty about their sexual orientation. We have also heard that many of those seeking NHS support identify as non-binary, gender non-conforming, or gender fluid. We understand that some

young people who identify as non-binary feel their needs are not met by clinical services unless they give a binary narrative about their gender preferences.

Issues for parents

4.6. We have also heard about the distress parents may feel as they try to work out how best to support their children and how tensions and conflict may arise where parents and their children have different views. For example, some parents have highlighted the importance of ensuring that children and young people are able to keep their options fluid until such time as it becomes essential to commit to a hormonal course of action, whilst their children may want more rapid hormone intervention.

4.7. We have heard about families trying to balance the risks of obtaining unregulated and potentially dangerous hormone supplies over the internet or from private providers versus the ongoing trauma of prolonged waits for assessment.

4.8. Parents have also raised concerns about the vulnerability of neurodiverse children and young people and expressed that the communication needs of these children and young people are not adequately reflected during assessment processes or treatment planning.

4.9. GIDS has always required consent/ assent from both the child and parents/ carers and has sought ways to resolve family conflict, which in the worst-case scenario can lead to family breakdown. It has been highlighted to us that the future service model should provide more targeted support for parents and carers.

Service issues

4.10. Another significant issue raised with us is one of diagnostic overshadowing – many of the children and young people presenting have complex needs, but once they are identified as having gender-related distress, other important healthcare issues that would normally be managed by local services can sometimes be subsumed by the label of gender dysphoria. This issue is compounded by the waiting list, which means that there can be a significant period of time without appropriate assessment, treatment or care.

4.11. Stakeholders have spoken of the need for appropriate assessment when first accessing NHS services to aid both the exploration of the child or young person's wellbeing and gender distress and any other challenges they may be facing.

Information

4.12. We have also heard about the lack of access to accurate, balanced information upon which children, young people and their families/carers can inform their decisions.

4.13. We have heard that distress may be exacerbated by pressure to identify with societal stereotyping and concerns over the influence of social media, which can be seen to perpetuate unrealistic images of gender and set unhealthy expectations, especially given how long

children and young people are waiting to access services.

Other issues

4.14. Several issues that were raised with us are not explored further in this interim report, but we have taken note of them. These will be considered further during the lifetime of the Review and include:

- The important role of schools and the challenges they face in responding appropriately to gender-questioning children and young people.
- The complex interaction between sexuality and gender identity, and societal responses to both; for example, we have heard from young lesbians who felt pressured to identify as transgender male, and conversely transgender males who felt pressured to come out as lesbian rather than transgender. We have also heard from adults who identified as transgender through childhood, and then reverted to their birth-registered gender in teen years.
- The issues faced by detransitioners highlight the need for better services and pathways for this group, many of whom are living with irreversible effects of transition but for whom there is no clear access to services as they fall outside the responsibility of NHS gender identity services.
- The age at which adult gender identity clinics can receive referrals, with concerns about the inclusion of 17-year-olds. The service offer in adult services is perceived to be quite different from that of GIDS, and young people presenting later may therefore not be afforded the same level of therapeutic input under the adult service model. There is also concern about the impact on the young person of changing clinicians at a crucial point in their care. The movement of young people with special educational needs between children's and adult services raises particular concerns.

What we have heard from healthcare professionals

Lack of professional consensus

4.15. Clinicians and associated professionals we have spoken to have highlighted the lack of an agreed consensus on the different possible implications of gender-related distress – whether it may be an indication that the child or young person is likely to grow up to be a transgender adult and would benefit from physical intervention, or whether it may be a manifestation of other causes of distress. Following directly from this is a spectrum of opinion about the correct clinical approach, ranging broadly between those who take a more gender-affirmative approach to those who take a more cautious, developmentally-informed approach.

4.16. Speaking to current and ex-GIDS staff, we have heard about the pressure on GIDS clinicians, many of whom feel overwhelmed by the numbers of children and young people being referred and who are demoralised by the media coverage of their service. Although the clinical team attempt to manage risk on the waiting list by engaging with local services, there is limited capacity and/or capability to respond appropriately to the needs of this group in primary and secondary care. The Review has already referred to this issue as the most pressing priority in its letter to NHS England (**Appendix 2**), alongside potential risks relating to safeguarding and/or mental health issues, and diagnostic overshadowing.

4.17. With respect to GIDS, we have been told that although there are forums for staff to discuss difficult cases with senior colleagues, it is still difficult for staff to raise concerns about the clinical approach. Also that many individuals who are more cautious and advocate the need for an exploratory approach have left the service.

Consistency and standards

4.18. GIDS staff have confirmed that judgements are very individual, with some clinicians taking a more gender-affirmative approach and others emphasising the need for caution and for careful exploration of broader issues. The Review has been told that there is considerable variation in the approach taken between the London, Leeds and Bristol teams.

4.19. Speaking to professionals outside GIDS, we have heard widespread concern about the lack of guidance and evidence on how to manage this group of young people.

4.20. Some secondary care providers told us that their training and professional standards dictate that when working with a child or young person they should be taking a mental health approach to formulating a differential diagnosis of the child or young person's problems. However, they are afraid of the consequences of doing so in relation to gender distress because of the pressure to take a purely affirmative approach. Some clinicians feel that they are not supported by their professional body on this matter. Hence the practice of passing referrals straight through to GIDS is not just a reflection of local service capacity problems, but also of professionals' practical concerns about the appropriate clinical management of this group of children and young people.

4.21. GPs have expressed concern about being pressurised to prescribe puberty blockers or feminising/masculinising hormones after these have been initiated by private providers.

4.22. This also links to professional concerns about parents being anxious for hormone treatment to be initiated when the child or young person does not seem ready.

Other issues

4.23. We have also heard that parents and carers play a huge role and are instrumental in helping young people

to keep open their developmental opportunities. In discussion with social workers, we heard concerns about how looked after children are supported in getting the help and support they need.

4.24. Therapists who work with detransitioners and people with regret have highlighted a lack of services and pathways and a need for services to support this population. There is also the need for more research to understand what factors contribute to the decision to detransition.

4.25. The importance of broad holistic interventions to help reduce distress has been emphasised to the Review, with therapists and other clinicians advocating the importance of careful developmentally informed assessment and of showing children and young people a range of different narratives, experiences and outcomes.

4.26. Clinicians have raised concerns about children and young people's NHS numbers being changed inconsistently, as there is no specific guidance for GPs and others as to when this should be done for this population and under what consent. This has implications for safeguarding and clinical management of these children and young people and it also makes it difficult to do research exploring long-term outcomes.

4.27. As with the comments made by service users, their families and support and advocacy groups, we have heard similar views from professionals about the transition from children's to adult services, and the role of schools.

Structured engagement with primary, secondary and specialist clinicians

4.28. The Review's letter to NHS England (**Appendix 2**) set out some of the immediate issues with the current provision of gender identity services for children and young people and suggested how its work might help with the challenging problem of establishing an infrastructure outside GIDS. This included looking at the capacity, capability and confidence of the wider workforce and how this could be built and sustained, and the establishment of potential assessment frameworks for use in primary and/or secondary care.

Professional panel – primary and secondary care

4.29. In order to understand the challenges and establish a picture of current competency, capacity and confidence among the workforce outside the specialist gender development service, an online professional panel was established to explore issues around gender identity services for children and young people. The role of the panel was aimed at better comprehending how it looks and feels for clinicians and other professionals working with these young people, as well as any broader thoughts about the work, and to start exploring how the care of these

children and young people can be better managed in the future.

4.30. The project was designed to capture a broad mix of professional views and experiences, recruiting from the professional groups that are most likely to have a role in the care pathway – GPs, paediatricians, child psychiatrists, child psychologists and child psychotherapists, nurses and social workers.

4.31. A total of 102 clinicians and other professionals were involved in the panel. The panel represented a balanced professional mix, and participant ages and gender were broadly representative of the overall sector workforce. Participants were self-selecting and were recruited via healthcare professional networks and Royal Colleges.

4.32. Each week the panel was set an independent activity comprised of two or more tasks. Additionally, a sub-set of the panel was invited to participate in focus groups at the midway and endpoint of the project. Activities were designed to capture an understanding of:

- experiences of working with gender-questioning children and young people and panel members' confidence and competence to manage their care;
- changes they may have experienced in the presentation of children and young people with gender-related distress;
- areas where professionals feel they require more information in order to support gender-questioning children and young people;
- where professionals currently go to find that information;
- the role of different professions in the care pathway;
- the role of professionals in the assessment framework; and
- what participants felt should be included in an assessment framework across the whole service pathway.

Gender specialist questionnaire

4.33. Having concluded the professional panel exercise, we wanted to triangulate what we had heard with the thoughts and views of professionals working predominantly or exclusively with gender-questioning children and young people.

4.34. To do this in a systematic way, we conducted an online survey which contained some service-specific questions, but also reflected and sought to test some of what we had heard from primary and secondary care professionals.

Findings

4.35. This structured engagement has yielded valuable insights from clinicians and professionals with experience working with gender-questioning children and young people both within and outside the specialist gender service. It has contributed to the thinking of the Review and informed some of the interim advice set out in this report.

4.36. There are a number of consistent messages arising from these activities:

- The current long waiting lists that gender-questioning children and young people and their families/carers face are unacceptable for all parties involved, including professionals.
- Many professionals in our sample said that not only are gender-questioning children and young people having to wait a long time before receiving treatment, but they also do not receive appropriate support during this waiting period.
- Another impact of the long wait that clinicians reported is that when a child or young person is seen at GIDS, they may have a more fixed view of what they need and are looking for action to be taken quickly. This reportedly can lead to frustration with the assessment process.
- When considering the more holistic support that children and young people may need, gender specialists further highlighted the difficulties that children and young people face accessing local support, for example, from CAMHS, whilst being seen at GIDS.
- It is clear from the professionals who took part in these activities that there is a strong professional commitment to provide quality care to gender-questioning children and young people and their families/carers. However, this research indicates that levels of confidence and competence do vary among primary and secondary care professionals in our sample.
- Concerns were expressed by professionals who took part in this research about the lack of consensus among the clinical community on the right clinical approach to take when working with a gender-questioning child or young person and their families/carers.
- In order to support clinicians and professionals more widely, participants felt there is a need for a robust evidence base, consistent legal framework and clinical guidelines, a stronger assessment process and different pathway options that holistically meet the needs of each gender-questioning child or young person and their families/carers.

4.37. There are also several areas where further discussion and consensus is needed:

- There is not a consistent view among the professionals participating in the panel and questionnaire about the nature of gender dysphoria and therefore the role of assessment for children and young people experiencing gender dysphoria.

- Some clinicians felt that assessment should be focused on whether medical interventions are an appropriate course of action for the individual. Other clinicians believe that assessment should seek to make a differential diagnosis, ruling out other potential causes of the child or young person's distress.
- There are different perspectives on the roles of primary, secondary and specialist services in the care pathway(s) and what support or action might best be provided at different levels.
- While there was general consensus that diagnostic or psychological formulation needs to form part of the assessment process, there were differing views as to whether a mental state assessment is needed, and should it be, where in the pathway and by whom this should be done.

4.38. It is important to note that the information gathered represents the views and insights of the panel participants and survey respondents at a moment in time and findings should be read in the context of a developing narrative on the subject, where perspectives may evolve. This relates to both the experiences of professionals, but also the extent to which this subject matter is discussed in the public sphere.

4.39. The Review is grateful to all the participants for their time and high level of engagement. The Review will build on the work we have undertaken and, alongside our academic research, will continue with a programme of engagement with professionals, service users and their families, which will help to further develop the evidence base.

The full reports from the professional panel and gender specialist questionnaire are on the Review's website (https://cass.independent-review.uk/).

5. Principles of evidence based service development

Evidence based service development

5.1. This chapter integrates the information regarding the development of the current service (see Chapter 3) with the views we have heard to date (see Chapter 4) and sets this in the context of how evidence is routinely used to develop and improve services in the NHS.

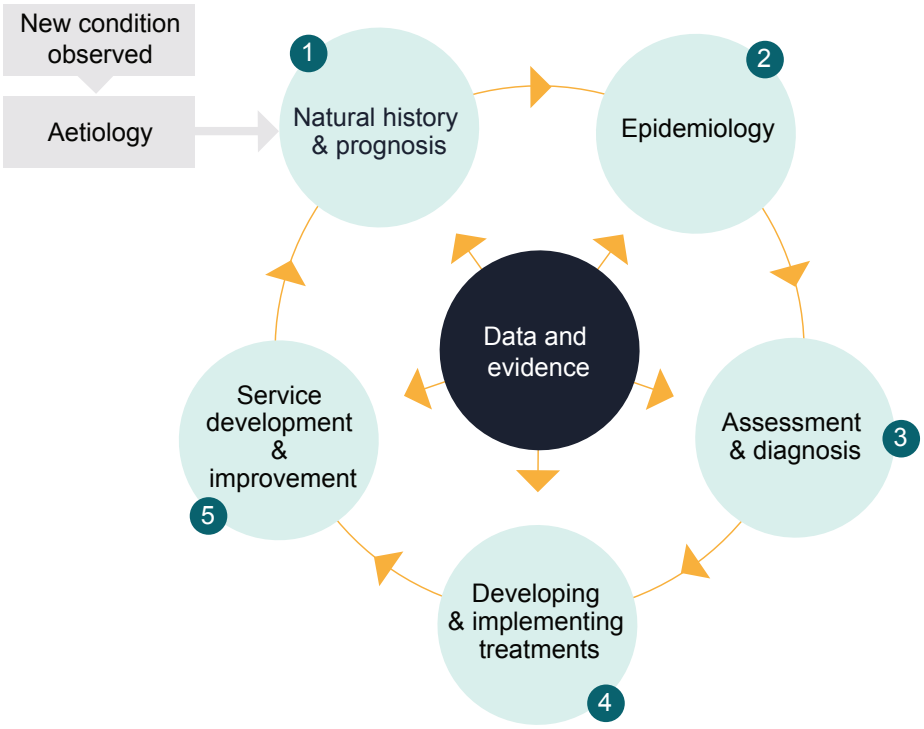
5.2. Some earlier information is necessarily repeated here, but this is with the intention of providing a more accessible explanation of the standards and processes which govern clinical service development. This is essential to an understanding of the rationale for the Review's recommendations.

5.3. Because the specialist service has evolved rapidly and organically in response to demand, the clinical approach and overall service design has not been subjected to some of the normal quality controls that are typically applied when new or innovative treatments are introduced. This Review now affords everyone concerned the opportunity to step back and consider from first principles what this cohort of children and young people now need from NHS services, based on the evidence that exists, or additional evidence that the Review hopes to collect.

5.4. In **Appendix 4** we have described the service development process for three different conditions which may help to illustrate what would be expected to happen at each different stage of developing a clinical service. The steps may proceed in a different sequence for different conditions, but each step is important in the development of evidence based care.

5.5. We recognise that for some of those reading this report it may feel wrong to compare gender incongruence or dysphoria to clinical conditions, and indeed this approach would not be justified if individuals presenting with these conditions did not require clinician intervention. However, where a clinical intervention is given, the same ethical, professional and scientific standards have to be applied as to any other clinical condition.

Key stages of service development



New condition observed: This often begins with a few case reports and then clinicians begin to recognise a recurring pattern and key clinical features, and to develop fuller descriptions of the condition.

Aetiology: Clinicians and scientists try to work out the cause of the condition or the underlying physical or biological basis. Sometimes the answers to this are never found.

Natural history and prognosis: It is important to understand how a condition usually evolves over time, with or without treatment. The latter is important if treatment has limited efficacy and the condition is 'self-limiting' (that is, it resolves without treatment), because otherwise there is a risk that treatments create more difficulties than the condition itself.

5.6. The first UK service for gender-questioning children and young people was established in 1989. At that time there were very few children and young people being seen by medical services internationally. The most common presentation in the early years of the service was of birth-registered

boys who had demonstrated gender incongruence from an early age.[51,52,53]

5.7. There is extensive literature discussing the possible aetiology of gender incongruence. Based on the available evidence, many authors would suggest that it is likely that biological, cultural, social and psychological factors all contribute. The examples in **Appendix 4** show that this is not an uncommon situation; many conditions do not have a single clear causation – they are in other words 'multifactorial'.

5.8. Regardless of aetiology, the more contentious and important question is how fixed or fluid gender incongruence is at different ages and stages of development, and whether, regardless of aetiology, can be an inherent characteristic of the individual concerned. There is a spectrum of academic, clinical and societal opinion on this. At one end are those who believe that gender identity can fluctuate over time and be highly mutable and that, because gender incongruence or gender-related distress may be a response to many psychosocial factors, identity may sometimes change or the distress may resolve in later adolescence or early adulthood, even in those whose early incongruence or distress was quite marked. At the other end are those who believe that gender incongruence or dysphoria in childhood or adolescence is generally a clear indicator of that child or young person being transgender and question the methodology of some of the desistance studies. Previous literature has indicated that if gender incongruence continues into puberty, desistance is unlikely.[54,55] However, it should be noted that these older studies were not based on the current changed case-mix or the different socio-cultural climate of recent years, which may have led to different outcomes. Having an open discussion about these questions is essential if a shared understanding of how to provide appropriate assessment and treatment is to be reached.

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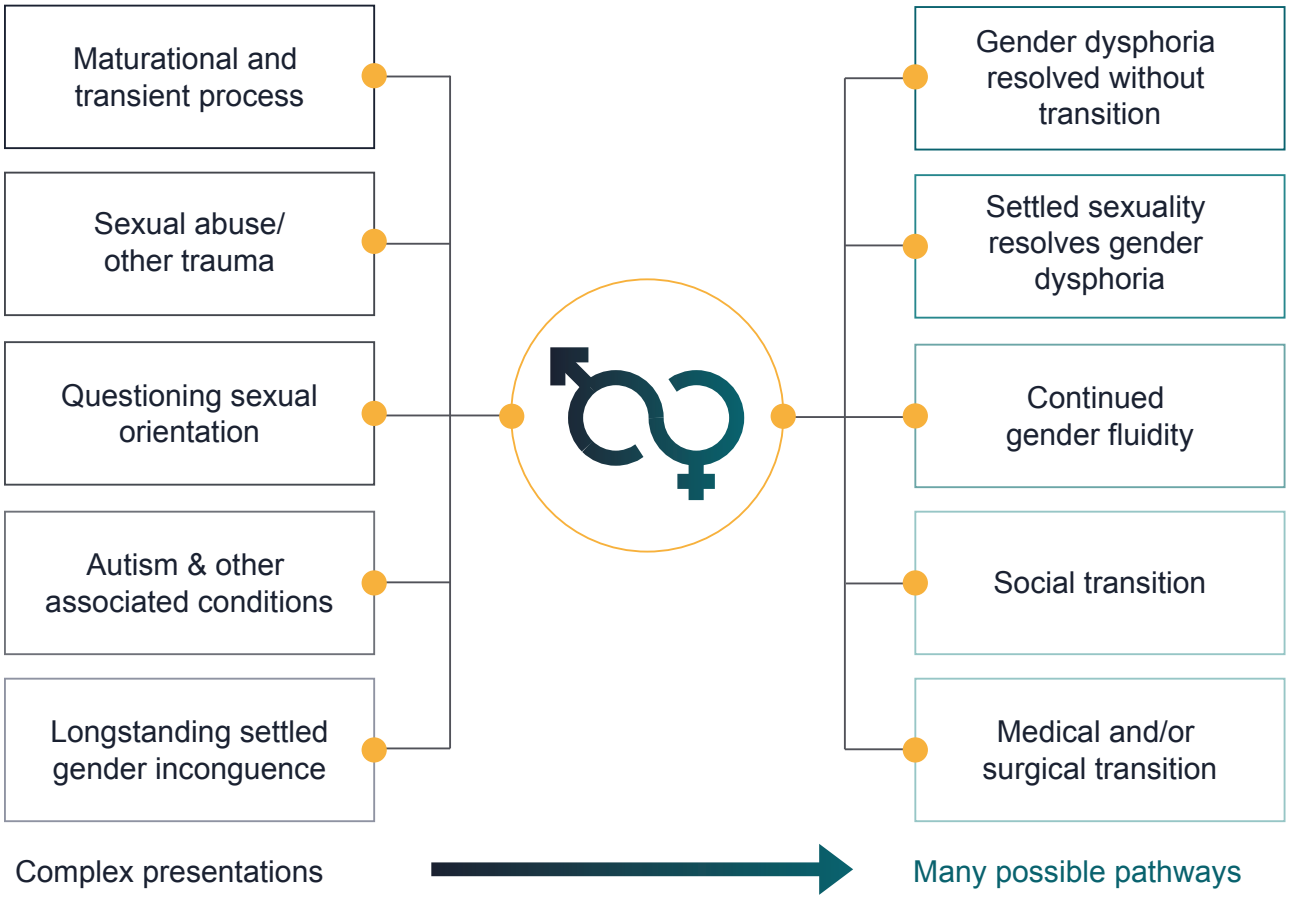
[51] Zucker KJ (2017). Epidemiology of gender dysphoria and transgender identity. Sex Health 14(5): 404–11. DOI:10.1071/SH1.
[52] Zucker KJ, Lawrence AA (2009). Epidemiology of gender identity disorder: recommendations for the Standards of Care of the World Professional Association for Transgender Health. Int J Transgend 11(1): 8-18. DOI: 10.1080/15532730902799946.
[53] de Graaf NM, Giovanardi G, Zitz C, Carmichael P (2018). Sex ratio in children and adolescents referred to the gender identity development service in the UK (2009-2016). Arch Sex Behav 47(5): 1301–4.
[54] Steensma TD, Biemond R, de Boer F, Cohen-Kettenis PT (2011). Desisting and persisting gender dysphoria after childhood: a qualitative follow-up study. Clin Child Psychol Psychiatry 16(4): 485-97. DOI: 10.1177/135910451037803.
[55] Steensma TD, McGuire JK, Kreukels BPC, Beekman AJ, Cohen-Kettenis PT (2013). Factors associated with desistence and persistence of childhood gender dysphoria: a quantitative follow-up study. J Am Acad Child Adolesc Psychiatry 52: 582-590. DOI: 10.1016/j.jaac.2013.03.016.

Complex presentations and complex pathways – exemplars, not comprehensive lists



Epidemiology: Epidemiologists collect data to find out how common a condition is, who is most likely to be affected, what the age distribution is and so on. This allows health service planners to work out how many services are needed, where they should be established, and what staff are needed.

They also report on changes in who is most affected, which may mean that either the disease is changing, or the susceptibility of the population is changing.

5.9. As previously indicated, the epidemiology of gender dysphoria is changing, with an increase in the numbers of birth-registered females presenting in early teens.[56,57] In addition, the majority of children and young people presenting to GIDS have other complex mental health issues and/or neurodiversity.[58] There is also an over-representation of looked after children.[59]

5.10. There are several implications arising from the change in epidemiology:

- Firstly, the speed of change in the numbers presenting means that services have not kept pace with demand.
- Secondly, the cohort that the original Dutch Approach was based on is different from the current more complex NHS cohort, and also from the current case-mix internationally, and therefore it is difficult to extrapolate from older literature to this current group.
- Thirdly, different subgroups may have quite different needs and outcomes, and these must be built into any service design, so that it works for all children and young people.

5.11. At present we have the least information for the largest group of patients – birth-registered females first presenting in early teen years. Since the rapid increase in this group began around 2015, they will not reach late 20s for another 5+ years, which would be the best time to assess longer-term wellbeing.

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[56] Steensma TD, Cohen-Kettenis PT, Zucker KJ (2018). Evidence for a change in the sex ratio of children referred for gender dysphoria: Data from the Center of Expertise on Gender Dysphoria in Amsterdam (1988-2016). Journal of Sex & Marital Therapy 44(7): 713–5. DOI: 10.1080/0092623X.2018.1437580.
[57] de Graaf NM, Carmichael P, Steensma TD, Zucker KJ (2018). Evidence for a change in the sex ratio of children referred for Gender Dysphoria: Data from the Gender Identity Development Service in London (2000–2017). J Sex Med 15(10): 1381–3. DOI: 10.1016/j.jsxm.2018.08.002.
[58] Van Der Miesen AIR, Hurley H, De Vries ALC (2016). Gender dysphoria and autism spectrum disorder: A narrative review. Int Rev Psychiatry 28: 70-80. DOI: 10.3109/09540261.2015.1111199.
[59] Matthews T, Holt V, Sahin S, Taylor A, Griksaitis (2019). Gender Dysphoria in looked-after and adopted young people in a gender identity development service. Clinical Child Psychol Psychiatry 24: 112-128. DOI: 10.1177/1359104518791657.

Assessment and diagnosis: Clinicians will usually take a history from (that is, of their symptoms) and examine the patient (that is, for signs and symptoms), and where appropriate undertake a series of investigations or tests, to help them reach an accurate diagnosis.

Sometimes the whole process of making a diagnosis through talking to the patient and asking them to complete formal questionnaires, examining them and/or undertaking investigations is called 'clinical assessment'.

As well as diagnosing and ruling out a particular condition, clinicians often need to consider and exclude other, sometimes more serious, conditions that present in a similar way but may need quite different treatment – this process is called 'differential diagnosis'.

5.12. For children and young people with gender-related distress, many people would dispute the notion that 'making a diagnosis' is a meaningful concept, arguing that gender identity is a personal, internal perception of oneself. However, there are several reasons to why a diagnostic framework is used:

- Firstly, the clinician will seek to determine whether the child or young person has a stable transgender identity, or whether there might be other causes for the gender-related distress.
- Secondly, the clinician will determine whether there are other issues or diagnoses that might be having an impact on the young person's mental health. The Dutch Approach suggesting that these should be addressed prior to or alongside initiation of any medical treatments.
- Thirdly, in any situation where life-altering treatments are being administered, the clinician holds the responsibility for ensuring that they are being administered based on an appropriate decision making process. Therefore, it is usual practice for a diagnosis of gender dysphoria to be made prior to referring for any physical treatments.

5.13. When the word 'diagnosis' is used, people often associate this with the use of blood tests, X-rays, or other laboratory tests. As set out in the **Appendix 4**, the public is very familiar with diagnosis of Covid-19 and understands that there need to be tests that give a high degree of certainty about whether an individual is Covid-19 positive or not. False positive lateral flow tests are rare, but caused problems for schools, while PCR has been treated as the 'gold standard' test for accuracy.

5.14. When it comes to gender dysphoria, there are no blood tests or other laboratory tests, so assessment and diagnosis in children and young people with gender-related distress is reliant on the judgements of experienced clinicians. Because medical, and subsequently possibly surgical treatments will follow, it may be argued that a highly sensitive and specific assessment process is required. The assessment should be able to accurately identify those children or young people for whom physical intervention is going to be the best course of action, but it is equally important that it identifies those who need an alternative pathway or treatment.

5.15. The formal criteria for diagnosing gender dysphoria (DSM-5) are listed in **Appendix 3**. However, there are two problems associated with the use of these criteria:

- Firstly, several of the criteria are based on gender stereotyping which may not be deemed relevant in current society, although the core criteria remain valid.
- Secondly, and more importantly, these criteria give a basis on which to make a diagnosis that a young person is clinically distressed by the incongruence between their birth-registered and their experienced gender, but they do not help in determining which factors may have led to this distress and how they might best be resolved.

5.16. At present, the assessment process varies considerably, dependent on the perceptions, experience and beliefs of different clinicians. There are some existing measurement tools, but it is suggested that these have substantial limitations.[60]

5.17. The challenges are similar to the early difficulties in diagnosing autism, as set out in **Appendix 4**. As with autism, the framework for assessment needs to become formalised so there are clearer criteria for diagnosis and treatment pathways which are shared more widely. These should incorporate not just whether the child or young person meets DSM-5 criteria for gender dysphoria, but how a broader psychosocial assessment should be conducted and evaluated, and what other factors need to be considered to gain a holistic understanding of the child or young person's experience. Professional judgement and experience will still be important, but if the frameworks and criteria for assessment and diagnosis were more consistent and reproducible, there would be a greater likelihood that two different people seeing the same child or young person would come to the same conclusion. This would also mean that any research on interventions or long-term outcomes would be more reliable because the criteria on which a diagnosis was made, and hence the patients within the sample, would have the same characteristics.

[60] Bloom TM, Nguyen TP, Lami F, Pace CC, Poulakis Z, Telfer N (2021). Measurement tools for gender identity, gender expression, and gender dysphoria in transgender and gender-diverse children and adolescents: a systematic review. Lancet Child Adolescent Health. 5: 582-588. DOI: 10.1016/s2352-4642(21)00098-5.

5.18. As outlined above, it is standard clinical practice to undertake a process called differential diagnosis. This involves summarising the main points of the clinical assessment, the most likely diagnosis, other possible diagnoses and the reasons for including or excluding them, as well as any further assessments that may be required to clarify the diagnosis and the treatment options and plan. This is important when a medical intervention is being provided on the basis of the assessment, so the process is robust, explicit and reproducible. These considerations need to be applied to the assessment of children and young people presenting with gender-related distress. In mental health services, practitioners may also undertake a diagnostic or psychological formulation, which is a holistic summary of how the patient is feeling and why, and how to make sense of it, and a plan for moving forward with management or treatment.

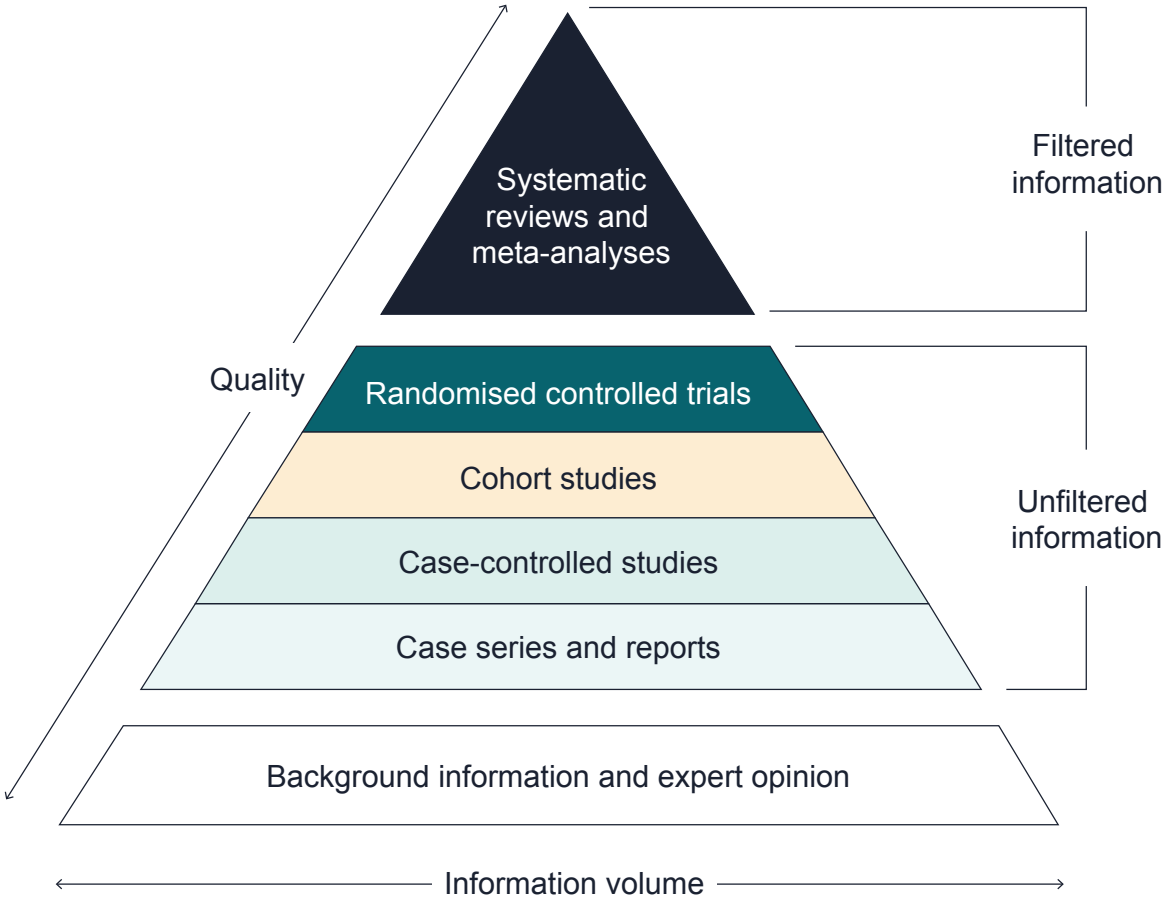
Developing and implementing new treatments: Clinicians and scientists work on developing treatments. This involves clinical trials and, where there are new treatments, comparing them to any existing treatments. Questions include: What are the intended outcomes or benefits of treatment? What are the complications or side effects? What are the costs? To initiate a new treatment, it must be both safe and effective. Questions of affordability can sometimes become controversial.

The best type of single study is considered to be the randomised controlled trial (RCT), but sometimes this is not feasible. Even where RCTs are not available, it is usual to at least have data on the outcomes of sufficient cases or cohorts to understand the risk/benefit of the treatment under consideration. As demonstrated in Fig. 4, the highest level of evidence is when the results of several different studies are pooled, but this is only useful if the individual studies themselves are of high quality.

In many instances, evidence is not perfect and difficult decisions have to be made. Where treatments are innovative or life-changing, the whole multi-disciplinary team will usually meet to consider the available options, and how to advise the child or young person and family so that a shared decision can be made. Sometimes an ethics committee is involved. This is one of the most challenging areas of medicine and is underpinned by GMC guidance.[61,62]

[61] General Medical Council (2020). Decision making and consent.
[62] National Institute for Health and Care Excellence (2021). Shared decision making.

Figure 3: Pyramid of standards of evidence



Source: Levels of evidence pyramid, OpenMD. Reproduced with permission[63]

5.19. There are three types of intervention or treatment for children and young people with gender-related distress, which may be introduced individually or in combination with one another:

- **Social transition** – this may not be thought of as an intervention or treatment, because it is not something that happens within health services. However, it is important to view it as an active intervention because it may have significant effects on the child or young person in terms of their psychological functioning.[64,65] There are different views on the benefits versus the harms of early social transition. Whatever position one

[63] OpenMD (2021). New Evidence in Medical Research.
[64] Sievert EDC, Schweizer K, Barkmann C, Fahrenkrug S, Becker-Hebly I (2020). Not social transition status, but peer relations and family functioning predict psychological functioning in a German clinical sample of children with Gender Dysphoria.Clin Child Psychol Psychiatry 26(1): 79–95. DOI: 10.1177/1359104520964530
[65] Ehrensaft D, Giammattei SV, Storck K, Tishelman AC, Colton K-M (2018). Prepubertal social gender transitions: What we know; what we can learn—A view from a gender affirmative lens. Int J Transgend 19(2): 251–68. DOI: 10.1080/15532739.2017.1414649.

takes, it is important to acknowledge that it is not a neutral act, and better information is needed about outcomes.

- **Counselling, social or psychological interventions** – these may be offered before, instead of, or alongside physical interventions. Again, they should be viewed as active interventions which require robust evaluation in their own right.
- **Physical treatments** – these comprise puberty blockers and feminising/masculinising hormones (administered by endocrinologists) and surgery. The latter is not considered as part of this Review since it is not available to those under age 18.

5.20. It should also be recognised that 'doing nothing' cannot be considered a neutral act.

5.21. The lack of available high-level evidence was reflected in the recent NICE review into the use of puberty blockers and feminising/masculinising hormones commissioned by NHS England, with the evidence being too inconclusive to form the basis of a policy position.[66,67] Assessing treatments for gender dysphoria has many of the same problems as assessing treatment for children with autism – it can take many years to get a full appreciation of outcomes and there may be other complicating factors in the child or young person's life during this period. However, this of itself is not an adequate reason for the major gaps in the international literature.

5.22. It is still common that drugs are not specifically licensed for children because the trials have only taken place on adults. This does not preclude their use or make their use inherently unsafe, particularly if they are used very commonly in children. However, where their use is innovative, patients receiving the drug should ideally do so under trial conditions.

5.23. The same considerations apply to 'off-label' drugs, where the drug is used for a condition different to the one for which it was licensed. This is the case for puberty blockers, which are licensed for use in precocious puberty, but not for puberty suppression in gender dysphoria. Again, it is important that it is not assumed that outcomes for, and side effects in, children treated for precocious puberty will necessarily be the same in children or young people with gender dysphoria.

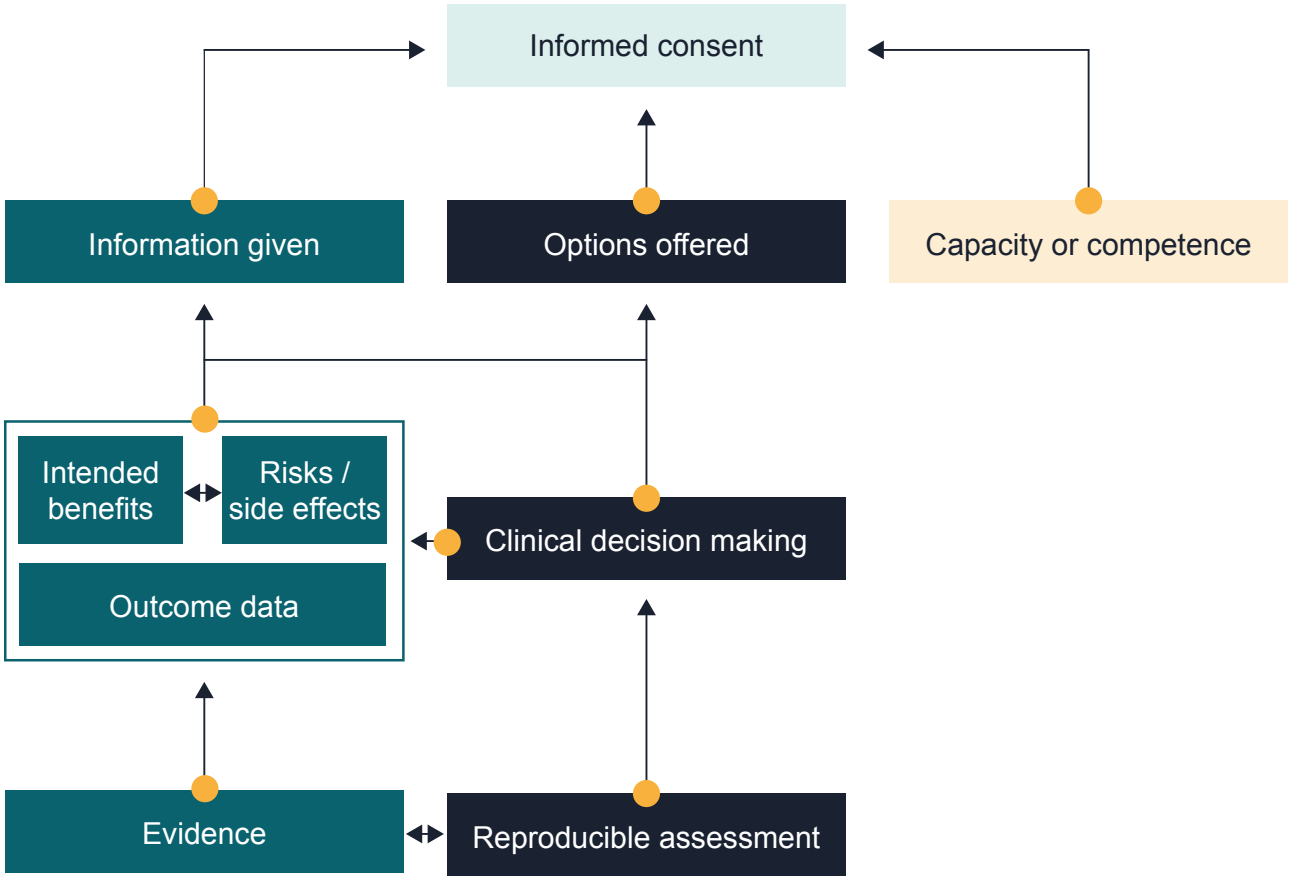
5.24. As outlined above, in other areas of practice where complex or potentially life-altering treatment is being considered for a child or young person, it is usual for the case to be discussed by an MDT including all professionals involved in their care. In gender services for children and young people in the Netherlands, as well as a number of other countries, there are full

[66] National Institute for Health and Care Excellence (2020). Evidence Review: Gonadotrophin Releasing Hormone Analogues for Children and Adolescents with Gender Dysphoria
[67] National Institute for Health and Care Excellence (2020). Evidence review: gender-affirming hormones for children and adolescents with gender dysphoria.

MDT meetings, including psychiatrists and endocrinologists, to make decisions about suitability for hormone intervention and to review progress.[68,69]

5.25. Recent legal proceedings have examined the question of the competence and capacity of children and young people to consent to hormone treatment. However, there are some essential components that underpin informed consent; the robustness of the options offered to the patient, the information provided to them about those options, and their competence and capacity to consider them. The courts have given consideration to competence and capacity, and it is incumbent on this Review to consider the soundness of the decision making which underpins the options offered, and the quality and accuracy of the information provided about those options.

Elements of informed consent



[68] Kyriakou A, Nicolaides NC, Skordis N (2020). Current approach to the clinical care of adolescents with gender dysphoria. Acta Biomed 91(1): 165–75. DOI: 10.23750/abm.v91i1.9244.
[69] Cohen-Kettenis PT, Steensma TD, de Vries ALC. Treatment of adolescents with gender dysphoria in the Netherlands. Child Adolesc Psychiatr Clin N Am 20. 689–700. 2001. DOI: 10.1016/j.chc.2011.08.001.

Service development and service improvement: Central to any service improvement is the systematic and consistent collection of data on outcomes of treatment. There is a process of continuous service improvement as new presentations or variations on the original condition are recognised, diagnosis or screening improves and/or trials on new treatments or variations on existing treatments are ongoing.

There should be consistent treatment protocols or guidelines in place, in order to make sense of variations in outcomes. Where possible, these should be compared between and across multiple different centres.

As time passes, services need to be changed or extended based on patient need, and on what resources are needed to deliver the available treatments. They need to be accessible where the prevalence of the condition is highest. The relevant workforce to deliver the service needs to be recruited and trained, contingent on the type of treatments or therapy that is required.

5.26. When a pioneering treatment or specialist service starts, it is often delivered in a single centre. Thereafter, additional centres take on the work as increasing numbers of patients need to access the treatment. Current provision of NHS specialist gender identity services for children and young people has remained concentrated within a single organisation, but demand has grown dramatically.

5.27. The situation has been exacerbated because there are not many local services seeing gender-questioning children at an earlier stage in their journey, which means that GIDS is carrying an unsustainable workload of increasingly complex young people.

5.28. As a condition evolves, rigorous data collection and quantitative research is an essential prerequisite to refining understanding and treatment. Historically, The Tavistock and Portman NHS Foundation Trust built its international reputation as the home of psychoanalysis, psychotherapy and family therapy, with a strong track record of publishing qualitative rather than quantitative research; consequently its approach to quantitative data collection about this important group of children and young people has been weak.

5.29. A further anomaly is a public perception that The Tavistock and Portman NHS Foundation Trust is the responsible organisation for leading the management of children receiving hormone treatment for their gender dysphoria. In reality, the hormone treatment is delivered by paediatric services in University College London Hospitals NHS Foundation Trust and The Leeds Teaching Hospitals NHS Trust.

5.30. In practice, it is important that for children and young people who need physical intervention, paediatric and mental health services are seen as equal partners, with seamless joint working and shared responsibility. When there were very small numbers of patients, it was easier for this to be achieved, but cross-site working with a very large caseload has made this more difficult to achieve, despite the best intentions of the staff.

5.31. Over the last two years there have been strong efforts on the part of The Tavistock and Portman NHS Foundation Trust to make practice within GIDS more consistent, with tighter procedures for case management, consent, and safeguarding. However, although this has resulted in better documentation, variations and inconsistencies in clinical decision making remain. In responding to a changing legal framework, some processes have become more cumbersome and complex, and the team are working hard to streamline the process.

5.32. Overall, GIDS faces a daunting task as a single provider in managing risk on the waiting list, seeing new referrals, reviewing and supporting those on hormone treatment, undertaking an ongoing transformation programme, recruiting and training new staff and trying to retain existing staff. This suggests that the current model is not sustainable and that another model is needed.

6. Interim advice, research programme and next steps

Dealing with uncertainty

6.1. As outlined throughout this report, there are major gaps in the research base underpinning the clinical management of children and young people with gender incongruence and gender dysphoria, including the appropriate approaches to assessment and treatment.

6.2. As with any other area of medicine, where there are gaps in the evidence base and uncertainties about the correct clinical approach, three tasks must be undertaken:

- Clinical services must be run as safely and effectively as possible, within the constraints of current knowledge; treatment options must be weighed carefully; and treatment decisions must be made in partnership between the clinicians and the children, young people and their families and carers, based on our current understanding about outcomes.
- Consistent data must be collected by clinical services, for both audit and research purposes so that knowledge gaps can be filled, alongside an active research programme.
- Where there is not an immediate prospect of filling research gaps, professional consensus should be developed on the correct way to proceed pending clearer research evidence, supported by input from service users.

6.3. The additional problem with the current service model is that safety and access are further compromised by the pace at which referrals have grown and outstripped capacity at tertiary level, and the lack of service availability at local level.

6.4. The Review's approach to these tasks is as follows:

- Our **interim advice** focuses on the issues of capacity, safety, and standards around treatment decisions, as well as data and audit.
- Our **research streams** will provide the Review with an independent collation of published evidence relevant to epidemiology, clinical management, models of care, and outcomes, as well as delivering qualitative and quantitative research relevant to the Terms of Reference of the Review. This offers a real opportunity to contribute to the international evidence base for this service area.
- There will be an ongoing and wide-ranging **programme of engagement** to address areas on which we will not be able to obtain definitive evidence during the lifetime of the Review.

Interim advice

6.5. The Review considers that there are some areas where there is sufficient clarity about the way forward and we are therefore offering some specific observations and interim advice. The Review will work with NHS England, providers and the broader stakeholder community to progress action in these areas.

Service model

6.6. It has become increasingly clear that a single specialist provider model is not a safe or viable long-term option in view of concerns about lack of peer review and the ability to respond to the increasing demand.

6.7. Additionally, children and young people with gender-related distress have been inadvertently disadvantaged because local services have not felt adequately equipped to see them. It is essential that they can access the same level of psychological and social support as any other child or young person in distress, from their first encounter with the NHS and at every level within the service.

6.8. A fundamentally different service model is needed which is more in line with other paediatric provision, to provide timely and appropriate care for children and young people needing support around their gender identity. This must include support for any other clinical presentations that they may have.

6.9. The Review supports NHS England's plan to establish regional services, and welcomes the move from a single highly specialist service to regional hubs.

6.10. Expanding the number of providers will have the advantages of:

- creating networks within each area to improve early access and support;
- reducing waiting times for specialist care;
- building capacity and training opportunities within the workforce;
- developing a specialist network to ensure peer review and shared standards of care; and
- providing opportunities to establish a more formalised service improvement strategy.

Service provision

6.11. The primary remit of NHS England's proposed model is for the regional hubs to provide support and advice to referrers and professionals. However, it includes limited provision for direct contact with children and young people and their families.

1: The Review advises that the regional centres should be developed, as soon as feasibly possible, to become direct service providers, assessing and treating children and young people who may need specialist care, as part of a wider pathway. The Review team will work with NHS England and stakeholders to further define the proposed model and workforce implications.

2: Each regional centre will need to develop links and work collaboratively with a range of local services within their geography to ensure that appropriate clinical, psychological and social support is made available to children and young people who are in early stages of experiencing gender distress.

3: Clear criteria will be needed for referral to services along the pathway from primary to tertiary care so that gender-questioning children and young people who seek help from the NHS have equitable access to services.

4: Regional training programmes should be run for clinical practitioners at all levels, alongside the online training modules developed by Health Education England (HEE). In the longer-term, clearer mapping of the required workforce, and a series of competency frameworks will need to be developed in collaboration with relevant professional organisations.

Data, audit and research

6.12. A lack of routine and consistent data collection means that it is not possible to accurately track the outcomes and pathways children and young people take through the service. Standardised data collection is required in order to audit service standards and inform understanding of the epidemiology, assessment and treatment of this group. This, alongside a national network which brings providers together, will help build knowledge and improve outcomes through shared clinical standards and systematic data collection. In the longer-term, formalisation of such a network into a learning health system[70] with an academic host would mean that there was systematised use of data to produce a continuing research programme with rapid translation into clinical practice and a focus on training.

5: The regional services should have regular co-ordinated national provider meetings and operate to shared standards and operating procedures with a view to establishing a formal learning health system.

6: Existing and future services should have standardised data collection in order to audit standards and inform understanding of the epidemiology, assessment and treatment of this group of children and young people.

[70] Scobie S, Castle-Clarke S (2019). Implementing learning health systems in the UK NHS: Policy actions to improve collaboration and transparency and support innovation and better use of analytics. Learning Health Systems 4(1): e10209. DOI:10.1002/lrh2.10209.

7: Prospective consent of children and young people should be sought for their data to be used for continuous service development, to track outcomes, and for research purposes. Within this model, children and young people put on hormone treatment should be formally followed up into adult services, ideally as part of an agreed research protocol, to improve outcome data.

Clinical approach

Assessment processes

6.13. We have heard that there are inconsistencies and gaps in the assessment process. Our work to date has also demonstrated that clinical staff have different views about the purpose of assessment and where responsibility lies for different components of the process within the pathway of care. The Review team has commenced discussions with clinical staff across primary, secondary and tertiary care to develop a framework for these processes.

8: There needs to be agreement and guidance about the appropriate clinical assessment processes that should take place at primary, secondary and tertiary level.

9: Assessments should be respectful of the experience of the child or young person and be developmentally informed. Clinicians should remain open and explore the patient's experience and the range of support and treatment options that may best address their needs, including any specific needs of neurodiverse children and young people.

Hormone treatment

6.14. The issues raised by the Multi-Professional Review Group echo several of the problems highlighted by the CQC. It is essential that principles of the General Medical Council's Good Practice in Prescribing and Managing Medicine's and Devices[71] are closely followed, particularly given the gaps in the evidence base regarding hormone treatment. Standards for decision making regarding endocrine treatment should also be consistent with international best practice.[72,73,74]

[71] General Medical Council (2021). Good practice in prescribing and managing medicines and devices (76-78).
[72] Hembree WC, Cohen-Kettenis PT, Gooren L, Hannema SE, Meyer WJ, Murad MH, et al (2017). Endocrine treatment of gender-dysphoric/gender-incongruent persons: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 102(11): 3869–903. DOI: 10.1210/jc.2017-01658.
[73] Cohen-Kettenis PT, Steensma TD, de Vries ALC (2001). Treatment of adolescents with gender dysphoria in the Netherlands. Child Adolesc Psychiatr Clin N Am 20: 689–700. DOI: 10.1016/j.chc.2011.08.001.
[74] Kyriakou A, Nicolaides NC, Skordis N (2020). Current approach to the clinical care of adolescents with gender dysphoria. Acta Biomed 91(1): 165–75. DOI: 10.23750/abm.v91i1.9244.

10: Any child or young person being considered for hormone treatment should have a formal diagnosis and formulation, which addresses the full range of factors affecting their physical, mental, developmental and psychosocial wellbeing. This formulation should then inform what options for support and intervention might be helpful for that child or young person.

11: Currently paediatric endocrinologists have sole responsibility for treatment, but where a life-changing intervention is given there should also be additional medical responsibility for the differential diagnosis leading up to the treatment decision.

6.15. Paediatric endocrinologists develop a wide range of knowledge within their paediatric training, including safeguarding, child mental health, and adolescent development. Being party to the discussions and deliberations that have led up to the decision for medical intervention supports them in carrying out their legal responsibility for consent to treatment and the prescription of hormones.

12: Paediatric endocrinologists should become active partners in the decision making process leading up to referral for hormone treatment by participating in the multidisciplinary team meeting where children being considered for hormone treatment are discussed.

6.16. Given the uncertainties regarding puberty blockers, it is particularly important to demonstrate that consent under this circumstance has been fully informed and to follow GMC guidance[75] by keeping an accurate record of the exchange of information leading to a decision in order to inform their future care and to help explain and justify the clinician's decisions and actions.

13: Within clinical notes, the stated purpose of puberty blockers as explained to the child or young person and parent should be made clear. There should be clear documentation of what information has been provided to each child or young person on likely outcomes and side effects of all hormone treatment, as well as uncertainties about longer-term outcomes.

[75] General Medical Council (2020). Decision making and consent.

14: In the immediate term the Multi-Professional Review Group (MPRG) established by NHS England should continue to review cases being referred by GIDS to endocrine services.

Research programme

6.17. The Review's formal academic research programme, comprising a literature review, quantitative analysis and primary qualitative research, has been based on the identified gaps in the evidence and the feasibility of filling them within the lifetime of the Review.

6.18. Initial work has identified the existing evidence base on epidemiology, natural history, and the treatment and outcomes of children and young people with gender dysphoria/gender-related distress. It has also assessed the feasibility of linking data between local, regional or national datasets in order to assess intermediate and longer-term outcomes.

Literature review

6.19. A literature review is being undertaken, which will interface with evidence gathering from the professional community (see qualitative research section below). Its aim is to systematically identify, collate and synthesise the existing evidence on the changing epidemiology of gender-related distress in children and young people and the appropriate social, clinical, psychological and medical management of that distress.

6.20. The literature review will capture primary studies of any design, including experimental, observational, survey and qualitative, and is looking to answer the following questions:

1. How has the population of children and young people presenting with gender dysphoria and/or gender-related distress changed over time?
2. What are the appropriate referral, assessment and treatment pathways for children and young people with gender dysphoria and/or gender-related distress?
3. What are the short-, medium- and long-term outcomes for children and young people with gender dysphoria and/or gender-related distress?
4. How do children and young people and their families negotiate distress, present this distress to services, and what are their expectations, following presentation?
5. How do children, young people and their families/carers experience referral, assessment and treatment? And how are these negotiated among children and young people, parents/carers, families and healthcare professionals?

6.21. A separate synthesis for each question will be undertaken. The systematic review has been registered on PROSPERO [ID:289659].

Quantitative research

6.22. The National Institute for Health and Care Excellence (NICE) recently published two evidence reviews.[76,77] These highlight shortcomings in the follow-up data collected about children and young people, when they are referred to a specialist gender identity service. The quantitative research will therefore focus on the collection and analysis of data to uncover patterns and quantify problems, thereby helping the Review to address some of these shortcomings.

6.23. The aim of the quantitative study is to supplement the material collected by the literature review, further examining the changing epidemiology of gender-related distress in children and young people, in addition to exploring the appropriate social, clinical, psychological and medical management. Its objectives are to:

a) describe the clinical and demographic characteristics of this population of children and young people and their clinical management in the GIDS service; and

b) assess the intermediate and longer-term outcomes of this population of children and young people utilising national healthcare data.

6.24. This research will provide an evidence base to facilitate informed decision making among children and young people and their families. It will also provide an evidence base for those responsible for commissioning, delivering and managing services.

Qualitative research

6.25. The qualitative research will capture a diverse range of trajectories experienced by gender-questioning children and young people, exploring a range of different experiences and outcomes. This will include talking to children and young people and their families/carers who are currently negotiating gender-related distress, young adults who have gone through the process of resolving their distress and care professionals.

[76] National Institute for Health and Care Excellence (2020). Evidence Review: Gonadotrophin Releasing Hormone Analogues for Children and Adolescents with Gender Dysphoria.
[77] National Institute for Health and Care Excellence (2020). Evidence review: gender-affirming hormones for children and adolescents with gender dysphoria.

The objectives of the qualitative research are to:

1. Explore how children and young people understand, respond and negotiate gender-related distress within the context of their social networks, alongside the perspectives of young adults who experienced gender distress as children.
2. Examine the perspectives, understandings and responses of parents (or carers), including how they support their child.
3. Investigate how children, young people, young adults and their families experience(d) and negotiate(d) referral, assessment and possible treatment and intervention options.
4. Understand the role and experiences of care professionals who offer support, including identifying shared and potentially divergent views among care professionals, children and young people, and parents of what constitutes optimal care.

Progress

6.26. The literature review is already underway and is identifying relevant studies. Initial meetings have also taken place with voluntary organisations and other researchers working in the area to ensure there is no duplication and in recognition of research fatigue among this population.

6.27. Children and young people and young adults who have experienced gender-related distress are involved in the research programme. Their advice has been, and will continue to be, sought throughout this work, including in relation to the focus of the research and interpretation of findings and the design and content of dissemination materials.

6.28. Three research protocols have been produced setting out how the research will be undertaken, and the research team is currently gaining the necessary ethical and governance approvals to progress the study. The systematic review is published on the PROSPERO website and will be published on the Review website in due course, along with the qualitative and quantitative research proposals once ethical and governance approvals have been received.

6.29. The research findings will be subject to peer review through the publication process and various summaries, aimed at different audiences, will be available on the project website and distributed via support organisations. These summaries will also be made available on the Review website.

Ongoing engagement

6.30. In recognition that not all the published evidence is likely to be of high enough quality to form the sole basis for our recommendations, a consensus development approach will be used to synthesise the published evidence and research outputs of the academic work with stakeholder submissions and expert opinion.

6.31. Over the coming months, the Review will build on its engagement to date and, alongside the academic research programme, will continue informal and structured engagement with service users, their families, support and advocacy groups and professionals to test emerging thinking, provide opportunities for challenge and further develop the evidence base.

6.32. This review is an iterative process and we will share important findings when they become available. For the latest updates, please visit our website: https://cass.independent-review.uk/

6.33. We thank those who have participated in the Review to date and welcome engagement with us as work progresses towards final recommendations.

Glossary

Glossary

There is sometimes no consensus on the best language to use relating to this subject. The language surrounding this area has also changed rapidly and young people have developed varied ways of describing their experiences using different terms and constructs that are relevant to them.

The Review tries as far as possible to use language and terms that are respectful and acknowledge diversity, but that also accurately illustrate the complexity of what we are trying to describe and articulate.

The terms we have used may not always feel right to some; nevertheless, it is important to emphasise that the language used is not an indication of a position being taken by the Review. The glossary below sets out a description of some of the terms we have used in the Review.

Term		Description
Affirmative model		A model of gender healthcare that originated in the USA[78,79,80,81] which affirms a young person's subjective gender experience while remaining open to fluidity and changes over time. This approach is used in some key child and adolescent clinics across the Western world.
Assent		To agree to or approve of something (idea, plan or request), especially after thoughtful consideration.
Autonomy		Personal autonomy is the ability of a person to make their own decisions. In health this refers specifically to decisions about their care.

[78] Hidalgo MA, Ehrensaft D, Tishelman AC, Clark LF, Garofalo R, Rosenthal SM, et al (2013). The gender affirmative model: What we know and what we aim to learn [Editorial]. Human Dev 56(5): 285–290. DOI:10.1159/000355235.
[79] Chen D, Abrams M, Clark L, Ehrensaft D, Tishelman AC, Chan YM, et al (2021). Psychosocial characteristics of transgender youth seeking gender-affirming medical treatment: baseline findings from the trans youth care study. J Adol Health 68(6): 1104–11.
[80] Olson-Kennedy J, Chan YM, Rosenthal S, Hidalgo MA, Chen D, Clark L, et al (2019). Creating the Trans Youth Research Network: A collaborative research endeavor. Transgend Health 4(12): 304–12. DOI: 10.1089/trgh.2019.0024.
[81] Ehrensaft D, Giammattei SV, Storck K, Tishelman AC, Colton K-M (2018). Prepubertal social gender transitions: What we know; what we can learn—A view from a gender affirmative lens. Int J Transgend 19(2): 251–68. DOI: 10.1080/15532739.2017.1414649.

Term		Description
Best interests		Clinicians and the courts seek to act in the best interests of children and young people. For the Mental Capacity Act (MCA) 2005, decisions for someone who cannot decide for themselves must be made in their best interests. Under the Children Act 1989, in any decision of the court about a child (under 18), the welfare of the child must be paramount. For these purposes, there is little or no material difference between the welfare and best interests, and we have used "best interests" throughout the report. Although there is no standard definition of "best interests of the child," the General Medical Council advises that an assessment of best interests will include what is clinically indicated as well as additional factors such as the child or young person's views, the views of parents and others close to the child or young person and cultural, religious and other beliefs and values of the child or young person.[82]
		The MCA s4,[83] and extensive Court of Protection case law, deals with the approach to best interests under that legislation. Whether in the Court of Protection or the High Court, when the court is asked to make an assessment of a child or young person's best interests, it will consider their welfare/best interests in the widest sense. This will include not just medical factors but also social and psychological factors.
Case-mix		The mix of patients within a particular group.
Child and adolescent mental health services	CAMHS	NHS children and young people's mental health services.[84]

[82] General Medical Council (2018). 0-18 years – guidance for all doctors.
[83] Mental Health Law Online. MCA 2005 s4.
[84] Young Minds. Guide to CAMHS: a guide for young people.

Term		Description
Child and/or young person		In law, everyone under 18 years of age is a child (Children Act 1989) but we recognise that it may be more appropriate to refer to those approaching the age of 18 as a young person, and that such young people may not recognise themselves as a "child". In places, we have referred only to "young person", or only to "child", for example where treatment in question is only given towards the later stages of childhood, closer to the age of 18, or in reference to the parent/child relationship, in which they remain the parents' child, regardless of their age. Otherwise, we have used the phrase "child and/or young person" throughout the report for this reason only, and do not intend there to be a material difference between them other than that.
Cognitive		Relating to, or involving, the process of thinking and reasoning.
Consent		Permission for a clinical intervention (such as an examination, test or treatment) to happen. For consent to be 'informed', information must be disclosed to the person about relevant risks, benefits and alternatives (including the option to take no action), and efforts made to ensure that the information is understood. In legal terms, consent is seen as needing: 1 – capacity (or *Gillick* competence under 16) to make the relevant decision; 2 – to be fully informed (ie the information provided about the available options, the material risks and benefits of each option, and of doing nothing, "material" meaning (per the Montgomery Supreme Court judgment in 2015) what a reasonable patient would want to know, and what this patient actually wants to know, NOT what a reasonable doctor would tell them); and 3 – to be freely given (that is,without coercion).
Contraindications		A condition or circumstance that suggests or indicates that a particular technique or drug should not be used in the case in question.

Term		Description
Court of Appeal		(England and Wales) The Court of Appeal hears appeals against both civil and criminal judgments from the Crown Courts, High Court and County Court. It is second only to the Supreme Court.
Detransition/ detransitioners		Population of individuals who experienced gender dysphoria, chose to undergo medical and/or surgical transition and then detransitioned by discontinuing medications, having surgery to reverse the effects of transition, or both.[85]
Diagnostic and Statistical Manual of Mental Disorders Fifth edition	DSM-5	The American diagnostic manual used to diagnose mental health disorders, and commonly used in UK practice. See **Appendix 3**.
Diagnostic formulation		The comprehensive assessment that includes a patient's history, results of psychological tests, and diagnosis of mental health difficulties.
Divisional Court		(England and Wales) When the High Court of Justice of England and Wales hears a case with at least two judges sitting, it is referred to as the Divisional Court. This is typically the case for certain judicial review cases (as well as some criminal cases).
Dutch Approach		Protocol published in 1998 by the Amsterdam child and adolescent gender identity clinic.[86]
Endocrine treatment		In relation to this clinical area, this term is used to describe the use of gonadotropin-releasing hormones (see below) and feminising and masculinising hormones (see below).
Endocrinologist		An endocrinologist is a medical doctor specialising in diagnosing and treating disorders relating to problems with the body's hormones.
Endocrinology		The study of hormones.

[85] Littman L (2021). Individuals treated for gender dysphoria with medical and/or surgical transition who subsequently detransitioned: a survey of 100 detransitioners. Arch Sex Abuse 50: 3353–69. DOI: 10.1007/s10508-021-02163-w

[86] de Vries ALC, Cohen-Kettenis PT (2012). Clinical management of gender dysphoria in children and adolescents: The Dutch approach. J Homosex 59: 301-320. DOI: 10.1080/00918369.2012.653300.

Term		Description
Epidemiology		Epidemiology is the study of the distribution and determinants of health-related states or events in specified populations, and the application of this study to the control of health problems.[87]
Exploratory approaches		Therapeutic approaches that acknowledge the young person's subjective gender experience, whilst also engaging in an open, curious, non-directive exploration of the meaning of a range of experiences that may connect to gender and broader self-identity.[88,89,90,91]
Feminising and masculinising hormones (also known as cross-sex hormones, and gender affirming hormones).		Hormones given as part of a medical transition for gender dysphoric individuals, where sex hormones (testosterone for transgender males and oestrogen for transgender females).
Gender dysphoria		Diagnostic term used in DSM-5.[92] Gender dysphoria describes "a marked incongruence between one's experienced/expressed gender and assigned gender of at least 6 months duration" which must be manifested by a number of criterion – see **Appendix 3** for further detail.
Gender fluid		An experience of gender that is not fixed, but changes between two or more identities.
Gender identity		This term is used to describe an individual's internal sense of being male or female or something else.
Gender identity development		The developmental experience of a child or young person in seeking to understand their gender identity over time.
Gender Identity Development Service	GIDS	The service that NHS England commissions for children and adolescents with gender dysphoria.

[87] Centers for Disease Control and Prevention (2012). Principles of Epidemiology in Public Health Practice: An introduction to Applied Epidemiology and Biostatistics, 3rd ed.
[88] Di Ceglie D (2009). Engaging young people with atypical gender identity development in therapeutic work: A developmental approach. J Child Psychother 35(1): 3–12. DOI: 10.1080/00754170902764868.
[89] Spiliadis A (2019). Towards a gender exploratory model: Slowing things down, opening things up and exploring identity development. Metalogos Systemic Ther J 35: 1–9.
[90] Churcher Clarke A, Spiliadis A (2019). 'Taking the lid off the box': The value of extended clinical assessment for adolescents presenting with gender identity difficulties. Clin Child Psychol Psychiatry 24(2): 338–52. DOI:10.1177/1359104518825288.
[91] Bonfatto M, Crasnow E (2018). Gender/ed identities: an overview of our current work as child psychotherapists in the Gender Identity Development Service. J Child Psychother 44(1): 29–46. DOI:10.1080/007541 7X.2018.1443150.
[92] American Psychiatric Association (2013). Diagnostic and Statistical Manual of Mental Health Disorders: DSM-5™, 5th ed.

Term		Description
Gender incongruence		Diagnostic term used in ICD-11.[93] Gender incongruence is characterised by "a marked and persistent incongruence between an individual's experienced gender and the assigned sex". See **Appendix 3** for further detail.
Gender-questioning		A broader term that might describe children and young people who are in a process of working out how they want to present in relation to their gender.
Gender-related distress		A way of describing distress that may arise from a broad range of experiences connected to a child or young person's gender identity development. Often used for young people whereby any formal diagnosis of gender dysphoria has not yet been made.
Gillick competence/ Fraser guidelines		A term derived from *Gillick v West Norfolk And Wisbech AHA*, 1984 that is used to decide whether a child or young person up to the age of 16 years is able to consent to their own medical treatment, without the need for parental permission or knowledge. A child or young person will be 'Gillick competent' for that decision if they have the necessary maturity and understanding to make the decision.
Gonadotropin-releasing hormone analogues (also known as the hormone blocker/s and puberty blocker/s)	GnRH	GnRH analogues competitively block GnRH receptors to prevent the spontaneous release of two gonadotropin hormones, Follicular Stimulating Hormone (FSH) and Luteinising Hormone (LH) from the pituitary gland. This arrests the progress of puberty.
General Practitioner	GP	GPs deal with a whole range of health problems and manage the care of their patients, referring onto specialists as appropriate.[94]
High Court		The third highest court in the UK. It deals with all high value and high importance civil law (non-criminal) cases and appeals of decisions made in lower courts. When the High Court sits with more than one judge, as required for certain kinds of cases, it is called the Divisional Court.
International Classification of Diseases, Version 11	ICD-11	ICD-11[95] is the World Health Organization (WHO) mandated health data standard used for medical diagnosis.

[93] World Health Organization (2022). International Classification of Diseases Eleventh Revision.
[94] NHS. GP services.
[95] World Health Organization (2022). International Classification of Diseases Eleventh Revision.

Term		Description
Looked after children		Children who are in the care of their Local Authority who may be living with foster parents or in a residential care setting.
Multi-disciplinary-team	MDT	The identified group of professional staff who provide a clinical service.
Neurodiverse		Displaying or characterised by autistic or other neurologically atypical patterns of thought or behaviour; not neurotypical.
Non-binary		A gender identity that does not fit into the traditional gender binary of male and female.[96]
Paediatrics		The branch of medicine dealing with children and their medical conditions.
Pass/passing		A person's gender being seen and read in the way they identify.
Precocious puberty		This is when a child's body begins changing into that of an adult (puberty) too soon – before age 8 in girls and before age 9 in boys.
Primary care		Primary care includes general practice, community pharmacy, dental and optometry (eye health) services. This tends to be the first point of access to healthcare.
Psychological formulation		A structured approach to understanding the factors underlying distressing states in a way that informs the changes needed and the therapeutic intervention for these changes to occur.
Psychosocial		Describes the psychological and social factors that encompass broader wellbeing.
Puberty blockers		See gonadotropin-releasing hormone above.
Secondary care		Hospital and community health care services that do not provide specialist care and are usually relatively close to the patient. For children this will include Child and Adolescent Mental Health Services (CAMHS), child development and general paediatric services.
Tanner Stage		Classification of puberty by stage of development. This ranges from Stage 1, before physical signs of puberty appear, to Stage 5 at full maturity.

[96] Twist J, de Graaf NM (2019). Gender diversity and non-binary presentations in young people attending the United Kingdom's National Gender Identity Development Service. Clin Child Psychol Psychiatry 24(2): 277–90. DOI: 10.1177/1359104518804311.

Term		Description
Tertiary care		Tertiary care is the specialist end of the NHS. These services relate to complex or rare conditions. Services are usually delivered in a number of hospitals/centres.
Transgender	trans	This is an umbrella term that includes a range of people whose gender identity is different from the sex they were registered at birth.
Transition		These are the steps a person may take to live in the gender in which they identify. This may involve different things, such as changing elements of social presentation and role and/or medical intervention for some.

Appendix 1

Terms of reference

TERMS OF REFERENCE FOR REVIEW OF GENDER IDENTITY DEVELOPMENT SERVICE FOR CHILDREN AND ADOLESCENTS

INTRODUCTION

1. NHS England is the responsible commissioner for specialised gender identity services for children and adolescents. The Gender Identity Development Service for children and adolescents is currently managed by the Tavistock and Portman NHS Foundation Trust.

2. In recent years there has been a significant increase in the number of referrals to the Gender Identity Development Service, and this has occurred at a time when the service has moved from a psychosocial and psychotherapeutic model to one that also prescribes medical interventions by way of hormone drugs. This has contributed to growing interest in how the NHS should most appropriately assess, diagnose and care for children and young people who present with gender incongruence and gender identity issues.

3. It is in this context that NHS England and NHS Improvement's Quality and Innovation Committee has asked Dr Hilary Cass to chair an independent review, and to make recommendations on how to improve services for children and young people experiencing issues with their gender identity or gender incongruence, and ensure that the best model/s for safe and effective services are commissioned.

REVIEW SCOPE

The independent review, led by Dr Cass, will be wide ranging in scope and will conduct extensive engagement with all interested stakeholders. The review is expected to set out findings and make recommendations in relation to:

i. Pathways of care into local services, including clinical management approaches for individuals with less complex expressions of gender incongruence who do not need specialist gender identity services;
ii. Pathways of care into specialist gender identity services, including referral criteria into a specialist gender identity service; and referral criteria into other appropriate specialist services;
iii. Clinical models and clinical management approaches at each point of the specialised pathway of care from assessment to discharge, including a description of objectives, expected benefits and expected outcomes for each clinical intervention in the pathway;
iv. Best clinical approach for individuals with other complex presentations.
v. The use of gonadotropin-releasing hormone analogues and gender affirming drugs, supported by a review of the available evidence by the National Institute for Health and Care Excellence; any treatment recommendations will include a description of treatment objectives, expected benefits and expected outcomes, and potential risks, harms and effects to the individual;
vi. Ongoing clinical audit, long term follow-up, data reporting and future research priorities;
vii. Current and future workforce requirements;
viii. Exploration of the reasons for the increase in referrals and why the increase has disproportionately been of natal females, and the implications of these matters; and,

TERMS OF REFERENCE FOR REVIEW OF GENDER IDENTITY DEVELOPMENT SERVICE FOR CHILDREN AND ADOLESCENTS

ix. Any other relevant matters that arise during the course of the review

4. In addition, and with support from the Royal College of Paediatrics and Child Health and other relevant professional associations, the Chair will review current clinical practice concerning individuals referred to the specialist endocrine service. It is expected that findings and any recommendations on this aspect of the review will be reported early in 2021 with the review's wider findings and recommendations delivered later in 2021.

5. The review will not immediately consider issues around informed consent as these are the subject of an ongoing judicial review. However, any implications that might arise from the legal ruling could be considered by the review if appropriate or necessary.

Appendix 2

Letter to NHS England from Dr Cass – May 2021

The Cass Review
Independent review into gender identity services for children and young people

Dr Hilary Cass
Chair
Review of GIDS for Children and Young People

John Stewart
National Director
Specialised Commissioning
NHS England and NHS Improvement

Sent by email

10 May 2021

Dear John

INDEPENDENT REVIEW INTO GENDER IDENTITY SERVICES FOR CHILDREN AND YOUNG PEOPLE

I am writing to update you on my current approach to the work of the independent review into gender identity services for children and young people. However, the most pressing issue is how we augment the immediate support for children and young people currently needing assessment and treatment, some of whom have already been waiting for an extended period for an appointment. I will therefore also make some suggestions about interim arrangements and ways in which the review team could help to support and strengthen these.

Commissioned research programme

As you know, a key principle of the review is that it should be evidence-based, and that final conclusions will be developed through a consensus development process contingent on the synthesised evidence.

I am pleased to see that the National Institute for Health and Care Excellence (NICE) evidence reviews of gonadotrophin releasing hormone analogues and gender affirming hormones for children and adolescents with gender dysphoria have now been published. Although this is a helpful starting point, despite following a standard and robust process the NICE review findings are not conclusive enough to inform policy decisions. As part of my review, I am therefore exploring other methodologies to give increased confidence and clarity about the optimal treatment approaches.

My team is commissioning a broader literature review of the existing evidence base on the epidemiology, management and outcomes of children with gender dysphoria. We are also commissioning qualitative and quantitative research, including considering other approaches which might be employed to understand the intermediate and longer-term outcomes of children with gender dysphoria. We intend to include a review of international models and data in this programme of work.

Addressing the immediate situation

Recognising that the outcome of the review is going to take some time, I have been reflecting on the recent court rulings on puberty blockers and consent and the Care Quality Commission (CQC) report on the Gender Identity Development Service (GIDS) run by the Tavistock and Portman NHS Foundation Trust. These significant developments have changed the context in which the review is taking place, and further added to the service pressures.

I note the proposal to establish an independent multidisciplinary professional review group to confirm decision-making has followed a robust process, which seems an appropriate interim measure pending further clarification of the legal situation.

I know that everyone concerned with the delivery of services – both commissioners and providers – are worried about the increasing number of children on the waiting list for assessment by the GIDS service and the resulting distress for the children and young people and their families. The difficulty in managing risk for those on the waiting list is exacerbated by the staff vacancies at GIDS, the increasing volume of new referrals, and the fact that the support and engagement from local services is highly variable and, in some cases, very limited.

Having a single provider may have been a logical position when the GIDS service was first set up, given that this is a highly specialised service that was seeing a relatively small number of cases each year. As the epidemiology has changed and there has been an exponential increase in numbers of children with gender incongruence or dysphoria, concentration of expertise within a single service has become unsustainable. At the same time, local services have not developed the skills and competencies to provide support for children on the waiting list and those with lesser degrees of gender incongruence who may not wish to pursue specialist medical intervention, and / or to provide help for children with additional complex needs.

I know from discussions we have had that your team is working hard to find some practical alternative arrangements, and that you have been in discussion with relevant professional bodies to come up with creative interim solutions while awaiting the outcome of my review.

The review team has also been in discussion with CQC, with the Tavistock and Portman NHS Foundation Trust and with colleagues within and external to NHS England and NHS Improvement to consider which aspects of this situation we can help with in the short to medium term, whilst keeping our focus on the longer-term questions of the appropriate clinical management and whole care pathway for these children and young people. In the past months I have also met with many groups and individuals with expertise and lived experience relevant to the review, including charities and support groups, Royal Colleges and healthcare professionals.

Recommendations to NHS England and NHS Improvement

I would encourage you to consider the following when developing an interim pathway for children and young people experiencing gender dysphoria:

- **Access and referral:** Children and young people need ready access to services. However, it is unusual for a specialist service to take direct referrals. The risk of having a national service as the first point of access is that assessment and treatment of children and young people who have the greatest need for specialist care is delayed because of the lack of differentiation of those on the waiting list. In addition, many children and

young people have complex needs, but once they are identified as having gender dysphoria, other important healthcare issues which would normally be managed by local services can sometimes be overlooked.

- **Assessment and management:** All children and young people who are referred to specialist services should have a competent local multi-disciplinary assessment and should remain under active holistic local management until they are seen at a specialist centre.

  I recognise that developing capacity and capability outside of the existing GIDS service to provide such initial assessment and support will be difficult to achieve at speed and will be incremental. This means that there will likely be a range of different models and options around the country, dependent on local resources, with some of the work being delivered through existing secondary service teams, and some being delivered at regional level. The support of wider services is vital.

- **Data:** The lack of systematic data collection is a significant issue. Therefore, when employing interim measures, I would suggest that particular attention is paid to the gathering of good quality data, which can then be used to inform the evidence base and future model of provision.

Actions for the review team

I would like to suggest how the review team might help with the challenging problem of growing an infrastructure outside of GIDS. From my conversations to date, I believe there are three barriers to the involvement of local services:

- **Capacity** – the staff most appropriately trained to be involved in initial assessment are those who are already most stretched within Child and Adolescent Mental Health Services (CAMHS) and paediatric services, and this situation has been significantly worsened through the impact of the Covid-19 pandemic on children's mental health. However, I know that there is substantial investment in CAMHS services, so close engagement with the relevant national policy teams at NHS England and NHS Improvement and at Health Education England (HEE) will be crucial.

- **Capability and confidence** – clinical teams outside of GIDS do not feel confident in initial assessment and support of children and young people with gender incongruence and dysphoria, in large part because they have not had the necessary training and experience, but also because of the societal polarisation and tensions surrounding the management of this group.

- **Lack of an explicit assessment framework** – currently expertise in assessment of children and young people presenting to GIDS is held in a small body of clinicians and their assessment processes have not been made explicit. The CQC report drew attention to the lack of structured assessment in the GIDS notes, and this is something that the Tavistock and Portman NHS Foundation Trust is already working to address internally. However, it is equally important to develop an initial assessment approach that can be used by first contact professionals, not just those working in the specialist service.

In the first instance, it is important that we test these assumptions with a range of clinical staff and ascertain whether there are other barriers that are preventing local engagement in this work. Then we would plan to prioritise a series of workshops, in collaboration with relevant professional groups, service users and close engagement with HEE. The purpose of these workshops would be to address identified barriers and develop:

- A framework for initial assessment of children and young people presenting with gender dysphoria.

- An approach to training for professionals at local and regional level.

- Some preliminary workforce recommendations, which will be particularly important in meeting the timelines of the three-year Comprehensive Spending Review.

These workshops will serve multiple purposes – firstly to support NHS England and NHS Improvement in the establishment of local and / or regional teams; secondly as an essential component of the work needed to inform the questions that the review is tackling; and thirdly to form the professional networks that will be needed to underpin future service and research networks.

Timelines

As you will recognise, setting up a complex national review is difficult and time consuming at the best of times. It requires a team to support the work and mechanisms for stakeholders to engage safely and with confidence. Starting a review in the midst of a pandemic is even more challenging.

I have committed to a review approach which is participative, consensus-based, evidence-based, transparent, and informed by lived and professional experience. This requires extensive engagement. Pending the appointment of our research team, the review has now launched its website and I have been proactively engaging with the stakeholder community.

It is critical that we get the approach right, particularly the engagement, the evidence review and the quantitative research given the gaps in the evidence highlighted through the NICE review, and this will take time.

My intention is that an interim report will be delivered in the summer, with a report next year setting out my final recommendations.

Yours sincerely

Dr Hilary Cass
Chair, Independent Review into Gender Identity Services for Children and Young People

Cc: Care Quality Commission
Health Education England
Tavistock and Portman NHS Foundation Trust

Appendix 3

Diagnostic criteria for gender dysphoria

DSM-5 diagnostic criteria for gender dysphoria

Gender Dysphoria in Children

A. A marked incongruence between one's experienced/expressed gender and assigned gender, of at least 6 months' duration, as manifested by at least six of the following (one of which must be Criterion A1):

1. A strong desire to be of the other gender or an insistence that one is the other gender (or some alternative gender different from one's assigned gender).
2. In boys (assigned gender), a strong preference for cross-dressing or simulating female attire; or in girls (assigned gender), a strong preference for wearing only typical masculine clothing and a strong resistance to the wearing of typical feminine clothing.
3. A strong preference for cross-gender roles in make-believe play or fantasy play.
4. A strong preference for the toys, games, or activities stereotypically used or engaged in by the other gender.
5. A strong preference for playmates of the other gender.
6. In boys (assigned gender), a strong rejection of typically masculine toys, games, and activities and a strong avoidance of rough-and-tumble play; or in girls (assigned gender), a strong rejection of typically feminine toys, games, and activities.
7. A strong dislike of one's sexual anatomy.
8. A strong desire for the primary and/or secondary sex characteristics that match one's experienced gender.

B. The condition is associated with clinically significant distress or impairment in social, school, or other important areas of functioning.

Specify if:

With a disorder of sex development (e.g., a congenital adrenogenital disorder such as congenital adrenal hyperplasia or androgen insensitivity syndrome).

Gender Dysphoria in Adolescents and Adults

A. A marked incongruence between one's experienced/expressed gender and assigned gender, of at least 6 months' duration, as manifested by at least two of the following:

1. A marked incongruence between one's experienced/expressed gender and primary and/or secondary sex characteristics (or in young adolescents, the anticipated secondary sex characteristics).
2. A strong desire to be rid of one's primary and/or secondary sex characteristics because of a marked incongruence with one's experienced/expressed gender (or in young adolescents, a desire to prevent the development of the anticipated secondary sex characteristics).

3. A strong desire for the primary and/or secondary sex characteristics of the other gender.
4. A strong desire to be of the other gender (or some alternative gender different from one's assigned gender).
5. A strong desire to be treated as the other gender (or some alternative gender different from one's assigned gender).
6. A strong conviction that one has the typical feelings and reactions of the other gender (or some alternative gender different from one's assigned gender).

B. The condition is associated with clinically significant distress or impairment in social, occupational, or other important areas of functioning.

Specify if:

With a disorder of sex development (e.g., a congenital adrenogenital disorder such as congenital adrenal hyperplasia or androgen insensitivity syndrome).

Specify if:

Post transition: the individual has transitioned to full-time living in the desired gender (with or without legalization of gender change) and has undergone (or is preparing to have) at least one cross-sex medical procedure or treatment regimen – namely, regular cross-sex hormone treatment or gender reassignment surgery confirming the desired gender (e.g., penectomy, vaginoplasty in a natal male; mastectomy or phalloplasty in a natal female).

ICD-11: HA60 Gender incongruence of adolescence or adulthood

Gender Incongruence of Adolescence and Adulthood is characterised by a marked and persistent incongruence between an individual´s experienced gender and the assigned sex, which often leads to a desire to 'transition', in order to live and be accepted as a person of the experienced gender, through hormonal treatment, surgery or other health care services to make the individual´s body align, as much as desired and to the extent possible, with the experienced gender. The diagnosis cannot be assigned prior the onset of puberty. Gender variant behaviour and preferences alone are not a basis for assigning the diagnosis.

Exclusions:

Paraphilic disorders.

ICD-11: HA61 Gender incongruence of childhood

Gender incongruence of childhood is characterised by a marked incongruence between an individual's experienced/expressed gender and the assigned sex in pre-pubertal children. It includes a strong desire to be a different gender than the assigned sex; a strong dislike on the child's part of his or her sexual anatomy or anticipated secondary sex characteristics and/or a strong desire for the primary and/or anticipated secondary sex characteristics that match the experienced gender; and make-believe or fantasy play, toys, games, or activities and playmates that are typical of the experienced gender rather than the assigned sex. The incongruence must have persisted for about 2 years. Gender variant behaviour and preferences alone are not a basis for assigning the diagnosis.

Exclusions:

Paraphilic disorders.

Appendix 4

The standard approach to clinical service development

The standard approach to clinical service development

The three examples below illustrate the usual process of developing a clinical service: Covid-19 is included because this is a new condition that everyone is familiar with; childhood epilepsy because it is a complex condition with physical manifestations; and autism because it is a condition with neuro-behavioural manifestations.

By comparing these examples of clinical service development, it is possible to demonstrate some of the challenges in developing services for children and young people with gender incongruence or dysphoria, and to identify where there are gaps and questions that need to be addressed for this population, in order to ensure any future service model delivers the highest possible standards of care.

The stages below may proceed in a different sequence for different conditions, but each stage is important in the development of evidence based care.

Stage	Covid-19	Childhood Epilepsy	Autism
New condition is observed This often begins with a few case reports and then clinicians begin to recognise a recurring pattern and key clinical features, and to develop fuller descriptions of the condition.	Covid-19 is an example of a recent new condition that we all recognise, and this started with a few unusual cases of respiratory illness being described in Wuhan.	Childhood epilepsy has been recognised for centuries, but over the last century there has been growing understanding of the many different subtypes.	Individuals with autism have probably also existed for an indefinite period, but it wasn't until 1943 and 1944 that Leo Kanner and Hans Asperger wrote the first scientific accounts about the condition.

Stage	Covid-19	Childhood Epilepsy	Autism
Aetiology Clinicians and scientists try to work out the cause of the condition or the underlying physical or biological basis. Sometimes the answers to this are never found.	The cause of Covid-19 was identified at a very early stage as being due to a novel coronavirus, although it remains unclear where and how this originated.	It is now known that there are numerous different types of epilepsy, with many different causes – for example, epilepsy can be caused by specific epilepsy genes, by birth trauma, by metabolic conditions, by brain tumours and many other mechanisms. Epilepsies due to a change in the brain structure which occur after birth are called 'symptomatic' – they are a symptom of something else. Epilepsies for which there is no identified cause are called 'idiopathic'.	The first theory about the aetiology of autism was that it was caused by so called 'refrigerator parents'. This was inaccurate and damaging. It has subsequently been shown that there are many complex genetic and physical or chemical brain changes underpinning this condition.
Natural history and prognosis It is important to understand how a condition usually evolves over time, with or without treatment. The latter is important if treatment has limited efficacy and the condition is 'self-limiting' (that is, it resolves without treatment), because otherwise there is a risk that treatments create more difficulties than the condition itself.	Covid-19 is an example of a condition where there are quite polarised views about management based on its prognosis and natural history. A relatively small proportion of people are seriously affected and need treatment, and for the majority the natural history is that it will get better by itself. This has led some people to question the need for lockdowns, vaccinations and other measures which they see as impacting personal freedoms.	In epilepsy the natural history is very important. Some epilepsies get better through puberty and into adulthood, and some can get worse with hormonal changes. This is important to know when monitoring and reviewing drug treatment.	

Stage	Covid-19	Childhood Epilepsy	Autism
Epidemiology Epidemiologists collect data to find out how common a condition is, who is most likely to be affected, what the age distribution is and so on. This allows health service planners to work out how many services are needed, where they should be established, and what staff are needed. They also report on changes in who is most affected, which may mean that either the disease is changing, or the susceptibility of the population is changing.	Epidemiologists have been crucial in supporting the management of Covid-19 because they have extracted and analysed the data on which patients are at greater risk from the virus. This has been fundamental to planning a vaccination strategy and other protective measures.		The epidemiology of autism has changed considerably, with a dramatic increase in the numbers of children diagnosed over the last 20 years. This has had major implications for service provision. There is ongoing debate about the cause of the increase – whether it is because of greater awareness and better diagnosis, or because there are more children with autism. Current opinion favours the first option.

Stage	Covid-19	Childhood Epilepsy	Autism
Assessment and diagnosis Clinicians will usually take a history from (that is, of their symptoms) and examine the patient (that is, for signs and symptoms), and where appropriate undertake a series of investigations or tests, to help them reach an accurate diagnosis. Sometimes the whole process of making a diagnosis through talking to the patient and asking them to complete formal questionnaires, examining them and/or undertaking investigations is called 'clinical assessment'. As well as diagnosing and ruling out a particular condition, clinicians often need to consider and exclude other, sometimes more serious, conditions that present in a similar way but may need quite different treatment – this process is called 'differential diagnosis'.	PCR has been used as a 'gold standard' test for diagnosis of Covid-19 since the beginning of the pandemic. Lateral flow testing was developed to provide a quicker and cheaper option, but it demonstrates the limitations of testing; it is 99.68% specific, which is a very high specificity. This means there are only a tiny number of false positives. It has lower sensitivity at 76.8%, which means it will miss about a quarter of all cases, so giving many more false negatives, BUT it will only miss 5% of cases with high viral load.	Epilepsy can only be definitively diagnosed by either getting a really clear description of the events from a parent or carer, or seeing the child or young person having a seizure on a video. An EEG (brain wave tracing) and other tests can provide information about the type of epilepsy, but unless a seizure happens during the recording, it does not demonstrate that they actually have seizures – only that they may be susceptible to seizures.	In autism there are no blood tests or X-rays to make the diagnosis. It is a 'clinical' diagnosis, which means it is dependent on taking a standardised history from the parents, and performing standardised assessments on the child or young person to distinguish between autism and other possible diagnoses (for example, language disorder, social anxiety). In the early days, these standardised measures did not exist; the diagnosis was very dependent on experts who were used to diagnosing autism by making a clinical judgement about each child. This made it difficult to teach new people how to do this without a long apprenticeship, and also made it difficult to know whether two different experts would come to the same conclusion about the same child or young person. Standardisation of the questions and process made diagnosis more reliable and consistent, as did an improved evidence base. At the same time, because children with autism all present differently, the assessment had to be flexible enough to accommodate, for example, non-verbal children with severe learning disability, as well as high-functioning children with strong verbal skills.

Stage	Covid-19	Childhood Epilepsy	Autism
Differential diagnosis As well as making a positive diagnosis, clinicians often need to exclude other, sometimes more serious conditions that present in a similar way, but may need quite different treatment.		There are conditions that can be mistaken for epilepsy, so it is important to accurately diagnose whether seizures are happening and exclude other conditions (differential diagnoses) by carrying out relevant tests.	There are many conditions that may be mistaken for autism – for example, children who have language disorders, learning disability, severe social anxiety for other reasons, or ADHD can all appear to have autism. It is important to exclude these other conditions as well as making a positive diagnosis of autism. Sometimes these conditions can exist alongside autism, and management must then be planned to address all the child's difficulties.

Stage	Covid-19	Childhood Epilepsy	Autism
Developing and implementing new treatments Clinicians and scientists work on developing treatments. This involves clinical trials and, where there are new treatments, comparing them to any existing treatments. Questions include: What are the intended outcomes or benefits of treatment? What are the complications or side effects? What are the costs? To initiate a new treatment, it must be both safe and effective. Questions of affordability can sometimes become controversial. The best type of single study is considered to be the randomised controlled trial (RCT), but sometimes this is not feasible. Even where RCTs are not available, it is usual to at least have data on the outcomes of sufficient cases or cohorts to understand the risk/benefit of the treatment under consideration. As demonstrated in Fig. 3, the highest level of evidence is when the results of several different studies are pooled, but this is only useful if the individual studies themselves are of high quality.	Developing treatments for Covid-19 has been possible at speed because of the large numbers of patients, and the fact that outcomes can be observed on each patient within a matter of days to weeks. Because Covid-19 was a new condition, clinicians also started in a position of 'equipoise' which means that they did not have reason to believe any one treatment might be more effective than another; this made it ethical to have one group having a treatment and another group having a different treatment or a placebo. There are also really clear outcome measures, such as whether or not patients survive or need hospitalisation. This has facilitated a high level of evidence through randomised controlled trials (see diagram below).	Similar considerations apply to the treatment of epilepsy in that there are 'hard' outcome measures (for example, frequency of seizures), but it can take several months to determine whether a new drug is better than an existing one for any one patient, and some side effects may be longer-term, so trials can take several years. In addition, children with epilepsy may have very different conditions causing their seizures which can also make trials more challenging. In the most severe cases of epilepsy, surgery may be the best option for controlling seizures. This can be very radical in certain cases and have lifelong implications for how they function. These options, which have a cost as well as a benefit to the child, will only be offered after a multi-disciplinary team meeting, including the paediatricians, therapists, neuropsychologists, radiologists, neurophysiologists and neurosurgeons have all discussed whether the benefits will outweigh the costs.	Evaluating interventions for autism is the most difficult of these three examples. This is because it can take many years to see developmental outcomes; it is hard to get uniform groups of children; outcomes are extremely sensitive to the social (and historical) response of others; and many other things happen in children's lives (such as changes of school, other medications, new diets). Isolating the effect of the target treatment is therefore challenging.

Stage	Covid-19	Childhood Epilepsy	Autism
In many instances, evidence is not perfect and difficult decisions have to be made. Where treatments are innovative or life-changing, the whole multi-disciplinary team will usually meet to consider the available options, and how to advise the child or young person and family so that a shared decision can be made. Sometimes an ethics committee is involved. This is one of the most challenging areas of medicine and is underpinned by GMC guidance.[97, 98]	The UK has been internationally recognised for its Recovery Trial, led by Oxford University. This has recruited over 46,000 participants, and resulted in several treatments being approved. A key factor in this success was the willingness of patients to participate in these studies – with over 46,000 being recruited and consented.		

[97] General Medical Council (2020). Decision making and consent.
[98] National Institute for Health and Care Excellence (2021). Shared decision making.

Stage	Covid-19	Childhood Epilepsy	Autism
Service development and service improvement Central to any service improvement is the systematic and consistent collection of data on outcomes of treatment. There is a process of continuous service improvement as new presentations or variations on the original condition are recognised, diagnosis or screening improves and/or trials on new treatments or variations on existing treatments are ongoing. There should be consistent treatment protocols or guidelines in place, in order to make sense of variations in outcomes. Where possible, these should be compared between and across multiple different centres. As time passes, services need to be changed or extended based on patient need, and on what resources are needed to deliver the available treatments. They need to be accessible where the prevalence of the condition is highest. The relevant workforce to deliver the service needs to be recruited and trained, contingent on the type of treatments or therapy that is required.	Service development to manage Covid-19 has been on a scale unlike any normal new service development ever experienced. It has also demonstrated how other non-Covid services have had to evolve alongside, including the need for isolation, and/or PCR testing prior to routine clinical appointments, use of remote consultation and an array of other changes across the NHS. Continuous audit and monitoring of outcomes has resulted in major improvements in survival – for example, changing ventilation approach to include 'proning' (putting patients on their front while on the ventilator) and delaying fully intubated ventilation by giving mask ventilation for as long as possible.	Paediatric epilepsy is a good example of how a national approach can be taken to service improvement through the Epilepy12 programme.[99] This is a nationally co-ordinated audit which collects a standardised dataset, incorporating NICE standards, and is used to drive up standards of care for children and young people with epilepsy.	Improvement in autism services has been driven by the changing epidemiology, NICE standards, extensive training of the workforce and attempts to improve public understanding. Where previously diagnosis was undertaken in a few specialist centres, the rising waiting times and NICE standards on access, assessment and appropriate multi-professional provision have led to almost every community child development service having an autism assessment clinic or team. Services are able to self-assess against national standards to inform local improvement strategies.

[99] Royal College of Paediatrics and Child Health (2021). Epilepsy 12 – national organisational audit and clinical audit.

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Evidence review: Gonadotrophin releasing hormone analogues for children and adolescents with gender dysphoria

This document will help inform Dr Hilary Cass' independent review into gender identity services for children and young people. It was commissioned by NHS England and Improvement who commissioned the Cass review. It aims to assess the evidence for the clinical effectiveness, safety and cost-effectiveness of gonadotrophin releasing hormone (GnRH) analogues for children and adolescents aged 18 years or under with gender dysphoria.

The document was prepared by NICE in October 2020.

The content of this evidence review was up to date on 14 October 2020. See summaries of product characteristics (SPCs), British National Formulary (BNF) or the Medicines and Healthcare products Regulatory Agency (MHRA) or NICE websites for up-to-date information.

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1. Introduction

This review aims to assess the evidence for the clinical effectiveness, safety and cost-effectiveness of gonadotrophin releasing hormone (GnRH) analogues for children and adolescents aged 18 years or under with gender dysphoria. The review follows the NHS England Specialised Commissioning process and template and is based on the criteria outlined in the PICO framework (see appendix A). This document will help inform Dr Hilary Cass' independent review into gender identity services for children and young people.

Gender dysphoria in children, also known as gender identity disorder or gender incongruence of childhood (World Health Organisation 2020), refers to discomfort or distress that is caused by a discrepancy between a person's gender identity (how they see themselves[1] regarding their gender) and that person's sex assigned at birth and the associated gender role, and/or primary and secondary sex characteristics (Diagnostic and Statistical Manual of Mental Disorders 2013).

GnRH analogues suppress puberty by delaying the development of secondary sexual characteristics. The intention is to alleviate the distress associated with the development of secondary sex characteristics, thereby providing a time for on-going discussion and exploration of gender identity before deciding whether to take less reversible steps. In England, the GnRH analogue triptorelin (a synthetic decapeptide analogue of natural GnRH, which has marketing authorisations for the treatment of prostate cancer, endometriosis and precocious puberty [onset before 8 years in girls and 10 years in boys]) is used for this purpose. The use of triptorelin for children and adolescents with gender dysphoria is off-label.

For children and adolescents with gender dysphoria it is recommended that management plans are tailored to the needs of the individual, and aim to ameliorate the potentially negative impact of gender dysphoria on general developmental processes, support young people and their families in managing the uncertainties inherent in gender identity development and provide on-going opportunities for exploration of gender identity. The plans may also include psychological support and exploration and, for some individuals, the use of GnRH analogues in adolescence to suppress puberty; this may be followed later with gender-affirming hormones of the desired sex (NHS England 2013).

2. Executive summary of the review

Nine observational studies were included in the evidence review. Five studies were retrospective observational studies (Brik et al. 2020, Joseph et al. 2019, Khatchadourian et al. 2014, Klink et al. 2015, Vlot et al. 2017), 3 studies were prospective longitudinal observational studies (Costa et al. 2015, de Vries et al. 2011, Schagen et al. 2016) and 1 study was a cross-sectional study (Staphorsius et al. 2015). Two studies (Costa et al. 2015

[1] Gender refers to the roles, behaviours, activities, attributes and opportunities that any society considers appropriate for girls and boys, and women and men (World Health Organisation, Health Topics: Gender).

and Staphorsius et al. 2015) provided comparative evidence and the remaining 7 studies used within-person, before and after comparisons.

The terminology used in this topic area is continually evolving and is different depending on stakeholder perspectives. In this evidence review we have used the phrase 'people's assigned sex at birth' rather than natal or biological sex, gonadotrophin releasing hormone (GnRH) analogues rather than 'puberty blockers' and gender-affirming hormones rather than 'cross sex hormones'. The research studies included in this evidence review may use historical terms which are no longer considered appropriate.

In children and adolescents with gender dysphoria, what is the clinical effectiveness of treatment with GnRH analogues compared with one or a combination of psychological support, social transitioning to the desired gender or no intervention?

Critical outcomes

The critical outcomes for decision making are the impact on gender dysphoria, mental health and quality of life. The quality of evidence for these outcomes was assessed as very low certainty using modified GRADE.

Impact on gender dysphoria
The study by de Vries et al. 2011 in 70 adolescents with gender dysphoria found that treatment with GnRH analogues before starting gender-affirming hormones does not affect gender dysphoria (measured using the Utrecht Gender Dysphoria Scale [UGDS]). The mean (±SD) gender dysphoria (UGDS) score was not statistically significantly different at baseline compared with follow-up (n=41, 53.20 [±7.91] versus 53.9 [±17.42], p=0.333).

Impact on mental health
The study by de Vries et al. 2011 in 70 adolescents with gender dysphoria found that treatment with GnRH analogues before starting gender-affirming hormones may reduce depression (measured using the Beck Depression Inventory-II [BDI-II]). The mean [±SD] BDI score was statistically significantly lower (improved) from baseline compared with follow-up (n=41, 8.31 [±7.12] versus 4.95 [±6.72], p=0.004).

The study by de Vries et al. 2011 in 70 adolescents with gender dysphoria found that treatment with GnRH analogues before starting gender-affirming hormones does not affect anger (measured using the Trait Anger Scale [TPI]). The mean [±SD] anger (TPI) score was not statistically significantly different at baseline compared with follow-up (n=41, 18.29 [±5.54] versus 17.88 [±5.24], p=0.503).

The study by de Vries et al. 2011 in 70 adolescents with gender dysphoria found that treatment with GnRH analogues before starting gender-affirming hormones does not affect anxiety (measured using the Trait Anxiety Scale [STAI]). The mean [±SD] anxiety (STAI) score was not statistically significantly different at baseline compared with follow-up (n=41, 39.43 [±10.07] versus 37.95 [±9.38], p=0.276).

Impact on quality of life
No evidence was identified.

Important outcomes

The important outcomes for decision making are impact on body image, psychosocial impact, engagement with health care services, impact on extent of and satisfaction with surgery and stopping treatment. The quality of evidence for all these outcomes was assessed as very low certainty using modified GRADE.

Impact on body image
The study by de Vries et al. 2011 in 70 adolescents with gender dysphoria found that treatment with GnRH analogues before starting gender-affirming hormones does not affect body image (measured using the Body Image Scale [BIS]). The mean [±SD] body image (BIS) scores were not statistically significantly different from baseline compared with follow-up for primary sexual characteristics (n=57, 4.10 [±0.56] versus 3.98 [±0.71], p=0.145), secondary sexual characteristics (n=57, 2.74 [±0.65] versus 2.82 [±0.68], p=0.569) or neutral body characteristics (n=57, 2.41 [±0.63] versus 2.47 [±0.56], p=0.620).

Psychosocial impact
The study by de Vries et al. 2011 in 70 adolescents with gender dysphoria found that treatment with GnRH analogues before starting gender-affirming hormones may improve psychosocial impact over time (measured using the Children's Global Assessment Scale [CGAS]). The mean [±SD] CGAS score was statistically significantly higher (improved) from baseline compared with follow-up (n=41, 70.24 [±10.12] versus 73.90 [±9.63], p=0.005).

This study also found that psychosocial functioning may improve over time (measured using the Child Behaviour Checklist [CBCL] and the self-administered Youth Self-Report [YSR]). The mean [±SD] CBCL scores were statistically significantly lower (improved) from baseline compared with follow-up for Total T score (n=54, 60.70 [±12.76] versus 54.46 [±11.23], p<0.001), internalising T score (n=54, 61.00 [±12.21] versus 52.17 [±9.81], p<0.001) and externalising T score (n=54, 58.04 [±12.99] versus 53.81 [±11.86], p=0.001). The mean [±SD] YSR scores were statistically significantly lower (improved) from baseline compared with follow-up for Total T score (n=54, 55.46 [±11.56] versus 50.00 [±10.56], p<0.001), internalising T score (n=54, 56.04 [±12.49] versus 49.78 [±11.63], p<0.001) and externalising T score (n=54, 53.30 [±11.87] versus 49.98 [±9.35], p=0.009). The proportion of adolescents scoring in the clinical range decreased from baseline to follow up on the CBCL total problem scale (44.4% versus 22.2%, p=0.001) and the internalising scale of the YSR (29.6% versus 11.1%, p=0.017).

The study by Costa et al. 2015 in 201 adolescents with gender dysphoria who had 6 months of psychological support followed by either GnRH analogues and continued psychological support or continued psychological support only, found that during treatment with GnRH analogues psychosocial impact in terms of global functioning may improve over time (measured using the CGAS). In the group receiving GnRH analogues, the mean [±SD] CGAS score was statistically significantly higher (improved) after 6 months (n=60, 64.70 [±13.34]) and 12 months (n=35, 67.40 [±13.39]) compared with baseline (n=101, 58.72 [±11.38], p=0.003 and p<0.001, respectively). However, there was no statistically significant difference in global functioning (CGAS scores) between the group receiving GnRH analogues plus psychological support and the group receiving psychological support only at any time point.

The study by Staphorsius et al. 2015 in 40 adolescents with gender dysphoria (20 of whom were receiving GnRH analogues) gave mean [±SD] CBCL scores for each group, but statistical analysis is unclear (transfemales receiving GnRH analogues 57.4 [±9.8], transfemales not receiving GnRH analogues 58.2 [±9.3], transmales receiving GnRH analogues 57.5 [±9.4], transmales not receiving GnRH analogues 63.9 [±10.5]).

Engagement with health care services

The study by Brik et al. 2018 in 143 children and adolescents with gender dysphoria receiving GnRH analogues found that 9 adolescents in the original sampling frame (9/214, 4.2%) were excluded from the study because they stopped attending appointments.

The study by Costa et al. 2015 in 201 adolescents with gender dysphoria who had 6 months of psychological support followed by either GnRH analogues and continued psychological support or continued psychological support only had a large loss to follow-up over time. The sample size at baseline and 6 months was 201, which dropped by 39.8% to 121 after 12 months and by 64.7% to 71 at 18 months follow-up. No explanation of the reasons for loss to follow-up are reported.

Impact on extent of and satisfaction with surgery

No evidence was identified.

Stopping treatment

The study by Brik et al. 2018 in 143 children and adolescents with gender dysphoria receiving GnRH analogues reported the reasons for stopping GnRH analogues. During the follow-up period 6.2% (9/143) of adolescents had stopped GnRH analogues after a median duration of 0.8 years (range 0.1 to 3.0). Five adolescents stopped treatment because they no longer wished to receive gender-affirming treatment for various reasons. In 4 adolescents (all transmales), GnRH analogues were stopped mainly because of adverse effects (such as mood and emotional lability), although they wanted to continue treatments for gender dysphoria.

The study by Khatchadourian et al. 2014 in 27 adolescents with gender dysphoria who started GnRH analogues reported the reasons for stopping them. Eleven out of 26 where data was available (42%) stopped GnRH analogues during follow up.

In children and adolescents with gender dysphoria, what is the short-term and long-term safety of GnRH analogues compared with one or a combination of psychological support, social transitioning to the desired gender or no intervention?

Evidence was available for bone density, cognitive development or functioning, and other safety outcomes. The quality of evidence for all these outcomes was assessed as very low certainty using modified GRADE.

Bone density

The study by Joseph et al. 2019 in 70 adolescents with gender dysphoria found that GnRH analogues may reduce the expected increase in lumbar or femoral bone density (measured with the z-score). However, the z-scores were largely within 1 standard deviation of normal,

and actual lumbar or femoral bone density values were not statistically significantly different between baseline and follow-up:

- The mean z-score [±SD] for lumbar bone mineral apparent density (BMAD) was statistically significantly lower at 1 year compared with baseline in transfemales (baseline 0.859 [±0.154], 1 year −0.228 [±1.027], p=0.000) and transmales (baseline −0.186 [±1.230], 1 year −0.541 [±1.396], p=0.006).
- The mean z-score [±SD] for lumbar BMAD was statistically significantly lower after receiving GnRH analogues for 2 years compared with baseline in transfemales (baseline 0.486 [±0.809], 2 years −0.279 [±0.930], p=0.000) and transmales (baseline −0.361 [±1.439], 2 years −0.913 [±1.318], p=0.001).
- The mean z-score [±SD] for femoral neck bone mineral density (BMD) was statistically significantly lower after receiving GnRH analogues for 2 years compared with baseline in transfemales (baseline 0.0450 [±0.781], 2 years −0.600 [±1.059], p=0.002) and transmales (baseline −1.075 [±1.145], 2 years −1.779 [±0.816], p=0.001).

The study by Klink et al. 2015 in 34 adolescents with gender dysphoria found that GnRH analogues may reduce the expected increase in lumbar (transmales only), but not femoral bone density. However, the z-scores are largely within 1 standard deviation of normal. Actual lumbar or femoral bone density values were not statistically significantly different between baseline and follow-up (apart from BMD measurements in transmales):

- The mean z-score [±SD] for lumbar BMAD was not statistically significantly different between starting GnRH analogues and starting gender-affirming hormones in transfemales, but was statistically significantly lower when starting gender-affirming hormones in transmales (GnRH analogues 0.28 [±0.90], gender-affirming hormones −0.50 [±0.81], p=0.004).

The study by Vlot et al. 2017 in 70 adolescents with gender dysphoria found that GnRH analogues may reduce the expected increase in lumbar or femoral bone density. However, the z-scores were largely within 1 standard deviation of normal. Actual lumbar or femoral bone density values were not statistically significantly different between baseline and follow-up (apart from in transmales with a bone age ≥14 years). This study reported change in bone density from starting GnRH analogues to starting gender-affirming hormones by bone age:

- The median z-score [range] for lumbar BMAD in transfemales with a bone age of <15 years was statistically significantly lower at starting gender-affirming hormones than at starting GnRH analogues (GnRH analogues −0.20 [−1.82 to 1.18], gender-affirming hormones −1.52 [−2.36 to 0.42], p=0.001) but was not statistically significantly different in transfemales with a bone age ≥15 years.
- The median z-score [range] for lumbar BMAD in transmales with a bone age of <14 years was statistically significantly lower at starting gender-affirming hormones than at starting GnRH analogues (GnRH analogues −0.05 [−0.78 to 2.94], gender-affirming hormones −0.84 [−2.20 to 0.87], p=0.003) and in transmales with a bone age ≥14 years (GnRH analogues 0.27 [−1.60 to 1.80], gender-affirming hormones −0.29 [−2.28 to 0.90], p≤0.0001).

- The median z-score [range] for femoral neck BMAD in transfemales with a bone age of <15 years was not statistically significantly lower at starting gender-affirming hormones than at starting GnRH analogues (GnRH analogues −0.71 [−3.35 to 0.37], gender-affirming hormones −1.32 [−3.39 to 0.21], p≤0.1) or in transfemales with a bone age ≥15 years (GnRH analogues −0.44 [−1.37 to 0.93], gender-affirming hormones −0.36 [−1.50 to 0.46]).
- The z-score for femoral neck BMAD in transmales with a bone age of <14 years was not statistically significantly lower at starting gender-affirming hormones than at starting GnRH analogues (GnRH analogues −0.01 [−1.30 to 0.91], gender-affirming hormone −0.37 [−2.28 to 0.47]) but was statistically significantly lower in transmales with a bone age ≥14 years (GnRH analogues 0.27 [−1.39 to 1.32], gender-affirming hormones −0.27 [−1.91 to 1.29], p=0.002).

Cognitive development or functioning

The study by Staphorsius et al. 2015 in 40 adolescents with gender dysphoria (20 of whom were receiving GnRH analogues) measured cognitive development or functioning (using an IQ test, and reaction time and accuracy measured using the Tower of London task):

- The mean (±SD) IQ in transfemales receiving GnRH analogues was 94.0 (±10.3) and 109.4 (±21.2) in the control group. In transmales receiving GnRH analogues the mean (±SD) IQ was 95.8 (±15.6) and 98.5 (±15.9) in the control group.
- The mean (±SD) reaction time in transfemales receiving GnRH analogues was 10.9 (±4.1) and 9.9 (±3.1) in the control group. In transmales receiving GnRH analogue it was 9.9 (±3.1) and 10.0 (±2.0) in the control group.
- The mean (±SD) accuracy score in transfemales receiving GnRH analogues was 73.9 (±9.1) and 83.4 (±9.5) in the control group. In transmales receiving GnRH analogues it was 85.7 (±10.5) and 88.8 (±9.7) in the control group.

No statistical analyses or interpretation of the results was reported.

Other safety outcomes

The study by Schagen et al. 2016 in 116 adolescents with gender dysphoria found that GnRH analogues do not affect renal or liver function:

- There was no statistically significant difference between baseline and 1 year results for serum creatinine in transfemales, but there was a statistically significant decrease between baseline and 1 year in transmales (p=0.01).
- Glutamyl transferase, alanine aminotransferase (ALT), and aspartate aminotransferase (AST) levels did not significantly change from baseline to 12 months of treatment.

The study by Khatchadourian et al. 2014 in 27 adolescents with gender dysphoria who started GnRH analogues narratively reported adverse effects from GnRH analogues in 26 adolescents:

- 1 transmale developed sterile abscesses; they were switched from leuprolide acetate to triptorelin, and this was well tolerated
- 1 transmale developed leg pains and headaches, which eventually resolved
- 1 participant gained 19 kg within 9 months of starting GnRH analogues.

In children and adolescents with gender dysphoria, what is the cost-effectiveness of GnRH analogues compared to one or a combination of psychological support, social transitioning to the desired gender or no intervention?

No cost-effectiveness evidence was found for GnRH analogues in children and adolescents with gender dysphoria.

From the evidence selected, are there any subgroups of children and adolescents with gender dysphoria that may benefit from GnRH analogues more than the wider population of interest?

Some studies reported data separately for the following subgroups of children and adolescents with gender dysphoria: sex assigned at birth males (transfemales) and sex assigned at birth females (transmales). This included some direct comparisons of these subgroups, and differences were largely seen at baseline as well as follow up. No evidence was found for other specified subgroups.

Sex assigned at birth males (transfemales)
Impact on gender dysphoria
The study by Costa et al. 2015 in 201 adolescents with gender dysphoria who had 6 months of psychological support followed by either GnRH analogues and continued psychological support or continued psychological support only, found that gender dysphoria (measured using the UGDS) in sex assigned at birth males is lower than in sex assigned at birth females. Sex assigned at birth males had a statistically significantly lower (improved) mean [±SD] UGDS score of 51.6 [±9.7] compared with sex assigned at birth females (56.1 [±4.3], p<0.001), but it was not reported if this was at baseline or follow-up.

The study by de Vries et al. 2011 in 70 adolescents with gender dysphoria found that gender dysphoria (measured using the UGDS) in sex assigned at birth males is lower than in sex assigned at birth females at baseline and follow up. The mean [±SD] UGDS score was statistically significantly lower (improved) in sex assigned at birth males compared with sex assigned at birth females at baseline (n=not reported, mean UGDS score: 47.95 [±9.70] versus 56.57 [±3.89]) and follow up (n=not reported, 49.67 [±9.47] versus 56.62 [±4.00]); between sex difference p<0.001).

Impact on mental health
The study by de Vries et al. 2011 in 70 adolescents with gender dysphoria found that the impact on mental health (depression, anger and anxiety) may be different in sex assigned at birth males compared with sex assigned at birth females. Over time there was no statistically significant difference between sex assigned at birth males and sex assigned at birth females for depression, but sex assigned at birth males had statistically significantly lower levels of anger and anxiety than sex assigned at birth females at baseline and follow up.

- The mean [±SD] depression (BDI-II) score was not statistically significantly different in sex assigned at birth males compared with sex assigned at birth females at baseline (n=not reported, mean BDI score [±SD]: 5.71 [±4.31] versus 10.34 [±8.24]) and follow-up (n=not reported, 3.50 [±4.58] versus 6.09 [±7.93]), between sex difference p=0.057
- The mean [±SD] anger (TPI) score was statistically significantly lower (improved) in sex assigned at birth males compared with sex assigned at birth females at baseline (n=not reported, mean TPI score [±SD]: 5.22 [±2.76] versus 6.43 [±2.78]) and follow-

up (n=not reported, 5.00 [±3.07] versus 6.39 [±2.59]), between sex difference p=0.022
- The mean [±SD] anxiety (STAI) score was statistically significantly lower (improved) in sex assigned at birth males compared with sex assigned at birth females at baseline (n=not reported, mean STAI score [±SD]: 4.33 [±2.68] versus 7.00 [±2.36]) and follow-up (n=not reported, 4.39 [±2.64] versus 6.17 [±2.69]), between sex difference p<0.001.

Impact on body image

The study by de Vries et al. 2011 in 70 adolescents with gender dysphoria found that the impact on body image may be different in sex assigned at birth males compared with sex assigned at birth females. Sex assigned at birth males are less dissatisfied with their primary and secondary sex characteristics than sex assigned at birth females at both baseline and follow up, but the satisfaction with neutral body characteristics is not different.

- The mean [±SD] BIS score for primary sex characteristics was statistically significantly lower (improved) in sex assigned at birth males compared with sex assigned at birth females at baseline (n=not reported, mean BIS score [±SD]: 4.02 [±0.61] versus 4.16 [±0.52]) and follow up (n=not reported, 3.74 [±0.78] versus 4.17 [±0.58]) between sex difference p=0.047.
- The mean [±SD] BIS score for secondary sex was statistically significantly lower (improved) in sex assigned at birth males compared with sex assigned at birth females at baseline (n=not reported, mean BIS score [±SD]: 2.66 [±0.50] versus 2.81 [±0.76]) and follow up (n=not reported, 2.39 [±0.69] versus 3.18 [±0.42]), between sex difference p=0.001.
- The mean [±SD] BIS score for neutral body characteristics was not statistically significantly different in sex assigned at birth males compared with sex assigned at birth females at baseline (n=not reported, 2.60 [±0.58] versus 2.24 [±0.62], between sex difference p=0.777).

Psychosocial impact

The study by Costa et al. 2015 in 201 adolescents with gender dysphoria who had 6 months of psychological support followed by either GnRH analogues and continued psychological support or continued psychological support only, found that sex assigned at birth males had statistically significant lower mean [±SD] CGAS scores at baseline compared with sex assigned at birth females (n=201, 55.4 [±12.7] versus 59.2 [±11.8], p=0.03), but no conclusions could be drawn.

The study by de Vries et al. 2011 in 70 adolescents with gender dysphoria found that psychosocial impact in terms of global functioning (CGAS) and psychosocial functioning (CBCL and YSR) may be different in sex assigned at birth males compared with sex assigned at birth females, but no conclusions could be drawn.

- There was no statistically significant difference between sex assigned at birth males and sex assigned at birth females (at baseline or follow up) for the CBCL Total T score, the CBCL internalising T score, the YSR Total T score or the YSR internalising T score.

- Sex assigned at birth males had statistically higher mean [±SD] CGAS scores compared with sex assigned at birth females at baseline (n=54, 73.10 [±8.44] versus 67.25 [±11.06]) and follow up (n=54, 77.33 [±8.69] versus 70.30 [±9.44]), between sex difference p=0.021.
- Sex assigned at birth males had statistically lower mean [±SD] CBCL externalising T scores compared with sex assigned at birth females at baseline (n=54, 54.71 [±12.91] versus 60.70 [±12.64]) and follow up (n=54, 48.75 [±10.22] versus 57.87 [±11.66]), between sex difference p=0.015.
- Sex assigned at birth males had statistically lower mean [±SD] YSR externalising T scores compared with sex assigned at birth females at both baseline (n=54, 48.72 [±11.38] versus 57.24 [±10.59]) and follow up (n=54, 46.52 [±9.23] versus 52.97 [±8.51]), between sex difference p=0.004.

Bone density

The studies by Joseph et al. 2019, Klink et al. 2015 and Vlot et al. 2017 provided evidence on bone density in sex assigned at birth males (see above for details).

Cognitive development or functioning

The study by Staphorsius et al. 2015 provided evidence on cognitive development or functioning in sex assigned at birth males (see above for details).

Other safety outcomes

The study by Schagen et al. 2016 provided evidence on renal function in sex assigned at birth males (see above).

Sex assigned at birth females (transmales)

Impact on gender dysphoria

The studies by de Vries et al. 2011 and Costa et al. 2015 found that gender dysphoria (measured using the UGDS) in sex assigned at birth females is higher than in sex assigned at birth males at baseline and follow up (see above for details).

Impact on mental health

The study by de Vries et al. 2011 found that the impact on mental health (depression, anger and anxiety) may be different in sex assigned at birth females compared with sex assigned at birth males. Over time there was no statistically significant difference between sex assigned at birth females and sex assigned at birth males for depression, but sex assigned at birth females had statistically significantly greater levels of anger and anxiety than sex assigned at birth males at both baseline and follow up (see above for details).

Impact on body image

The study by de Vries et al. 2011 found that the impact on body image may be different in sex assigned at birth females compared with sex assigned at birth males. Sex assigned at birth females are more dissatisfied with their primary and secondary sex characteristics than sex assigned at birth males at both baseline and follow up, but the satisfaction with neutral body characteristics is not different (see above for details).

Psychosocial impact

The studies by de Vries et al. 2011 and Costa et al. 2015 found that psychosocial impact in terms of global functioning (CGAS) and psychosocial functioning (CBCL and YSR) may be different in sex assigned at birth females compared with sex assigned at birth males, but no conclusions could be drawn (see above for details).

Bone density

The studies by Joseph et al. 2019, Klink et al. 2015 and Vlot et al. 2017 provided evidence on bone density in sex assigned at birth females (see above for details).

Cognitive development or functioning

The study by Staphorsius et al. 2015 provided evidence on cognitive development or functioning in sex assigned at birth females (see above for details).

Other safety outcomes

The study by Schagen et al. 2016 provided evidence on renal function in sex assigned at birth females (see above for details).

From the evidence selected:

(a) what are the criteria used by the research studies to define gender dysphoria, gender identity disorder and gender incongruence of childhood?

(b) what were the ages at which participants commenced treatment with GnRH analogues?

(c) what was the duration of treatment with GnRH analogues?

All studies that reported diagnostic criteria for gender dysphoria (6/9 studies) used the version of the Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria that was in use at the time. In 5 studies (Costa et al. 2015, Klink et al. 2015, Schagen et al. 2016, Staphorsius et al. 2015 and Vlot et al. 2017) the DSM-fourth edition, text revision (IV-TR) criteria were used. The study by Brik et al. 2020 used DSM-V criteria. It was not reported how gender dysphoria was defined in the remaining 3 studies.

The studies show variation in the age (11 to 18 years old) at which children and adolescents with gender dysphoria started GnRH analogues.

Most studies did not report the duration of treatment with GnRH analogues (Joseph et al. 2019, Khatchadourian et al. 2014, Vlot et al. 2017, Costa et al. 2015, de Vries et al. 2011, Schagen et al. 2016), but where this was reported (Brik et al. 2020, Klink et al. 2015, Staphorsius et al. 2015) there was a wide variation ranging from a few months to about 5 years.

Discussion

A key limitation to identifying the effectiveness and safety of GnRH analogues for children and adolescents with gender dysphoria is the lack of reliable comparative studies. The lack of clear, expected outcomes from treatment with a GnRH analogue (the purpose of which is to suppress secondary sexual characteristics which may cause distress from unwanted pubertal changes) also makes interpreting the evidence difficult.

The studies included in this evidence review are all small, uncontrolled observational studies, which are subject to bias and confounding, and all the results are of very low certainty using modified GRADE. They all reported physical and mental health comorbidities and concomitant treatments very poorly. All the studies are from a limited number of, mainly European, care facilities. They are described as either tertiary referral or expert services but the low number of services providing such care and publishing evidence may bias the results towards the outcomes in these services only and limit extrapolation.

Many of the studies did not report statistical significance or confidence intervals. Changes in outcome scores for clinical effectiveness and bone density were assessed with regards to statistical significance. However, there is relatively little interpretation of whether the changes in outcomes are clinically meaningful.

In the observational, retrospective studies providing evidence on bone density, participants acted as their own controls and change in bone density was determined between starting GnRH analogues and follow up. Observational studies such as these can only show an association with GnRH analogues and bone density; they cannot show that GnRH analogues caused any differences in bone density seen. Because there was no comparator group and participants acted as their own controls, it is not known whether the findings are associated with GnRH analogues or due to changes over time.

Conclusion

The results of the studies that reported impact on the critical outcomes of gender dysphoria and mental health (depression, anger and anxiety), and the important outcomes of body image and psychosocial impact (global and psychosocial functioning), in children and adolescents with gender dysphoria are of very low certainty using modified GRADE. They suggest little change with GnRH analogues from baseline to follow-up.

Studies that found differences in outcomes could represent changes that are either of questionable clinical value, or the studies themselves are not reliable and changes could be due to confounding, bias or chance. It is plausible, however, that a lack of difference in scores from baseline to follow-up is the effect of GnRH analogues in children and adolescents with gender dysphoria, in whom the development of secondary sexual characteristics might be expected to be associated with an increased impact on gender dysphoria, depression, anxiety, anger and distress over time without treatment. The study by de Vries et al. 2011 reported statistically significant reductions in the Child Behaviour Checklist (CBCL) and Youth Self-Report (YSR) scores from baseline to follow up, which include measures of distress. As the aim of GnRH analogues is to reduce distress caused by the development of secondary sexual characteristics, this may be an important finding. However, as the studies all lack appropriate controls who were not receiving GnRH analogues, any positive changes could be a regression to mean.

The results of the studies that reported bone density outcomes suggest that GnRH analogues may reduce the expected increase in bone density (which is expected during puberty). However, as the studies themselves are not reliable, the results could be due to confounding, bias or chance. While controlled trials may not be possible, comparative studies are needed to understand this association and whether the effects of GnRH analogues on bone density are seen after they are stopped. All the studies that reported safety outcomes provided very low certainty evidence.

No cost-effectiveness evidence was found to determine whether or not GnRH analogues are cost-effective for children and adolescents with gender dysphoria.

The results of the studies that reported outcomes for subgroups of children and adolescents with gender dysphoria, suggest there may be differences between sex assigned at birth males (transfemales) and sex assigned at birth females (transmales).

3. Methodology

Review questions

The review question(s) for this evidence review are:

1. For children and adolescents with gender dysphoria, what is the clinical effectiveness of treatment with GnRH analogues compared with one or a combination of psychological support, social transitioning to the desired gender or no intervention?
2. For children and adolescents with gender dysphoria, what is the short-term and long-term safety of GnRH analogues compared with one or a combination of psychological support, social transitioning to the desired gender or no intervention?
3. For children and adolescents with gender dysphoria, what is the cost-effectiveness of GnRH analogues compared to one or a combination of psychological support, social transitioning to the desired gender or no intervention?
4. From the evidence selected, are there any subgroups of children and adolescents with gender dysphoria that may derive more (or less) advantage from treatment with GnRH analogues than the wider population of children and adolescents with gender dysphoria?
5. From the evidence selected,
    a) what are the criteria used by the research studies to define gender dysphoria, gender identity disorder and gender incongruence of childhood?
    b) what were the ages at which participants commenced treatment with GnRH analogues?
    c) what was the duration of treatment with GnRH analogues?

See appendix A for the full review protocol.

Review process

The methodology to undertake this review is specified by NHS England in their ‘Guidance on conducting evidence reviews for Specialised Services Commissioning Products’ (2020).

The searches for evidence were informed by the PICO document and were conducted on 23 July 2020.

See appendix B for details of the search strategy.

Results from the literature searches were screened using their titles and abstracts for relevance against the criteria in the PICO framework. Full text references of potentially

relevant evidence were obtained and reviewed to determine whether they met the inclusion criteria for this evidence review.

See appendix C for evidence selection details and appendix D for the list of studies excluded from the review and the reasons for their exclusion.

Relevant details and outcomes were extracted from the included studies and were critically appraised using a checklist appropriate to the study design. See appendices E and F for individual study and checklist details.

The available evidence was assessed by outcome for certainty using modified GRADE. See appendix G for GRADE Profiles.

4. Summary of included studies

Nine observational studies were identified for inclusion. Five studies were retrospective observational studies (Brik et al. 2020, Joseph et al. 2019, Khatchadourian et al. 2014, Klink et al. 2015, Vlot et al. 2017), 3 studies were prospective longitudinal observational studies (Costa et al. 2015, de Vries et al. 2011, Schagen et al. 2016) and 1 study was a cross-sectional study (Staphorsius et al. 2015).

The terminology used in this topic area is continually evolving and is different depending on stakeholder perspectives. In this evidence review we have used the phrase 'people's assigned sex at birth' rather than natal or biological sex, gonadotrophin releasing hormone (GnRH) analogues rather than 'puberty blockers' and gender-affirming hormones rather than 'cross sex hormones'. The research studies included in this evidence review may use historical terms which are no longer considered appropriate.

Table 1 provides a summary of these included studies and full details are given in appendix E.

Table 1 Summary of included studies

Study	Population	Intervention and comparison	Outcomes reported
Brik et al. 2020 Retrospective observational single-centre study Netherlands	The study was conducted at the Curium-Leiden University Medical Centre gender clinic in Leiden, the Netherlands and involved adolescents with gender dysphoria. The sample size was 143 adolescents (median age at start of treatment was 15.0 years, range 11.1 to 18.6 years in transfemales; 16.1 years, range 10.1 to 17.9 years in transmales) from a sampling frame of 269 children and adolescents registered at the clinic between November 2010 and January 2018.	**Intervention** 143 children and adolescents receiving GnRH analogues (no specific treatment, dose, route or frequency of administration reported). The median duration was 2.1 years (range 1.6–2.8 years). **Comparison** No comparator.	**Critical Outcomes** • No critical outcomes reported **Important outcomes** • Stopping treatment

Study	Population	Intervention and comparison	Outcomes reported
	Participants were included in the study if they were diagnosed with gender dysphoria according to the DSM-5 criteria, registered at the clinic, were prepubertal and within the appropriate age range, and had started GnRH analogues. No concomitant treatments were reported.		
Costa et al. 2015 Prospective longitudinal observational single centre cohort study United Kingdom	The study was conducted at the Gender Identity Development Service in London and involved adolescents with gender dysphoria. The sample size was 201 adolescents (mean [±SD] age 15.52±1.41 years, range 12 to 17 years) from a sampling frame of 436 consecutive adolescents referred to the service between 2010 and 2014. The mean [±SD] age at the start of GnRH analogues was 16.48 [±1.26] years, range 13 to 17 years. Participants were invited to participate following a 6-month diagnostic process using DSM-IV-TR criteria. No concomitant treatments were reported.	**Intervention** 101 adolescents assessed as being immediately eligible for GnRH analogues (no specific treatment, dose or route of administration reported) plus psychological support. The average duration of treatment was approximately 12 months (no exact figure given). **Comparison** 100 adolescents assessed as not immediately eligible for GnRH analogues (more time needed to make the decision to start GnRH analogues) who had psychological support only. None received GnRH analogues throughout the study.	**Critical Outcomes** • No critical outcomes reported **Important outcomes** • Psychosocial impact
de Vries et al. 2011 Prospective longitudinal observational single centre before and after study Netherlands	The study was conducted at the Amsterdam gender identity clinic of the VU University Medical Centre and involved adolescents who were defined as “transsexual”. The sample size was 70 adolescents receiving GnRH analogues (mean age [±SD] at assessment 13.6±1.8 years) from a sampling frame of 196 consecutive adolescents referred to the service between 2000 and 2008. Participants were invited to participate if they subsequently started gender-affirming hormones between 2003 and 2009. No diagnostic criteria or concomitant treatments were reported.	**Intervention** 70 individuals assessed at baseline (T0) before the start of GnRH analogues (no specific treatment, dose or route of administration reported). **Comparison** No comparator.	**Critical Outcomes** • Gender dysphoria • Mental health (depression, anger and anxiety) **Important outcomes** • Body image • Psychosocial impact

Study	Population	Intervention and comparison	Outcomes reported
Joseph et al. 2019 Retrospective longitudinal observational single centre study United Kingdom	This study was conducted at the Early intervention clinic at University College London Hospital (all participants had been seen at the Gender Identity Development Service in London) and involved adolescents with gender dysphoria. The sample size was 70 adolescents with gender dysphoria (no diagnostic criteria described) all offered GnRH analogues. The mean age at the start of treatment was 13.2 years (SD ±1.4) for transfemales and 12.6 years (SD ±1.0) for transmales. Details of the sampling frame were not reported. Further details of how the sample was drawn are not reported. No concomitant treatments were reported.	**Intervention** GnRH analogues. No specific treatment, duration, dose or route of administration reported. **Comparison** No comparator.	**Critical Outcomes** • No critical outcomes reported **Important outcomes** • Safety: bone density
Khatchadourian et al. 2014 Retrospective observational chart review single centre study Canada	This study was conducted at the Endocrinology and Diabetes Unit at British Columbia Children's Hospital, Canada and involved youths with gender dysphoria. The sample size was 27 young people with gender dysphoria who started GnRH analogues (at mean age 14.7 [SD ±1.9] years) out of 84 young people seen at the unit between 1998 and 2011. Diagnostic criteria and concomitant treatments were not reported.	**Intervention** 84 young people with gender dysphoria. For GnRH analogues no specific treatment, duration, dose or route of administration reported. **Comparison** No comparator.	**Critical Outcomes** • No critical outcomes reported **Important outcomes** • Stopping treatment • Safety: adverse effects
Klink et al. 2015 Retrospective longitudinal observational single centre study Netherlands	This study was conducted in the Netherlands at a tertiary referral centre. It is unclear which centre this was. The sample size was 34 adolescents (mean age 14.9 [SD ±1.9] years for transfemales and 15.0 [SD ±2.0] years for transmales at start of GnRH analogues). Details of the sampling frame are not reported. Participants were included if they met DSM-IV-TR criteria for gender identity disorder of adolescence and had been treated with GnRH analogues and gender-affirming hormones during their pubertal years. No concomitant treatments were reported.	**Intervention** The intervention was GnRH analogue monotherapy (triptorelin 3.75 mg subcutaneously every 4 weeks) followed by gender-affirming hormones with discontinuation of GnRH analogues after gonadectomy. Duration of GnRH analogues was 1.3 years (range 0.5 to 3.8 years) in transfemales and 1.5 years (0.25 to 5.2 years in transmales. **Comparison** No comparator.	**Critical Outcomes** • No critical outcomes reported **Important outcomes** • Safety: bone density

Study	Population	Intervention and comparison	Outcomes reported
Schagen et al. 2016 Prospective longitudinal study Netherlands	This study was conducted at the Centre of Expertise on Gender Dysphoria at the VU University Medical Centre (Amsterdam, Netherlands) and involved adolescents with gender dysphoria. The sample size was 116 adolescents (median age [range] 13.6 years [11.6 to 17.9] in transfemales and 14.2 years [11.1 to 18.6] in transmales during first year of GnRH analogues) out of 128 adolescents who started GnRH analogues. Participants were included if they met DSM-IV-TR criteria for gender dysphoria, had lifelong extreme gender dysphoria, were psychologically stable and were living in a supportive environment. No concomitant treatments were reported.	**Intervention** The intervention was GnRH analogue monotherapy (triptorelin 3.75 mg at 0, 2 and 4 weeks followed by intramuscular injections every 4 weeks, for at least 3 months). **Comparison** No comparator.	**Critical Outcomes** • No critical outcomes reported **Important outcomes** • Safety: liver and renal function.
Staphorsius et al. 2015 Cross-sectional (single time point) assessment single centre study Netherlands	This study was conducted at the VU University Medical Centre (Amsterdam, Netherlands) and involved adolescents with gender dysphoria. The sample size was 85, of whom 40 were adolescents with gender dysphoria (20 of whom were being treated with GnRH analogues) and 45 were controls without gender dysphoria (not further reported here). Mean (±SD) age 15.1 (±2.4) years in transfemales and 15.8 (±1.9) years in transmales. Details of the sampling frame are not reported. Participants were included if they were diagnosed with Gender Identity Disorder according to the DSM-IV-TR and at least 12 years old and Tanner stage of at least B2 or G2 to G3 with measurable oestradiol and testosterone levels in girls and boys, respectively. No concomitant treatments were reported.	**Intervention** The intervention was a GnRH analogue (triptorelin 3.75 mg every 4 weeks subcutaneously or intramuscularly). The mean duration of treatment was 1.6 years (SD ±1.0). **Comparison** Adolescents with gender dysphoria not treated with GnRH analogues.	**Critical Outcomes** • No critical outcomes reported **Important outcomes** • Psychosocial impact • Safety: cognitive functioning
Vlot et al. 2017 Retrospective observational data analysis study Netherlands	This study was conducted at the VU University Medical Centre (Amsterdam, Netherlands) and involved adolescents with gender dysphoria. The sample size was 70 adolescents (median age [range] 15.1 years [11.7 to 18.6] for transmales and 13.5 years [11.5 to	**Intervention** The intervention was a GnRH analogue (triptorelin 3.75 mg every 4 weeks subcutaneously). **Comparison** No comparator.	**Critical Outcomes** • No critical outcomes reported **Important outcomes**

Study	Population	Intervention and comparison	Outcomes reported
	18.3] for transfemales at start of GnRH analogues). Details of the sampling frame are not reported. Participants were included if they had a diagnosis of gender dysphoria according to DSM-IV-TR criteria who were receiving GnRH analogues and then gender-affirming hormones. No concomitant treatments were reported.		• Safety: bone density
Abbreviations: DSM-IV-TR, Diagnostic and Statistical Manual of Mental Disorders, fourth edition, text revision; GnRH, Gonadotrophin releasing hormone; SD, Standard deviation.			

5. Results

In children and adolescents with gender dysphoria, what is the clinical effectiveness of treatment with GnRH analogues compared with one or a combination of psychological support, social transitioning to the desired gender or no intervention?

Outcome	Evidence statement
Clinical Effectiveness	
Critical outcomes	
Impact on gender dysphoria **Certainty of evidence: very low**	This is a critical outcome because gender dysphoria in children and adolescents is associated with significant distress and problems with functioning. One uncontrolled, prospective observational longitudinal study (de Vries et al. 2011) provided evidence relating to the impact on gender dysphoria in adolescents, measured using the Utrecht Gender Dysphoria Scale (UGDS). The UGDS is a validated screening tool for both adolescents and adults to assess gender dysphoria. It consists of 12 items, to be answered on a 1- to 5-point scale, resulting in a sum score between 12 and 60. The higher the UGDS score the greater the gender dysphoria. The study measured the impact on gender dysphoria at 2 time points: • before starting a GnRH analogue (mean [±SD] age: 14.75 [±1.92] years), and • shortly before starting gender-affirming hormones (mean [±SD] age: 16.64 [±1.90] years). The mean (±SD) UGDS score was not statistically significantly different at baseline compared with follow-up (n=41, 53.20 [±7.91] versus 53.9 [±17.42], p=0.333) **(VERY LOW)**. **This study provides very low certainty evidence that treatment with GnRH analogues, before starting gender-affirming hormones, does not affect gender dysphoria.**

Impact on mental health: depression **Certainty of evidence: very low**	This is a critical outcome because self-harm and thoughts of suicide have the potential to result in significant physical harm and, for completed suicides, the death of the young person. One uncontrolled, prospective observational longitudinal study (de Vries et al. 2011) provided evidence relating to the impact on depression in children and adolescents with gender dysphoria. Depression was measured using the Beck Depression Inventory-II (BDI-II). The BDI-II is a valid, reliable, and widely used tool for assessing depressive symptoms. There are no specific scores to categorise depression severity, but it is suggested that 0 to 13 is minimal symptoms, 14 to 19 is mild depression, 20 to 28 is moderate depression, and severe depression is 29 to 63. The study provided evidence for depression measured at 2 time points: • before starting a GnRH analogue (mean [±SD] age: 14.75 [±1.92] years), and • shortly before starting gender-affirming hormones (mean [±SD] age: 16.64 [±1.90] years). The mean (±SD) depression (BDI) score was statistically significantly lower (improved) from baseline compared with follow-up (n=41, 8.31 [±7.12] versus 4.95 [±6.72], p=0.004) **(VERY LOW)**. **This study provides very low certainty evidence that treatment with GnRH analogues, before starting gender-affirming hormones, may reduce depression.**
Impact on mental health: anger **Certainty of evidence: very low**	This is a critical outcome because self-harm and thoughts of suicide have the potential to result in significant physical harm and, for completed suicides, the death of the young person. One uncontrolled, prospective observational longitudinal study (de Vries et al. 2011) provided evidence relating to the impact on anger in children and adolescents with gender dysphoria. Anger was measured using the Trait Anger Scale of the State-Trait Personality Inventory (TPI). This is a validated 20-item inventory tool which measures the intensity of anger as the disposition to experience angry feelings as a personality trait. Higher scores indicate greater anger. The study provided evidence for anger measured at 2 time points: • before starting a GnRH analogue (mean [±SD] age: 14.75 [±1.92] years), and • shortly before starting gender-affirming hormones (mean [±SD] age: 16.64 [±1.90] years). The mean (±SD) anger (TPI) score was not statistically significantly different at baseline compared with follow-up (n=41, 18.29 [±5.54] versus 17.88 [±5.24], p=0.503) **(VERY LOW)**. **This study provides very low certainty evidence that treatment with GnRH analogues, before starting gender-affirming hormones, does not affect anger.**
Impact on mental health: anxiety	This is a critical outcome because self-harm and thoughts of suicide have the potential to result in significant physical harm and, for completed suicides, the death of the young person.

Certainty of evidence: very low	One uncontrolled, prospective observational longitudinal study (de Vries et al. 2011) provided evidence relating to the impact on anxiety in children and adolescents with gender dysphoria. Anxiety was measured using the Trait Anxiety Scale of the State-Trait Personality Inventory (STAI). This is a validated and commonly used measure of trait and state anxiety. It has 20 items and can be used in clinical settings to diagnose anxiety and to distinguish it from depressive illness. Higher scores indicate greater anxiety. The study provided evidence for anxiety at 2 time points: • before starting a GnRH analogue (mean [±SD] age: 14.75 [±1.92] years), and • shortly before starting gender-affirming hormones (mean [±SD] age: 16.64 [±1.90] years). The mean (±SD) anxiety (STAI) score was not statistically significantly different at baseline compared with follow-up (n=41, 39.43 [±10.07] versus 37.95 [±9.38], p=0.276) (**VERY LOW**). **This study provides very low certainty evidence that treatment with GnRH analogues, before starting gender-affirming hormones, does not affect levels of anxiety.**
Quality of life	This is a critical outcome because gender dysphoria in children and adolescents may be associated with a significant reduction in health-related quality of life. No evidence was identified.
Important outcomes	
Impact on body image **Certainty of evidence: very low**	This is an important outcome because some children and adolescents with gender dysphoria may want to take steps to suppress features of their physical appearance associated with their sex assigned at birth or accentuate physical features of their desired gender. One uncontrolled, prospective observational longitudinal study provided evidence relating to the impact on body image (de Vries et al. 2011). Body image was measured using the Body Image Scale (BIS) which is a validated 30-item scale covering 3 aspects: primary, secondary and neutral body characteristics. Higher scores represent a higher degree of body dissatisfaction. The study (de Vries et al. 2011) provided evidence for body image measured at 2 time points: • before starting a GnRH analogue (mean [±SD] age: 14.75 [±1.92] years), and • shortly before starting gender-affirming hormones (mean [±SD] age: 16.64 [±1.90] years). The mean (±SD) body image (BIS) scores for were not statistically significantly different from baseline compared with follow-up for: • primary sexual characteristics (n=57, 4.10 [±0.56] versus 3.98 [±0.71], p=0.145) • secondary sexual characteristics (n=57, 2.74 [±0.65] versus 2.82 [±0.68], p=0.569)

	• neutral body characteristics (n=57, 2.41 [±0.63] versus 2.47 [±0.56], p=0.620) **(VERY LOW)**. **This study provides very low certainty evidence that treatment with GnRH analogues, before starting gender affirming hormones, does not affect body image.**
Psychosocial impact: global functioning **Certainty of evidence: very low**	This is an important outcome because gender dysphoria in children and adolescents is associated with internalising and externalising behaviours, and emotional and behavioural problems which may impact on social and occupational functioning. One uncontrolled, observational, prospective cohort study (de Vries et al 2011) and one prospective cross-sectional cohort study (Costa et al. 2015) provided evidence relating to psychosocial impact in terms of global functioning. Global functioning was measured using the Children's Global Assessment Scale (CGAS). The CGAS tool is a validated measure of global functioning on a single rating scale from 1 to 100. Lower scores indicate poorer functioning. One study (de Vries et al. 2011) provided evidence for global functioning (CGAS) at 2 time points: • before starting a GnRH analogue (mean [±SD] age: 14.75 [±1.92] years), and • shortly before starting gender-affirming hormones (mean [±SD] age: 16.64 [±1.90] years). The mean (±SD) CGAS score was statistically significantly higher (improved) from baseline compared with follow-up (n=41, 70.24 [±10.12] versus 73.90 [±9.63], p=0.005) **(VERY LOW)**. One study (Costa et al. 2015) in adolescents with gender dysphoria who had 6 months of psychological support followed by either GnRH analogues and continued psychological support (the immediately eligible group) or continued psychological support only (the delayed eligible group who did not receive GnRH analogues) provided evidence for global functioning (CGAS) measured at 4 time points: • at baseline (T0) in both groups, • after 6 months of psychological support in both groups (T1), • after 6 months of GnRH analogues and 12 months of psychological support in the immediately eligible group and 12 months of psychological support only in the delayed eligible group (T2), and • after 18 months of psychological support and 12 months of GnRH analogues in the immediately eligible group and after 18 months of psychological support only in the delayed eligible group (T3). The mean [±SD] CGAS score was statistically significantly higher (improved) for all adolescents (including those not receiving GnRH analogues) at T1, T2 or T3 compared with baseline (T0). For the immediately eligible group (who received GnRH analogues) versus the delayed eligible group (who did not receive GnRH analogues) there were no statistically significant differences in CGAS

	scores between the 2 groups at baseline T0 (n=201, p=0.23), T1 (n=201, p=0.73), T2 (n=121, p=0.49) or T3 (n=71, p=0.14) time points. For the immediately eligible group (who received GnRH analogues), the mean (±SD) CGAS score was not statistically significantly different at: • T1 compared with T0 • T2 compared with T1 • T3 compared with T2. The mean (±SD) CGAS score was statistically significantly higher (improved) at: • T2 compared with T0 (n=60, 64.70 [±13.34] versus n=101, 58.72 [±11.38], p=0.003) • T3 compared with T0 (n=35, 67.40 [±13.39] versus n=101, 58.72 [±11.38], p<0.001) • T3 compared with T1 (n=35, 67.40 [±13.93] versus n=101, 60.89 [±12.17], p<0.001) **(VERY LOW)**. **These studies provide very low certainty evidence that during treatment with GnRH analogues, global functioning may improve over time. However, there was no statistically significant difference in global functioning between GnRH analogues plus psychological support compared with psychological support only at any time point.**
Psychosocial impact: psychosocial functioning **Certainty of evidence: very low**	This is an important outcome because gender dysphoria in children and adolescents is associated with internalising and externalising behaviours, and emotional and behavioural problems which may impact on social and occupational functioning. Two studies provided evidence for this outcome. One uncontrolled, observational, prospective cohort study (de Vries et al, 2011) and 1 cross-sectional observational study (Staphorsius et al. 2015) assessed psychosocial functioning using the Child Behaviour Checklist (CBCL) and the self-administered Youth Self-Report (YSR). The CBCL is a checklist parents complete to detect emotional and behavioural problems in children and adolescents. YSR is similar but is self-completed by the child or adolescent. The scales consist of a Total problems score, which is the sum of the scores of all the problem items. An internalising problem scale sums the anxious/depressed, withdrawn-depressed, and somatic complaints scores while the externalising problem scale combines rule-breaking and aggressive behaviour. The standard scores are scaled so that 50 is average for the child or adolescent's age and gender, with a SD of 10 points. Higher scores indicate greater problems, with a T-score above 63 considered to be in the clinical range. One study (de Vries et al. 2011) provided evidence for psychosocial functioning (CBCL and YSR scores) at 2 time points: • before starting a GnRH analogue (mean [±SD] age: 14.75 [±1.92] years), and • shortly before starting gender-affirming hormones (mean [±SD] age: 16.64 [±1.90] years).

	At follow up, the mean (±SD) CBCL scores were statistically significantly lower (improved) compared with baseline for: • Total T score (n=54, 60.70 [±12.76] versus 54.46 [±11.23], p<0.001 • Internalising T score (n=54, 61.00 [±12.21] versus 52.17 [±9.81], p<0.001) • Externalising T score (n=54, 58.04 [±12.99] versus 53.81 [±11.86], p=0.001). At follow up, the mean (±SD) YSR scores were statistically significantly lower (improved) compared with baseline for: • Total T score (n=54, 55.46 [±11.56] versus 50.00 [±10.56], p<0.001) • Internalising T score (n=54, 56.04 [±12.49] versus 49.78 [±11.63], p<0.001) • Externalising T score (n=54, 53.30 [±11.87] versus 49.98 [±9.35], p=0.009). The proportion of adolescents scoring in the clinical range decreased from baseline to follow up on the CBCL total problem scale (44.4% versus 22.2%, p=0.001) and the internalising scale of the YSR (29.6% versus 11.1%, p=0.017) **(VERY LOW)**. One study (Staphorsius et al. 2015) assessed CBCL in a cohort of adolescents with gender dysphoria (transfemale: n=18, mean [±SD] age 15.1 [±2.4] years and transmale: n=22, mean [±SD] age 15.8 [±1.9] years) either receiving GnRH analogues (transfemale, n=8 and transmale, n=12), or not receiving GnRH analogues (transfemale, n=10 and transmale, n=10). The mean (±SD) CBCL scores for each group were (statistical analysis unclear): • transfemales (total) 57.8 [±9.2] • transfemales receiving GnRH analogues 57.4 [±9.8] • transfemales not receiving GnRH analogues 58.2 [±9.3] • transmales (total) 60.4 [±10.2] • transmales receiving GnRH analogues 57.5 [±9.4] • transmales not receiving GnRH analogues 63.9 [±10.5] **(VERY LOW)**. **These studies provide very low certainty evidence that during treatment with GnRH analogues psychosocial functioning may improve, with the proportion of adolescents in the clinical range for some CBCL and YSR scores decreasing over time.**
Engagement with health care services **Certainty of evidence: very low**	This is an important outcome because patient engagement with health care services will impact on their clinical outcomes. Two uncontrolled observational cohort studies provided evidence relating to loss to follow up, which could be a marker of engagement with health care services (Brik et al. 2018 and Costa et al. 2015). In one retrospective study (Brik et al. 2018), 9 adolescents (9/214, 4.2%) who had stopped attending appointments were excluded from the study between November 2010 and July 2019 **(VERY LOW)**.

	One prospective study (Costa et al. 2015) had evidence for a large loss to follow-up over time. The sample size at baseline (T0) and 6 months (T1) was 201, which dropped by 39.8% to 121 after 12 months (T2) and by 64.7% to 71 at 18 months follow-up (T3). No explanation of the reasons for loss to follow-up are reported **(VERY LOW)**. Due to their design there was no reported loss to follow-up in the other 3 effectiveness studies (de Vries et al 2011; Khatchadourian et al. 2014; Staphorsius et al. 2015). **These studies provide very low certainty evidence about loss to follow up, which could be a marker of engagement with health care services, during treatment with GnRH analogues. Due to the large variation in rates between studies no conclusions could be drawn.**
Impact on extent of and satisfaction with surgery	This is an important outcome because some children and adolescents with gender dysphoria may proceed to transitioning surgery. No evidence was identified.
Stopping treatment **Certainty of evidence: very low**	This is an important outcome because there is uncertainty about the short- and long-term safety and adverse effects of GnRH analogues in children and adolescents with gender dysphoria. Two uncontrolled, retrospective, observational cohort studies provided evidence relating to stopping GnRH analogues. One study had complete reporting of the cohort (Brik et al. 2018), the other (Khatchadourian et al. 2014) had incomplete reporting of its cohort, particularly for transfemales where outcomes for only 4/11 were reported. Brik et al. 2018 narratively reported the reasons for stopping GnRH analogues in a cohort of 143 adolescents (38 transfemales and 105 transmales). Median age at the start of GnRH analogues was 15.0 years (range, 11.1–18.6 years) in transfemales and 16.1 years (range, 10.1–17.9 years) in transmales. Of these adolescents, 125 (87%, 36 transfemales, 89 transmales) subsequently started gender-affirming hormones after 1.0 (0.5–3.8) and 0.8 (0.3–3.7) years of GnRH analogues. At the time of data collection, the median duration of GnRH analogue use was 2.1 years (1.6–2.8). During the follow-up period 6.3% (9/143) of adolescents had discontinued GnRH analogues after a median duration of 0.8 years (range 0.1 to 3.0). The percentages and reasons for stopping were: • 2.8% (4/143) stopped GnRH analogues although they wanted to continue endocrine treatments for gender dysphoria: ○ 1 transmale stopped due to increase in mood problems, suicidal thoughts and confusion attributed to GnRH analogues ○ 1 transmale had hot flushes, increased migraines, fear of injections, stress at school and unrelated medical issues, and temporarily stopped treatment (after 4 months) and restarted 5 months later. ○ 1 transmale had mood swings 4 months after starting GnRH analogues. After 2.2 years had unexplained severe nausea and rapid weight loss and discontinued GnRH analogues after 2.4 years

	○ 1 transmale stopped GnRH analogues because of inability to regularly collect medication and attend appointments for injections. • 3.5% (5/143) stopped treatment because they no longer wished to receive gender-affirming treatment for various reasons **(VERY LOW)**. Khatchadourian et al. 2014 narratively reported the reasons for stopping GnRH analogues in a cohort of 26 adolescents (15 transmales and 11 transfemales), 42% (11/26) discontinued GnRH analogues during follow-up between 1998 and 2011. Of 15 transmales receiving GnRH analogues, 14 received testosterone during the observation period, of which: • 7 continued GnRH analogues after starting testosterone • 7 stopped GnRH analogues after a median of 3.0 years (range 0.2 to 9.2 years), of which: ○ 5 stopped after hysterectomy and salpingo-oophorectomy ○ 1 stopped after 2.2 years (transitioned to gender-affirming hormones) ○ 1 stopped after <2 months due to mood and emotional lability **(VERY LOW)**. Of 11 transfemales receiving GnRH analogues, 5 received oestrogen during the observation period, of which: • 4 continued GnRH analogues after starting oestrogen • 1 stopped GnRH analogues when taking oestrogen (no reason reported) **(VERY LOW)**. Of the remaining 6 transfemales taking GnRH analogues: • 1 stopped GnRH analogues after a few months due to emotional lability • 1 stopped GnRH analogues before taking oestrogen (the following year delayed due to heavy smoking) • 1 stopped GnRH analogues after 13 months due not to pursuing transition **(VERY LOW)**. **These studies provide very low certainty evidence for the number of adolescents who stop GnRH analogues and the reasons for this.**

Abbreviations: GnRH, gonadotrophin releasing hormone; SD, standard deviation.

In children and adolescents with gender dysphoria, what is the short-term and long-term safety of GnRH analogues compared with one or a combination of psychological support, social transitioning to the desired gender or no intervention?

Outcome	Evidence statement
Safety	
Change in bone density: lumbar	This is an important outcome because puberty is an important time for bone development and puberty suppression may affect bone development, as shown by changes in lumbar bone density.

Certainty of evidence: very low	Three uncontrolled, observational, retrospective studies provided evidence relating to the effect of GnRH analogues on bone density (based on lumbar BMAD) between starting with a GnRH analogue and at 1 and 2 year intervals (Joseph et al. 2019), and between starting GnRH analogues and starting gender-affirming hormones (Klink et al. 2015 and Vlot et al. 2017). All outcomes were reported separately for transfemales and transmales; also see subgroups table below. BMAD is a size adjusted value of BMD incorporating body size measurements using UK norms in growing adolescents. It was reported as g/cm^3 and as z-scores. Z-scores report how many standard deviations from the mean a measurement sits. A z-score of 0 is equal to the mean, a z-score of −1 is equal to 1 standard deviation below the mean, and a z-score of +1 is equal to 1 standard deviation above the mean. One retrospective observational study (Joseph et al. 2019, n=70) provided non-comparative evidence on change in lumbar BMAD increase using z-scores. • The z-score for lumbar BMAD was statistically significantly lower at 2 years compared with baseline in transfemales (z-score [±SD]: baseline 0.486 [0.809], 2 years −0.279 [0.930], p=0.000) and transmales (baseline −0.361 [1.439], 2 years −0.913 [1.318], p=0.001) **(VERY LOW)**. • The z-score for lumbar BMAD was statistically significantly lower at 1 year compared with baseline in transfemales (baseline 0.859 [0.154], 1 year −0.228 [1.027], p=0.000) and transmales (baseline −0.186 [1.230], 1 year −0.541 [1.396], p=0.006) **(VERY LOW)**. • Actual lumbar BMAD values in g/cm^3 were not statistically significantly different between baseline and 1 or 2 years in transfemales or transmales **(VERY LOW)**. Two retrospective observational studies (Klink et al. 2015 and Vlot et al. 2017, n=104 in total) provided non-comparative evidence on change in lumbar BMAD between starting GnRH analogues and starting gender-affirming hormones. All outcomes were reported separately for transfemales and transmales; also see subgroups table below. In Klink et al. 2015 the z-score for lumbar BMAD was not statistically significantly different between starting GnRH analogues and starting gender-affirming hormones in transfemales but was statistically significantly lower when starting gender-affirming hormones in transmales (z-score mean [±SD]: GnRH analogue 0.28 [±0.90], gender-affirming hormone −0.50 [±0.81], p=0.004). Actual lumbar BMAD values in g/cm^3 were not statistically significantly different between starting GnRH analogues and starting gender-affirming hormones in transfemales or transmales **(VERY LOW)**. Vlot et al. 2017 reported change from starting GnRH analogues to starting gender-affirming hormones in lumbar BMAD by bone age. • The z-score for lumbar BMAD in transfemales with a bone age of <15 years was statistically significantly lower at starting gender-affirming hormone treatment than at starting GnRH

	analogues (z-score median [range]: GnRH analogue −0.20 [−1.82 to 1.18], gender-affirming hormone −1.52 [−2.36 to 0.42], p=0.001) but was not statistically significantly different in transfemales with a bone age ≥15 years **(VERY LOW)**. • The z-score for lumbar BMAD in transmales with a bone age of <14 years was statistically significantly lower at starting gender-affirming hormone treatment than at starting GnRH analogues (z-score median [range]: GnRH analogue −0.05 [−0.78 to 2.94], gender-affirming hormone −0.84 [−2.20 to 0.87], p=0.003) and in transmales with a bone age ≥14 years (GnRH analogue 0.27 [−1.60 to 1.80], gender-affirming hormone −0.29 [−2.28 to 0.90], p≤0.0001) **(VERY LOW)**. • Actual lumbar BMAD values in g/cm^3 were not statistically significantly different between starting GnRH analogues and starting gender-affirming hormones in transfemales or transmales with young or old bone age **(VERY LOW)**. Two uncontrolled, observational, retrospective studies provided evidence for the effect of GnRH analogues on bone density (based on lumbar BMD) between starting GnRH analogues and either at 1 or 2 year intervals (Joseph et al. 2019), or starting gender-affirming hormones (Klink et al. 2015). All outcomes were reported separately for transfemales and transmales; also see subgroups table below. One retrospective observational study (Joseph et al. 2019, n=70) provided non-comparative evidence on change in lumbar BMD increase using z-scores. • The z-score for lumbar BMD was statistically significantly lower at 2 years compared with baseline in transfemales (z-score mean [±SD]: baseline 0.130 [0.972], 2 years −0.890 [±1.075], p=0.000) and transmales (baseline −0.715 [±1.406], 2 years −2.000 [1.384], p=0.000) **(VERY LOW)**. • The z-score for lumbar BMD was statistically significantly lower at 1 year compared with baseline in transfemales (z-score mean [±SD]: baseline −0.016 [±1.106], 1 year −0.461 [±1.121], p=0.003) and transmales (baseline −0.395 [±1.428], 1 year −1.276 [±1.410], p=0.000) **(VERY LOW)**. • With the exception of transmales, where lumbar BMD in kg/m^2 increased between baseline and 1 year (mean [±SD]: baseline 0.694 [±0.149], 1 year 0.718 [±0.124], p=0.006), actual lumbar BMD values were not statistically significantly different between baseline and 1 or 2 years in transfemales or between 0 and 2 years in transmales **(VERY LOW)**. One retrospective observational study (Klink et al. 2015, n=34) provided non-comparative evidence on change in lumbar BMD between starting GnRH analogues and starting gender-affirming hormones. • The z-score for lumbar BMD was not statistically significantly different between starting GnRH analogue and starting gender-affirming hormone treatment in transfemales, but was statistically significantly lower when starting gender-affirming hormones in transmales (z-score mean [±SD]: GnRH analogue 0.17 [±1.18], gender-affirming hormone −0.72 [±0.99], p<0.001) **(VERY LOW)**.

	• Actual lumbar BMD in g/cm^2 was not statistically significantly different between starting GnRH analogues and starting gender-affirming hormones in transfemales but was statistically significantly lower when starting gender-affirming hormones in transmales (mean [±SD]: GnRH analogues 0.95 [±0.12], gender-affirming hormones 0.91 [±0.10], p=0.006) **(VERY LOW)**. **These studies provide very low certainty evidence that GnRH analogues reduce the expected increase in lumbar bone density (BMAD or BMD) compared with baseline (although some findings were not statistically significant). These studies also show that GnRH analogues do not statistically significantly decrease actual lumbar bone density (BMAD or BMD).**
Change in bone density: femoral **Certainty of evidence: very low**	This is an important outcome because puberty is an important time for bone development and puberty suppression may affect bone development, as shown by changes in femoral bone density. Two uncontrolled, observational, retrospective studies provided evidence relating to the effect of GnRH analogues on bone density (based on femoral BMAD) between starting treatment with a GnRH analogue and starting gender-affirming hormones (Klink et al. 2015 and Vlot et al. 2017). All outcomes were reported separately for transfemales and transmales; also see subgroups table below. One retrospective observational study (Klink et al. 2015, n=34) provided non-comparative evidence on change in femoral area BMAD between starting GnRH analogues and starting gender-affirming hormones. All outcomes were reported separately for transfemales and transmales. • The z-score for femoral area BMAD was not statistically significantly different between starting GnRH analogues and starting gender-affirming hormones in transfemales or transmales **(VERY LOW)**. • Actual femoral area BMAD values were not statistically significantly different between starting GnRH analogues and starting gender-affirming hormones in transmales or transfemales **(VERY LOW)**. One retrospective observational study (Vlot et al. 2017, n=70) provided non-comparative evidence on change in femoral neck (hip) BMAD between starting GnRH analogues and starting gender-affirming hormones. All outcomes were reported separately for transfemales and transmales; also see subgroups table below. • The z-score for femoral neck BMAD in transfemales with a bone age of <15 years was not statistically significantly lower at starting gender-affirming hormones than at starting GnRH analogues (z-score median [range]: GnRH analogue −0.71 [−3.35 to 0.37], gender-affirming hormone −1.32 [−3.39 to 0.21], p≤0.1) or in transfemales with a bone age ≥15 years (GnRH analogue −0.44 [−1.37 to 0.93], gender-affirming hormone −0.36 [−1.50 to 0.46]) **(VERY LOW)**. • The z-score for femoral neck BMAD in transmales with a bone age of <14 years was not statistically significantly lower at starting gender-affirming hormones than at starting GnRH analogues (z-score median [range]: GnRH analogue −0.01

	[−1.30 to 0.91], gender-affirming hormone −0.37 [−2.28 to 0.47]) but was statistically significantly lower in transmales with a bone age ≥14 years (GnRH analogue 0.27 [−1.39 to 1.32], gender-affirming hormone −0.27 [−1.91 to 1.29], p=0.002) **(VERY LOW)**. • Actual femoral neck BMAD values were not statistically significantly different between starting GnRH analogues and starting gender-affirming hormones in transfemales or in transmales with a young bone age, but were statistically significantly lower in transmales with a bone age ≥14 years (GnRH analogue 0.33 [0.25 to 0.39), gender-affirming hormone 0.30 [0.23 to 0.41], p≤0.01) **(VERY LOW)**. Two uncontrolled, observational, retrospective studies provided evidence for the effect of GnRH analogues on bone density (based on femoral BMD) between starting GnRH analogues and either at 1 or 2 year intervals (Joseph et al. 2019), or starting gender-affirming hormones (Klink et al. 2015). All outcomes were reported separately for transfemales and transmales; also see subgroups table below. One retrospective observational study (Joseph et al. 2019, n=70) provided non-comparative evidence on change in femoral neck BMD increase using z-scores. All outcomes were reported separately for transfemales and transmales. • The z-score for femoral neck BMD was statistically significantly lower at 2 years compared with baseline in transfemales (z-score mean [±SD]: baseline 0.0450 [±0.781], 2 years −0.600 [±1.059], p=0.002) and transmales (baseline −1.075 [±1.145], 2 years −1.779 [±0.816], p=0.001) **(VERY LOW)**. • The z-score for femoral neck BMD was statistically significantly lower at 1 year compared with baseline in transfemales (z-score mean [±SD]: baseline 0.157 [±0.905], 1 year −0.340 [±0.816], p=0.002) and transmales (baseline −0.863 [±1.215], 1 year −1.440 [±1.075], p=0.000) **(VERY LOW)**. • Actual femoral neck BMD values in kg/m^2 were not statistically significantly different between baseline and 1 or 2 years in transmales or transfemales **(VERY LOW)**. One retrospective observational study (Klink et al. 2015, n=34) provided non-comparative evidence on change in femoral area BMD between starting GnRH analogues and starting gender-affirming hormones. All outcomes were reported separately for transfemales and transmales. • The z-score for femoral area BMD was not statistically significantly different between starting GnRH analogues and starting gender-affirming hormones in transfemales, but was statistically significantly lower in transmales (z-score mean [±SD]: GnRH analogue 0.36 [±0.88], gender-affirming hormone −0.35 [±0.79], p=0.001) **(VERY LOW)**. • Actual femoral area BMD values were not statistically significantly different between starting GnRH analogues and starting gender-affirming hormones in transfemales, but were statistically significantly lower in transmales (mean [±SD] GnRH analogue 0.92 [±0.10], gender-affirming hormone 0.88 [±0.09], p=0.005) **(VERY LOW)**.

	These studies provide very low certainty evidence that GnRH analogues may reduce the expected increase in femoral bone density (femoral neck or area BMAD or BMD) compared with baseline (although some findings were not statistically significant). These studies also show that GnRH analogues do not statistically significantly decrease actual femoral bone density (femoral area BMAD or femoral neck BMD), apart from actual femoral area BMD in transmales.
Cognitive development or functioning **Certainty of evidence: very low**	This is an important outcome because puberty is an important time for cognitive development and puberty suppression may affect cognitive development or functioning. One cross-sectional observational study (Staphorsius et al. 2015, n=70) provided comparative evidence on cognitive development or functioning in adolescents with gender dysphoria on GnRH analogues compared with adolescents with gender dysphoria not on GnRH analogues. Cognitive functioning was measured using an IQ test. Reaction time (in seconds) and accuracy (percentage of correct trials) were measured using the Tower of London (ToL) task. All outcomes were reported separately for transfemales and transmales; also see subgroups table below. No statistical analyses or interpretation of the results in these groups were reported: • IQ in transfemales (mean [±SD] GnRH analogue 94.0 [±10.3], control 109.4 [±21.2]). IQ transmales (GnRH analogue 95.8 [±15.6], control 98.5 [±15.9]. • Reaction time in transfemales (mean [±SD] GnRH analogue 10.9 [±4.1], control: 9.9 [±3.1]). Reaction time transmales (GnRH analogue 9.9 [±3.1], control 10.0 [±2.0]). • Accuracy score in transfemales (GnRH analogue 73.9 [±9.1], control 83.4 [±9.5]. Accuracy score in transmales (GnRH analogue 85.7 [±10.5], control 88.8 [±9.7]. **This study provides very low certainty evidence (with no statistical analysis) on the effects of GnRH analogues on cognitive development or functioning. No conclusions could be drawn.**
Other safety outcomes: kidney function **Certainty of evidence: very low**	This is an important outcome because if renal damage (raised serum creatinine is a marker of this) is suspected, GnRH analogues may need to be stopped. One prospective observational study (Schagen et al. 2016, n=116) provided non-comparative evidence on change in serum creatinine between starting GnRH analogues and at 1 year. All outcomes were reported separately for transfemales and transmales; also see subgroups table below. • There was no statistically significant difference between baseline and 1 year for serum creatinine in transfemales (mean [±SD] baseline 70 [±12], 1 year 66 [±13], p=0.20). • There was a statistically significant decrease between baseline and 1 year for serum creatinine in transmales (baseline 73 [±8], 1 year 68 [±13], p=0.01). **This study provides very low certainty evidence that GnRH analogues do not affect renal function.**

Other safety outcomes: liver function **Certainty of evidence: very low**	This is an important outcome because if treatment-induced liver injury (raised liver enzymes are a marker of this) is suspected, GnRH analogues may need to be stopped. One prospective observational study (Schagen et al. 2016, n=116) provided non-comparative evidence on elevated liver enzymes between starting GnRH analogues and during use. No comparative values or statistical analyses were reported. • Glutamyl transferase was not elevated at baseline or during use in any person. • Mild elevations of AST and ALT above the reference range were present at baseline but were not more prevalent during use than at baseline. • Glutamyl transferase, AST, and ALT levels did not significantly change from baseline to 12 months of use. **This study provides very low certainty evidence (with no statistical analysis) that GnRH analogues do not affect liver function.**
Other safety outcomes: adverse effects **Certainty of evidence: very low**	This is an important outcome because if there are adverse effects, GnRH analogues may need to be stopped. One uncontrolled, retrospective, observational cohort study (Khatchadourian et al. 2014) provided evidence relating to adverse effects from GnRH analogues. It had incomplete reporting of its cohort, particularly for transfemales where outcomes for only 4/11 were reported. Khatchadourian et al. 2014 reported adverse effects in a cohort of 26 adolescents (15 transmales and 11 transfemales) receiving GnRH analogues. Of these: • 1 transmale developed sterile abscesses; they were switched from leuprolide acetate to triptorelin, and this was well tolerated. • 1 transmale developed leg pains and headaches, which eventually resolved • 1 participant gained 19 kg within 9 months of starting GnRH analogues. **This study provides very low certainty evidence about potential adverse effects of GnRH analogues. No conclusions could be drawn.**

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMAD, bone mineral apparent density; BMD, bone mineral density; GnRH, gonadotrophin releasing hormone; IQ, intelligence quotient; NS, not significant; SD, standard deviation.

In children and adolescents with gender dysphoria, what is the cost-effectiveness of GnRH analogues compared to one or a combination of psychological support, social transitioning to the desired gender or no intervention?

Outcome	Evidence statement
Cost-effectiveness	No studies were identified to assess the cost-effectiveness of GnRH analogues for children and adolescents with gender dysphoria.

From the evidence selected, are there any subgroups of children and adolescents with gender dysphoria that may benefit from GnRH analogues more than the wider population of interest?

Subgroup	Evidence statement
Sex assigned at birth males (transfemales) **Certainty of evidence: Very low**	Some studies reported data separately for sex assigned at birth males (transfemales). This included some direct comparisons with sex assigned at birth females (transmales). **Impact on gender dysphoria** One uncontrolled prospective observational longitudinal study (de Vries et al. 2011) provided evidence for gender dysphoria in sex assigned at birth males. See the clinical effectiveness results table above for a full description of the study. The mean (±SD) UGDS score was statistically significantly lower (improved) in sex assigned at birth males compared with sex assigned at birth females at both baseline (T0) (n=not reported, mean UGDS score [±SD]: 47.95 [±9.70] versus 56.57 [±3.89]) and T1 (n=not reported, 49.67 [±9.47] versus 56.62 [±4.00]); between sex difference p<0.001 **(VERY LOW)**. One further prospective observational longitudinal study (Costa et al. 2015) provided evidence for the impact on gender dysphoria in sex assigned at birth males. See the clinical effectiveness results table above for a full description of the study. Sex assigned at birth males had a statistically significantly lower (improved) mean (±SD) UGDS score of 51.6 [±9.7] compared with sex assigned at birth females (56.1 [±4.3], p<0.001). However, it was not reported if this was baseline or follow-up **(VERY LOW)**. **These studies provide very low certainty evidence that in sex assigned at birth males (transfemales), gender dysphoria is lower than in sex assigned at birth females (transmales).** **Impact on mental health** One uncontrolled prospective observational longitudinal study (de Vries et al. 2011) provided evidence for the impact on mental health (depression, anger and anxiety) in sex assigned at birth males. See the clinical effectiveness results table above for a full description of the study. • The mean (±SD) depression (BDI-II) score was not statistically significantly different in sex assigned at birth males compared with sex assigned at birth females at both baseline (T0) (n=not reported, mean BDI score [±SD]: 5.71 [±4.31] versus 10.34 [±8.24]) and T1 (n=not reported, 3.50 [±4.58] versus 6.09 [±7.93]), between sex difference p=0.057 • The mean (±SD) anger (TPI) score was statistically significantly lower (improved) in sex assigned at birth males compared with sex assigned at birth females at both baseline (T0) (n=not reported, mean TPI score [±SD]: 5.22 [±2.76] versus 6.43 [±2.78]) and T1 (n=not reported, 5.00 [±3.07] versus 6.39 [±2.59]), between sex difference p=0.022 • The mean (±SD) anxiety (STAI) score was statistically significantly lower (improved) in sex assigned at birth males

compared with sex assigned at birth females at both baseline (T0) (n=not reported, mean STAI score [±SD]: 4.33 [±2.68] versus 7.00 [±2.36]) and T1 (n=not reported, 4.39 [±2.64] versus 6.17 [±2.69]), between sex difference p<0.001 **(VERY LOW)**.

This study provides very low certainty evidence that the impact on mental health (depression, anger and anxiety) may be different in sex assigned at birth males (transfemales) compared with sex assigned at birth females (transmales). Over time there was no statistically significant difference between sex assigned at birth males and sex assigned at birth females for depression. However, sex assigned at birth males had statistically significantly lower levels of anger and anxiety than sex assigned at birth females at both baseline and follow up.

Impact on body image

One uncontrolled prospective observational longitudinal study (de Vries et al. 2011) provided evidence relating to the impact on body image in sex assigned at birth males.

- The mean (±SD) BIS score for primary sex characteristics was statistically significantly lower (improved) in sex assigned at birth males compared with sex assigned at birth females at both baseline (T0) (n=not reported, mean BIS score [±SD]: 4.02 [±0.61] versus 4.16 [±0.52]) and T1 (n=not reported, 3.74 [±0.78] versus 4.17 [±0.58]), between sex difference p=0.047
- The mean (±SD) BIS score for secondary sex was statistically significantly lower (improved) in sex assigned at birth males compared with sex assigned at birth females at both baseline (T0) (n=not reported, mean BIS score [±SD]: 2.66 [±0.50] versus 2.81 [±0.76]) and T1 (n=not reported, 2.39 [±0.69] versus 3.18 [±0.42]), between sex difference p=0.001
- The mean (±SD) BIS score for neutral body characteristics was not statistically significantly different in sex assigned at birth males compared with sex assigned at birth females at both baseline (T0) (n=not reported, mean BIS score [±SD]: 2.60 [±0.58] versus 2.24 [±0.62]) and T1 (n=not reported, 2.32 [±0.59] versus 2.61 [±0.50]), between sex difference p=0.777 **(VERY LOW)**.

This study provides very low certainty evidence that the impact on body image may be different in sex assigned at birth males (transfemales) compared with sex assigned at birth females (transmales). Sex assigned at birth males are less dissatisfied with their primary and secondary sex characteristics than sex assigned at birth females at both baseline and follow up, but the satisfaction with neutral body characteristics is not different.

Psychosocial impact

One uncontrolled prospective observational longitudinal study (de Vries et al. 2011) provided evidence for psychosocial impact in terms of global functioning (CGAS) and psychosocial functioning (CBCL and YSR) in sex assigned at birth males.

- Sex assigned at birth males had statistically higher mean (±SD) CGAS scores compared with sex assigned at birth

	females at both baseline (T0) (n=54, 73.10 [±8.44] versus 67.25 [±11.06]) and T1 (n=54, 77.33 [±8.69] versus 70.30 [±9.44]), between sex difference p=0.021 • There was no statistically significant difference between sex assigned at birth males and sex assigned at birth females for the CBCL Total T score at T0 or T1 (n=54, p=0.110) • There was no statistically significant difference between sex assigned at birth males and sex assigned at birth females for the CBCL internalising T score at T0 or T1 (n=54, p=0.286) • Sex assigned at birth males had statistically lower mean (±SD) CBCL externalising T scores compared with sex assigned at birth females at both T0 (n=54, 54.71 [±12.91] versus 60.70 [±12.64]) and T1 (n=54, 48.75 [±10.22] versus 57.87 [±11.66]), between sex difference p=0.015 • There was no statistically significant difference between sex assigned at birth males and sex assigned at birth females for the YSR Total T score at T0 or T1 (n=54, p=0.164) • There was no statistically significant difference between sex assigned at birth males and sex assigned at birth females for the YSR internalising T score at T0 or T1 (n=54, p=0.825) • Sex assigned at birth males had statistically lower mean (±SD) YSR externalising T scores compared with sex assigned at birth females at both T0 (n=54, 48.72 [±11.38] versus 57.24 [±10.59]) and T1 (n=54, 46.52 [±9.23] versus 52.97 [±8.51]), between sex difference p=0.004 **(VERY LOW)**. One uncontrolled, observational, prospective cohort study (Costa et al. 2015) provided evidence for psychosocial impact in terms of global functioning (CGAS) in sex assigned at birth males. • Sex assigned at birth males had statistically significant lower mean (±SD CGAS scores at baseline) compared with sex assigned at birth females (n=201, 55.4 [±12.7] versus 59.2 [±11.8], p=0.03) **(VERY LOW)**. **These studies provide very low certainty evidence that psychosocial impact may be different in sex assigned at birth males (transfemales) compared with sex assigned at birth females (transmales). However, no conclusions could be drawn.** **Change in bone density: lumbar** Three uncontrolled, observational, retrospective studies provided evidence relating to the effect of GnRH analogues on lumbar bone density in sex assigned at birth males (Joseph et al. 2019, Klink et al. 2015 and Vlot et al. 2017). See the safety results table above for a full description of the results. **These studies provide very low certainty evidence that GnRH analogues reduce the expected increase in lumbar bone density (BMAD or BMD) in sex assigned at birth males (transfemales; although some findings were not statistically significant). These studies also show that GnRH analogues do not statistically significantly decrease actual lumbar bone density (BMAD or BMD) in sex assigned at birth males (transfemales).** **Change in bone density: femoral**

	Three uncontrolled, observational, retrospective studies provided evidence for the effect of GnRH analogues on femoral bone density in sex assigned at birth males (Joseph et al. 2019, Klink et al. 2015 and Vlot et al. 2017). See the safety results table above for a full description of the results. **These studies provide very low certainty evidence that GnRH analogues may reduce the expected increase in femoral bone density (femoral neck or area BMAD or BMD) in sex assigned at birth males (transfemales; although some findings were not statistically significant). These studies also show that GnRH analogues do not statistically significantly decrease actual femoral bone density (femoral area BMAD or femoral neck BMD) in sex assigned at birth males (transfemales).** **Cognitive development or functioning** One cross-sectional observational study (Staphorsius et al. 2015) provided comparative evidence on cognitive development or functioning in sex assigned at birth males. See the safety results table above for a full description of the results. **This study provides very low certainty evidence (with no statistical analysis) on the effects of GnRH analogues on cognitive development or functioning in sex assigned at birth males (transfemales). No conclusions could be drawn.** **Other safety outcomes: kidney function** One prospective observational study (Schagen et al. 2016) provided non-comparative evidence on change in serum creatinine in sex assigned at birth males. See the safety results table above for a full description of the results. **This study provides very low certainty evidence that GnRH analogues do not affect renal function in sex assigned at birth males (transfemales).**
Sex assigned at birth females (transmales) **Certainty of evidence: Very low**	Some studies reported data separately for sex assigned at birth females (transmales). This included some direct comparisons with sex assigned at birth males (transfemales). **Impact on gender dysphoria** One uncontrolled prospective observational longitudinal study (de Vries et al. 2011) and one prospective observational longitudinal study (Costa et al. 2015) provided evidence for gender dysphoria in sex assigned at birth females. See the sex assigned at birth males (transfemales) row above for a full description of the results. **These studies provide very low certainty evidence that in sex assigned at birth females (transmales), gender dysphoria is higher than in sex assigned at birth males (transfemales) at both baseline and follow up.** **Impact on mental health** One uncontrolled prospective observational longitudinal study (de Vries et al. 2011) provided evidence relating to the impact on mental health (depression, anger and anxiety) in sex assigned at birth

	females. See the sex assigned at birth males (transfemales) row above for a full description of the results. **This study provides very low certainty evidence that the impact on mental health (depression, anger and anxiety) may be different in sex assigned at birth females (transmales) compared with sex assigned at birth males (transfemales). Over time there was no statistically significant difference between sex assigned at birth females and sex assigned at birth males for depression. However, sex assigned at birth females had statistically significantly greater levels of anger and anxiety than sex assigned at birth males at baseline and follow up.** **Impact on body image** One uncontrolled prospective observational longitudinal study (de Vries et al. 2011) provided evidence relating to the impact on body image in sex assigned at birth females. See the sex assigned at birth males (transfemales) row above for a full description of the results. **This study provides very low certainty evidence that the impact on body image may be different in sex assigned at birth females (transmales) compared with sex assigned at birth males (transfemales). Sex assigned at birth females are more dissatisfied with their primary and secondary sex characteristics than sex assigned at birth males at both baseline and follow up, but the satisfaction with neutral body characteristics is not different.** **Psychosocial impact** One uncontrolled prospective observational longitudinal study (de Vries et al. 2011) provided evidence for psychosocial impact in terms of global functioning (CGAS) and psychosocial functioning (CBCL and YSR) in sex assigned at birth females. One uncontrolled, observational, prospective cohort study (Costa et al. 2015) provided evidence for psychosocial impact in terms of global functioning (CGAS) in sex assigned at birth females. See the sex assigned at birth males (transfemales) row above for a full description of the results. **These studies provide very low certainty evidence that psychosocial impact may be different in sex assigned at birth females (transmales) compared with sex assigned at birth males (transfemales). However, no conclusions could be drawn.** **Change in bone density: lumbar** Three uncontrolled, observational, retrospective studies provided evidence relating to the effect of GnRH analogues on lumbar bone density in sex assigned at birth females (Joseph et al. 2019, Klink et al. 2015 and Vlot et al. 2017). See the safety results table above for a full description of the results. **These studies provide very low certainty evidence that GnRH analogues reduce the expected increase in lumbar bone density (BMAD or BMD) in sex assigned at birth females (transmales; although some findings were not statistically significant). These studies also show that GnRH analogues do not statistically**

	significantly decrease actual lumbar bone density (BMAD or BMD) in sex assigned at birth females (transmales). **Change in bone density: femoral** Three uncontrolled, observational, retrospective studies provided evidence relating to the effect of GnRH analogues on femoral bone density in sex assigned at birth females (Joseph et al. 2019, Klink et al. 2015 and Vlot et al. 2017). See the safety results table above for a full description of the results. **These studies provide very low certainty evidence that GnRH analogues may reduce the expected increase in femoral bone density (femoral neck or area BMAD or BMD) in sex assigned at birth females (transmales; although some findings were not statistically significant). These studies also show that GnRH analogues do not statistically significantly decrease actual femoral bone density (femoral area BMAD or femoral neck BMD) in sex assigned at birth females (transmales), apart from actual femoral area.** **Cognitive development or functioning** One cross-sectional observational study (Staphorsius et al. 2015) provided comparative evidence on cognitive development or functioning in sex assigned at birth females. See the safety results table above for a full description of the results. **This study provides very low certainty evidence (with no statistical analysis) on the effects of GnRH analogues on cognitive development or functioning in sex assigned at birth females (transmales). No conclusions could be drawn.** **Other safety outcomes: kidney function** One prospective observational study (Schagen et al. 2016) provided non-comparative evidence on change in serum creatinine in sex assigned at birth females (transmales). See the safety results table above for a full description of the results. **This study provides very low certainty evidence that GnRH analogues do not affect renal function in sex assigned at birth females (transmales).**
Duration of gender dysphoria	No evidence was identified.
Age at onset of gender dysphoria	No evidence was identified.
Age at which GnRH analogue started	No evidence was identified.
Age at onset of puberty	No evidence was identified.
Tanner stage at which GnRH analogue started	No evidence was identified.
Diagnosis of autistic spectrum disorder	No evidence was identified.

Diagnosis of mental health condition	No evidence was identified.

Abbreviations: BDI-II, Beck Depression Inventory-II; BIS, Body Image Scale; CBCL, Child Behaviour Checklist; CGAS, Children's Global Assessment Scale; SD, standard deviation; STAI, Trait Anxiety Scale of the State-Trait Personality Inventory; TPI, Trait Anger Scale of the State-Trait Personality Inventory; UGDS, Utrecht Gender Dysphoria Scale; YSR, Youth Self-Report

From the evidence selected,

(a) what are the criteria used by the research studies to define gender dysphoria, gender identity disorder and gender incongruence of childhood?

(b) what were the ages at which participants commenced treatment with GnRH analogues?

(c) what was the duration of treatment with GnRH analogues?

<table>
<tr><th>Outcome</th><th>Evidence statement</th></tr>
<tr><td>Diagnostic criteria</td><td>In 5 studies (Costa et al. 2015, Klink et al. 2015, Schagen et al. 2016, Staphorsius et al. 2015 and Vlot et al. 2017) the DSM-IV-TR criteria of gender identity disorder was used.

The study by Brik et al. 2020 used DSM-V criteria. The DSM-V has one overarching definition of gender dysphoria with separate specific criteria for children and for adolescents and adults. The general definition describes a conflict associated with significant distress and/or problems functioning associated with this conflict between the way they feel and the way they think of themselves which must have lasted at least 6 months.

It was not reported how gender dysphoria was defined in the remaining 3 studies (VERY LOW).

From the evidence selected, all studies that reported diagnostic criteria for gender dysphoria (6/9 studies) used the DSM criteria in use at the time the study was conducted.</td></tr>
<tr><td>Age when GnRH analogues started</td><td>8/9 studies reported the age at which participants started GnRH analogues, either as the mean age (with SD) or median age (with the range):

<table>
<tr><th>Study</th><th>Mean age (±SD)</th></tr>
<tr><td>Costa et al. 2015</td><td>16.5 years (±1.3)</td></tr>
<tr><td>de Vries et al. 2011</td><td>13.6 years (±1.8)</td></tr>
<tr><td>Joseph et al. 2019</td><td>13.2 years (±1.4) in transfemales
12.6 years (±1.0) in transmales</td></tr>
<tr><td>Khatchadourian et al. 2014</td><td>14.7 years (±1.9)</td></tr>
<tr><td>Klink et al. 2015</td><td>14.9 years (±1.9) in transfemales
15.0 years (±2.0) in transmales</td></tr>
</table>

<table>
<tr><th>Study</th><th>Median age (range)</th></tr>
<tr><td>Brik et al. 2020</td><td>15.5 years (11.1–18.6) in transfemales
16.1 years (10.1–17.9) in transmales</td></tr>
</table>
</td></tr>
</table>

	<table><tr><td>Schagen et al. 2016</td><td>13.6 years (11.6–17.9) in transfemales 14.2 years (11.1–18.6) in transmales</td></tr><tr><td>Vlot et al. 2017</td><td>13.5 years (11.5–18.3) in transfemales 15.1 years (11.7–18.6) in transmales</td></tr></table> Age at the start of GnRH analogues was not reported in Staphorsius et al. 2015, but participants were required to be at least 12 years **(VERY LOW)**. **The evidence included showed wide variation in the age (11 to 18 years old) at which children and adolescents with gender dysphoria started GnRH analogues.**
Duration of treatment	The duration of treatment with GnRH analogues was reported in 3/9 studies. The median duration was: • 2.1 years (range 1.6–2.8) in Brik et al. 2020. • 1.3 years (range 0.5–3.8) in transfemales and 1.5 years (range 0.25–5.2) in transmales in Klink et al. 2015. In Staphorsius et al. 2015, the mean duration was 1.6 years (SD ±1.0). In de Vries et al. 2011, the mean duration of time between starting GnRH analogues and gender-affirming hormones was 1.88 years (SD ±1.05). **The evidence included showed wide variation in the duration of treatment with GnRH analogues, but most studies did not report this information. Treatment duration ranged from a few months up to about 5 years.**

Abbreviations: DSM, Diagnostic and Statistical Manual of Mental Disorders criteria; SD, standard deviation.

6. Discussion

A key limitation to identifying the effectiveness and safety of GnRH analogues for children and adolescents with gender dysphoria is the lack of reliable comparative studies. The lack of clear, expected outcomes from treatment with a GnRH analogue (the purpose of which is to suppress secondary sexual characteristics which may cause distress from unwanted pubertal changes) also makes interpreting the evidence difficult. The size of the population with gender dysphoria means conducting a prospective trial may be unrealistic, at least on a single centre basis. There may also be ethical issues with a ‘no treatment arm’ in comparative trials of GnRH analogues, where there may be poor mental health outcomes if treatment is withheld. However, the use of an active comparator such as close psychological support may reduce ethical concerns in future trials.

The studies included in this evidence review are all small, uncontrolled observational studies, which are subject to bias and confounding, and are of very low certainty as assessed using modified GRADE. All the included studies reported physical and mental health comorbidities and concomitant treatments very poorly. For example, very little data are reported on how many children and adolescents needed additional mental health support, and for what reasons, or whether additional interventions, and what form and duration (for example drug treatment or counselling) that took. This is a possible confounder for the treatment outcomes in the studies because changes in critical and important

outcomes may be attributable to external care rather than the psychological support or GnRH analogues used in the studies.

The studies that reported diagnostic criteria for gender dysphoria (6/9 studies) used the Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria in use at the time the study was conducted (either DSM-IV-TR or DSM-V). The definition was unclear in the remaining studies. There was wide variation in the ages at which participants started a GnRH analogue, typically ranging from about 11 to 18 years. Similarly, there was a wide variation in the duration of use, but few studies reported this.

Changes in outcome scores for clinical effectiveness were assessed for statistical significance in the 3 studies reporting these outcomes (Costa et al. 2015; de Vries et al. 2011; Staphorsius et al. 2015). However, there is relatively little interpretation of whether the changes in outcome scores seen in these studies are clinically meaningful.

For some outcomes there was no statistically significant difference from before starting GnRH analogues until just before starting gender-affirming hormones. These were the Utrecht Gender Dysphoria Scale (UGDS) (which was assessed in 1 study de Vries et al. 2011), the Trait Anger (TPI) and Trait Anxiety (STAI) Scales (which were assessed in 1 study de Vries et al. 2011), and Body Image Scale (BIS) which was assessed in 1 study (de Vries et al. 2011).

The Beck Depression Inventory (BDI-II) was used in 1 study (de Vries et al. 2011) to assess change in depression from before starting GnRH analogues to just before starting gender-affirming hormones. The result is statistically significant, with the mean (±SD) BDI-II score decreasing from 8.31 (±7.12) at baseline to 4.95 (±6.27) at follow up (p=0.004). However, both scores fall into the minimal range using the general guidelines for interpretation of BDI-II (0 to 13 minimal, 14 to 19 mild depression, 20 to 28 moderate depression and 29 to 63 severe depression), suggesting that while statistically significant, it is unclear if this is a clinically meaningful change.

Psychosocial outcomes were assessed in 3 studies (Costa et al. 2015; de Vries et al. 2011; Staphorsius et al. 2015) using the Children's Global Assessment Scale (CGAS) and Child Behavior Checklist/Youth Self-Report (CBCL/YSR). The CGAS score was assessed in 2 studies (Costa et al. 2015; de Vries et al. 2011). In de Vries et al. 2011 the mean (±SD) CGAS score statistically significantly increased over time from 70.24 [±10.12] at baseline to 73.90 [±9.63] at follow up. CGAS scores are clinically categorised into 10 categories (10 to 1, 20 to 11 and so on until 100 to 91) and both scores reported were in a single category (71 to 80, no more than slight impairment) suggesting that while statistically significant, it is unclear if this is a clinically meaningful change. The Costa et al. 2015 study does highlight a larger change in CGAS scores from baseline to follow-up (mean [±SD] 58.72 [±11.38] compared with 67.40 [±13.39]), but whether this is clinically meaningful is unclear. The average score moved from the clinical category of 60 to 51 (variable functioning with sporadic difficulties) at baseline to 70 to 61 (some difficulty in a single area, but generally functioning pretty well) at follow up, but the large standard deviations suggest clinically significant overlaps between the scores from baseline to follow-up.

Psychosocial functioning using the CBCL/YSR was assessed in 2 studies (de Vries et al. 2011; Staphorsius et al. 2015). In de Vries et al. 2011 there was a statistically significant reduction in both CBCL and YSR scores from before starting GnRH analogues to just before

starting gender-affirming hormones. The study interpreted the CBCL/YSR with a proportion of adolescents who scored in the clinical range (a T-score above 63), which allows changes in clinically meaningful scores to be assessed, and proportions of adolescents in the clinical range for some CBCL and YSR scores decreased over time. One cross-sectional study (Staphorsius et al. 2015) assessed CBCL scores only, but it was unclear if this was the Total T score, or whether subscales of internalising or externalising scores were also assessed, and whether the results were statistically significant.

The 2 prospective observational studies (Costa et al. 2015; de Vries et al. 2011) are confounded by a number of common factors. Firstly, the single assessment of scores at baseline means it is unclear if scores were stable, already improving or declining before starting treatment. Secondly, in an uncontrolled study any changes in scores from baseline to follow-up could be attributed to a regression-to-mean, for example getting older has been positively associated with maturity and wellbeing. The studies use mean and standard deviations in the descriptive statistics and analyses; however, they do not report testing the normality of data which would support the use of parametric measures. The study by de Vries et al. 2011 used general linear models (regression) to examine between and within group variances (changes in outcomes). In using such models, the data is assumed to be balanced (measured at regular intervals and without missing data), but the large ranges in ages at which participants were assessed and started on various interventions suggests that ascertainment of outcome was unlikely to be regular and missing data was likely. Missing data was handled through listwise deletion (omits those cases with the missing data and analyses the remaining data) which is acceptable if data loss is completely random but for some outcomes where there was incomplete data for individual items this was not random (items were introduced by the authors after the first eligible adolescents had started GnRH analogues). The study provided no detail on whether these assumptions for the modeling were met, they also provided no adequate assessment of whether any regression diagnostics (analysis that seek to assess the validity of a model) or model fit (how much of the variance in outcome is explained by the between and within group variance) were undertaken.

The 2 retrospective observational studies (Brik et al. 2020; Khatchadourian et al. 2014) both only report absolute numbers for each trajectory along with reasons for stopping GnRH analogues. It is difficult to assess outcomes from such single centre studies because there is little comparative data for outcomes from other such services. A lack of any critical or other important outcomes also means the success of the treatment across all the participants is difficult to judge.

Three uncontrolled, observational, retrospective studies provided evidence relating to the effect of GnRH analogues on bone density (Joseph et al. 2019; Klink et al. 2015; Vlot et al. 2017). In all 3 studies, the participants acted as their own controls and change in bone density was determined between starting GnRH analogues and either after 1 and 2 year follow-up timepoints (Joseph et al. 2019) or when gender-affirming hormones were started (Klink et al. 2015 and Vlot et al. 2017). Observational studies such as these can only show an association with GnRH analogues and bone density; they cannot show that GnRH analogues caused any differences in bone density seen. Because there was no comparator group and participants acted as their own controls, it is unclear whether the findings are associated with GnRH analogues or due to changes over time. The authors reported z-scores which allows for comparison with the expected increase in bone density in the

general population. However, because no concomitant treatments or comorbidities were reported it is possible that the findings may not be because of GnRH analogues and there is another way in which the study population differs from the general population.

All the studies are from a limited number of, mainly European, care facilities. They are described as either tertiary referral or expert services but the low number of services providing such care and publishing evidence may bias the results towards the outcomes in these services only and limit extrapolation.

The first study (Brik et al. 2020) was an uncontrolled, retrospective, observational study that assessed the outcome trajectories of adolescents receiving GnRH analogues for gender dysphoria. This study followed-up 143 individuals who had received GnRH analogues (38 transfemales and 105 transmales) using clinical records to show outcomes for up to 9 years (continuing use of GnRH analogues, reasons for stopping GnRH analogues and onward care such as gender-affirming hormone use). The methods and results are well reported, but no analysis of data was undertaken. The views of adolescents and their parents are particularly difficult to interpret because no data on how many responded to each question and in what ways are reported.

The second study (Costa et al. 2015) was an uncontrolled, prospective observational study which assessed global functioning in adolescents with gender dysphoria using CGAS every 6 months, including during the first 6 months where statistically significant improvements were seen without GnRH analogues. The study is confounded by significant unexplained loss to follow-up (64.7%: from n=201 adolescents to n=71 after 18 months). Missing data for those lost to follow-up maybe more than sufficient to change the direction of effects seen in the study if the reasons for loss to follow-up are systematic (such as deriving little or no benefit from treatment). The study uses clustered data in its analysis, a single outcome (CGAS) measured in clusters (at different visits), and the analysis does not take account of the correlation of scores (data at different time points are not independent) as a significant change in scores early in the study means the successive changes measured against baseline were also significant. The study relies on multiple (>20) pairwise independent *t*-tests to examine change in CGAS between the 4 time points, increasing the possibility of type-I error (a false positive which occurs when a researcher incorrectly rejects a true null hypothesis) because the more tests performed the more likely a statistically significant result will be observed by chance alone.

The Costa et al. 2015 study compares immediately eligible and delayed eligible cohorts, however, it is highly likely that they are non-comparable groups because the immediately eligible group were those able to start GnRH analogues straight away whilst those in the delayed eligible group were either not ready to make a decision about starting treatment (no age comparison was made between the 2 groups so it is unclear if they were a younger cohort than the immediately eligible group) or had comorbid mental health or psychological difficulties. The authors report that those with concomitant problems (such as mental health problems, substantial problems with peers, or conflicts with parents or siblings) were referred to local mental health services but no details are provided.

The third study (de Vries et al. 2011) was an uncontrolled, prospective observational study which assessed gender dysphoria and psychological functioning before and after puberty suppression in adolescents with gender dysphoria. Although the study mentions the DSM-IV-TR there is no explicit discussion of this, or any other criteria, being used as the

diagnostic criteria for study entry. There are no details reported for how the outcomes in the study were assessed, and by whom. The length of follow-up for the outcomes in the model are questionable in relation to whether there was sufficient time for GnRH analogues to have a measurable effect. The time points used are start of GnRH analogues and start of gender-affirming hormones. Overall, the mean time between starting GnRH analogues and gender-affirming hormones was 1.88 (±1.05) years, but the range is as low as just 5 months between the 2 time points, which may be insufficient for any difference in outcome to have occurred in some individuals.

The fourth study (Joseph et al. 2019) was a retrospective, longitudinal observational single centre study which assessed bone mineral density in adolescents with gender dysphoria in the UK. For inclusion in the study, participants had to have been assessed by the Gender Identity Development Service multi-disciplinary psychosocial health team for at least 4 assessments over a minimum of 6 months. No other diagnostic criteria, such as the DSM-IV-TR, are discussed. Bone density was assessed using dual energy X-ray absorptiometry (DAXA) scan of the lumbar spine (L1-L4) and the femoral neck at baseline (n=70), 1 year (n=70) and 2 years after starting GnRH analogues (n=39). The results suggest a possible association between GnRH analogues and bone mineral apparent density. However, the evidence is of poor quality, and the results could be due to bias or chance. No concomitant treatments or comorbidities were reported.

The fifth study (Khatchadourian et al. 2014) was an uncontrolled retrospective observational study which describes patient characteristics at presentation, treatment, and response to treatment in 84 adolescents with gender dysphoria, of whom 27 received GnRH analogues. The study used clinical records to show outcomes for up to 13 years (continuing use of GnRH analogues, reasons for stopping GnRH analogues and onward care such as gender-affirming hormone use). The methods are well reported but the results for those taking GnRH analogues are poorly and incompletely reported, particularly for transfemales, and no analysis of data was undertaken. It is difficult to assess the results for stopping GnRH analogues due to incomplete reporting of this outcome.

The sixth study (Klink et al. 2015) was a retrospective longitudinal observational single centre study which assessed bone mineral density in adolescents with gender dysphoria, diagnosed with the DSM-IV-TR criteria. Bone density was assessed when starting GnRH analogues and then when starting gender-affirming hormones. Results are reported for transmales and transfemales separately and no results for the whole cohort are given. Statistical analyses were reported for all outcomes of interest but, because there was no comparator group and participants acted as their own controls, it is not known whether the findings are associated with GnRH analogues or due to changes over time. The authors reported z-scores which allows for comparison with the expected increase in bone density in the general population. However, because no concomitant treatments or comorbidities were reported it is possible that the findings may not be because of GnRH analogues and there is another way in which the study population differs from the general population.

The seventh study (Schagen et al. 2016) was a prospective observational study of 116 adolescents which provided very low certainty non-comparative evidence on change in serum creatinine between starting GnRH analogues and 1 year, and liver function during treatment. Statistical analyses were reported for changes in serum creatinine but not for liver function. Because there was no comparator group and participants acted as their own

controls, it is not known whether the findings are associated with GnRH analogues or due to changes over time, or concomitant treatments.

The eighth study (Staphorsius et al. 2015) was a cross-sectional study of 85 adolescents, 40 with gender dysphoria (of whom 20 were receiving GnRH analogues) and 45 matched controls (not further reported in this evidence review). The study includes 1 outcome of interest for clinical effectiveness (CBCL) and 1 outcome of interest for safety (cognitive development or functioning). The mean (±SD) CBCL, IQ test, reaction time and accuracy scores were given for each group, but the statistical analysis is unclear. It is not reported what analysis was used or which of the groups were compared, therefore it is difficult to interpret the results.

The ninth study (Vlot et al. 2017) was a retrospective observational study which assessed bone mineral apparent density in adolescents with DSM-IV-TR gender dysphoria. Measurements were taken at the start of GnRH analogues and at the start of gender-affirming hormones. Results are reported for young bone age and old bone age in transmales and transfemales separately, and no results for the whole cohort are given. Statistical analyses were reported for all outcomes of interest but, because there was no comparator group and participants acted as their own controls, it is not known whether the findings are associated with GnRH analogues or due to changes over time. The authors reported z-scores which allows for comparison with the expected increase in bone density in the general population. However, because no concomitant treatments or comorbidities were reported it is possible that the findings may not be because of GnRH analogues and there is another way in which the study population differs from the general population.

7. Conclusion

The results of the studies that reported impact on the critical outcomes of gender dysphoria and mental health (depression, anger and anxiety), and the important outcomes of body image and psychosocial impact (global and psychosocial functioning) in children and adolescents with gender dysphoria are of very low certainty using modified GRADE. They suggest little change with GnRH analogues from baseline to follow-up.

Studies that found differences in outcomes could represent changes that are either of questionable clinical value, or the studies themselves are not reliable and changes could be due to confounding, bias or chance. It is plausible, however, that a lack of difference in scores from baseline to follow-up is the effect of GnRH analogues in children and adolescents with gender dysphoria, in whom the development of secondary sexual characteristics might be expected to be associated with an increased impact on gender dysphoria, depression, anxiety, anger and distress over time without treatment. One study reported statistically significant reductions in the Child Behaviour Checklist/Youth Self-Report (CBCL/YSR) scores from baseline to follow up, and given that the purpose of GnRH analogues is to reduce distress caused by the development of secondary sexual characteristics and the CBCL/YSR in part measures distress, this could be an important finding. However, as the studies all lack reasonable controls not receiving GnRH analogues, the natural history of the outcomes measured in the studies is not known and any positive changes could be a regression to mean.

The results of the studies that reported bone density outcomes suggest that GnRH analogues may reduce the increase in bone density which is expected during puberty. However, as the studies themselves are not reliable, the results could be due to confounding, bias or chance. While controlled trials may not be possible, comparative studies are needed to understand this association and whether the effects of GnRH analogues on bone density are seen after treatment is stopped. All the studies that reported safety outcomes provided very low certainty evidence.

No cost-effectiveness evidence was found to determine whether or not GnRH analogues are cost-effective for children and adolescents with gender dysphoria.

The results of the studies that reported outcomes for subgroups of children and adolescents with gender dysphoria, suggest there may be differences between sex assigned at birth males (transfemales) and sex assigned at birth females (transmales).

Appendix A PICO document

The review questions for this evidence review are:

1. For children and adolescents with gender dysphoria, what is the clinical effectiveness of treatment with GnRH analogues compared with one or a combination of psychological support, social transitioning to the desired gender or no intervention?
2. For children and adolescents with gender dysphoria, what is the short-term and long-term safety of GnRH analogues compared with one or a combination of psychological support, social transitioning to the desired gender or no intervention?
3. For children and adolescents with gender dysphoria, what is the cost-effectiveness of GnRH analogues compared to one or a combination of psychological support, social transitioning to the desired gender or no intervention?
4. From the evidence selected, are there any subgroups of children and adolescents with gender dysphoria that may derive more (or less) advantage from treatment with GnRH analogues than the wider population of children and adolescents with gender dysphoria?
5. From the evidence selected,
   a) what are the criteria used by the research studies to define gender dysphoria, gender identity disorder and gender incongruence of childhood?
   b) what were the ages at which participants commenced treatment with GnRH analogues?
   c) what was the duration of treatment with GnRH analogues?

PICO table

P – Population and Indication	Children and adolescents aged 18 years or less who have gender dysphoria, gender identity disorder or gender incongruence of childhood as defined by study: The following subgroups of children and adolescents with gender dysphoria, gender identity disorder or gender incongruence of childhood need to be considered: • Sex assigned at birth males. • Sex assigned at birth females. • The duration of gender dysphoria: less than 6 months, 6-24 months, and more than 24 months. • The age of onset of gender dysphoria. • The age at which treatment was initiated. • The age of onset of puberty. • Tanner stage at which treatment was initiated. • Children and adolescents with gender dysphoria who have a pre-existing diagnosis of autistic spectrum disorder. • Children and adolescents with gender dysphoria who had a significant mental health symptom load at diagnosis including anxiety, depression (with or without a history of self-harm and suicidality), suicide attempts, psychosis, personality disorder, Attention Deficit Hyperactivity Disorder and eating disorders.
I – Intervention	Any GnRH analogue including: triptorelin*; buserelin; histrelin; goserelin (Zoladex); leuprorelin/leuprolide (Prostap); nafarelin.

	* Triptorelin (brand names Gonapeptyl and Decapeptyl) are used in Leeds Hospital, England. The search should include brand names as well as generic names.
C – Comparator(s)	One or a combination of: • Psychological support. • Social transitioning to the gender with which the individual identifies. • No intervention.
O – Outcomes	There are no known minimal clinically important differences and there are no preferred timepoints for the outcome measures selected. **All outcomes should be stratified by:** • The age at which treatment with GnRH analogues was initiated. • The length of treatment with GnRH analogues where possible. **A: Clinical Effectiveness** *Critical to decision making* • **Impact on Gender Dysphoria** This outcome is critical because gender dysphoria in adolescents and children is associated with significant distress and problems functioning. Impact on gender dysphoria may be measured by the Utrecht Gender Dysphoria Scale. Other measures as reported in studies may be used as an alternative to the stated measure. • **Impact on mental health** Examples of mental health problems include self-harm, thoughts of suicide, suicide attempts, eating disorders, depression/low mood and anxiety. These outcomes are critical because self-harm and thoughts of suicide have the potential to result in significant physical harm and for completed suicides the death of the young person. Disordered eating habits may cause significant morbidity in young people. Depression and anxiety are also critical outcomes because they may impact on social, occupational, or other areas of functioning of children and adolescents. The Child and Adolescent Psychiatric Assessment (CAPA) may be used to measure depression and anxiety. The impact on self-harm and suicidality (ideation and behaviour) may be measured using the Suicide Ideation Questionnaire Junior. Other measures may be used as an alternative to the stated measures. • **Impact on Quality of Life** This outcome is critical because gender dysphoria in children and adolescents may be associated with a significant reduction in health-related quality of life. Quality of Life may be measured by the KINDL questionnaire, Kidscreen 52. Other measures as reported in studies may be used as an alternative to the stated measure. *Important to decision making* • **Impact on body Image** This outcome is important because some transgender young people may desire to take steps to suppress features of their physical appearance associated with their sex assigned at birth or accentuate physical features of their desired gender. The Body Image Scale could be used as a measure. Other measures

	as reported in studies may also be used as an alternative to the stated measure. • **Psychosocial Impact** Examples of psychosocial impact are: coping mechanisms which may impact on substance misuse; family relationships; peer relationships. This outcome is important because gender dysphoria in adolescents and children is associated with internalising and externalising behaviours and emotional and behavioural problems which may impact on social and occupational functioning. The child behavioural check list (CBCL) may be used to measure the impact on psychosocial functioning. Other measures as reported in studies may be used as an alternative to the stated measure. • **Engagement with health care services** This outcome is important because patient engagement with healthcare services will impact on their clinical outcomes. Engagement with health care services may be measured using the Youth Health Care measure-satisfaction, utilization, and needs (YHC-SUN) questionnaire. Loss to follow up should also be ascertained as part of this outcome. Alternative measures to the YHC-SUN questionnaire may be used as reported in studies. • **Transitioning surgery – Impact on extent of and satisfaction with surgery** This outcome is important because some children and adolescents with gender dysphoria may proceed to transitioning surgery. Stated measures of the extent of transitioning surgery and satisfaction with surgery in studies may be reported. • **Stopping treatment** The proportion of patients who stop treatment with GnRH analogues and the reasons why. This outcome is important to patients because there is uncertainty about the short- and long-term safety and adverse effects of GnRH analogues in children and adolescents being treated for gender dysphoria. **B: Safety** • Short and long-term safety and adverse effects of taking GnRH analogues are important because GnRH analogues are not licensed for the treatment of adolescents and children with gender dysphoria. Aspects to be reported on should include: ○ Impact of the drug use such as its impact on bone density, arterial hypertension, cognitive development/functioning ○ Impact of withdrawing the drug such as, slipped upper femoral epiphysis, reversibility on the reproductive system, and any others as reported. **C: Cost effectiveness** Cost effectiveness studies should be reported.
Inclusion criteria	
Study design	Systematic reviews, randomised controlled trials, controlled clinical trials, cohort studies. If no higher level quality evidence is found, case series can be considered.

Language	English only
Patients	Human studies only
Age	18 years or less
Date limits	2000-2020
Exclusion criteria	
Publication type	Conference abstracts, non-systematic reviews, narrative reviews, commentaries, letters, editorials, guidelines and pre-publication prints
Study design	Case reports, resource utilisation studies

Appendix B Search strategy

Medline, Embase, the Cochrane Library, HTA and APA PsycInfo were searched on 23 July 2020, limiting the search to papers published in English language in the last 20 years. Conference abstracts and letters were excluded.

Database: Medline
Platform: Ovid
Version: Ovid MEDLINE(R) <1946 to July 21, 2020>
Search date: 23/7/2020
Number of results retrieved: 144
Search strategy:

1 Gender Dysphoria/ (485)
2 Gender Identity/ (18452)
3 "Sexual and Gender Disorders"/ (75)
4 Transsexualism/ (3758)
5 Transgender Persons/ (3143)
6 Health Services for Transgender Persons/ (136)
7 exp Sex Reassignment Procedures/ (836)
8 (gender* adj3 (dysphori* or affirm* or incongruen* or identi* or disorder* or confus* or minorit* or queer*)).tw. (7435)
9 (transgend* or transex* or transsex* or transfem* or transwom* or transma* or transmen* or transperson* or transpeopl*).tw. (12678)
10 (trans or crossgender* or cross-gender* or crossex* or cross-sex* or genderqueer*).tw. (102343)
11 ((sex or gender*) adj3 (reassign* or chang* or transform* or transition*)).tw. (6974)
12 (male-to-female or m2f or female-to-male or f2m).tw. (114841)
13 or/1-12 (252702)
14 exp Infant/ or Infant Health/ or Infant Welfare/ (1137479)
15 (prematur* or pre-matur* or preterm* or pre-term* or infan* or newborn* or new-born* or perinat* or peri-nat* or neonat* or neo-nat* or baby* or babies or toddler*).ti,ab,in,jn. (852400)
16 exp Child/ or exp Child Behavior/ or Child Health/ or Child Welfare/ (1913257)

17 Minors/ (2574)
18 (child* or minor or minors or boy* or girl* or kid or kids or young*).ti,ab,in,jn. (2361686)
19 exp pediatrics/ (58118)
20 (pediatric* or paediatric* or peadiatric*).ti,ab,in,jn. (836269)
21 Adolescent/ or Adolescent Behavior/ or Adolescent Health/ (2024207)
22 Puberty/ (13278)
23 (adolescen* or pubescen* or prepubescen* or pre-pubescen* or pubert* or prepubert* or pre-pubert* or teen* or preteen* or pre-teen* or juvenil* or youth* or under*age*).ti,ab,in,jn. (424246)
24 Schools/ (38104)
25 Child Day Care Centers/ or exp Nurseries/ or Schools, Nursery/ (7199)
26 (pre-school* or preschool* or kindergar* or daycare or day-care or nurser* or school* or pupil* or student*).ti,ab,jn. (468992)
27 (("eight" or "nine" or "ten" or "eleven" or "twelve" or "thirteen" or "fourteen" or "fifteen" or "sixteen" or "seventeen" or "eighteen" or "nineteen") adj2 (year or years or age or ages or aged)).ti,ab. (89353)
28 (("8" or "9" or "10" or "11" or "12" or "13" or "14" or "15" or "16" or "17" or "18" or "19") adj2 (year or years or age or ages or aged)).ti,ab. (887838)
29 or/14-28 (5534171)
30 13 and 29 (79263)
31 (transchild* or transyouth* or transteen* or transadoles* or transgirl* or transboy*).tw. (7)
32 30 or 31 (79263)
33 Gonadotropin-Releasing Hormone/ (27588)
34 (pubert* adj3 block*).ti,ab. (78)
35 ((gonadotrophin or gonadotropin) and releasing).ti,ab. (17299)
36 (GnRH adj2 analog*).ti,ab. (2541)
37 GnRH*.ti,ab. (20991)
38 "GnRH agonist*".ti,ab. (4040)
39 Triptorelin Pamoate/ (1906)
40 triptorelin.ti,ab. (677)
41 arvekap.ti,ab. (1)
42 ("AY 25650" or AY25650).ti,ab. (1)
43 ("BIM 21003" or BIM21003).ti,ab. (0)
44 ("BN 52014" or BN52014).ti,ab. (0)
45 ("CL 118532" or CL118532).ti,ab. (0)
46 Debio.ti,ab. (83)
47 diphereline.ti,ab. (17)
48 moapar.ti,ab. (0)
49 pamorelin.ti,ab. (0)
50 trelstar.ti,ab. (3)
51 triptodur.ti,ab. (1)
52 ("WY 42422" or WY42422).ti,ab. (0)
53 ("WY 42462" or WY42462).ti,ab. (0)
54 gonapeptyl.ti,ab. (0)
55 decapeptyl.ti,ab. (210)
56 salvacyl.ti,ab. (0)
57 Buserelin/ (2119)
58 buserelin.ti,ab. (1304)

59 bigonist.ti,ab. (0)
60 ("hoe 766" or hoe-766 or hoe766).ti,ab. (69)
61 profact.ti,ab. (2)
62 receptal.ti,ab. (30)
63 suprecur.ti,ab. (4)
64 suprefact.ti,ab. (22)
65 tiloryth.ti,ab. (0)
66 histrelin.ti,ab. (55)
67 "LHRH-hydrogel implant".ti,ab. (1)
68 ("RL 0903" or RL0903).ti,ab. (1)
69 ("SPD 424" or SPD424).ti,ab. (1)
70 goserelin.ti,ab. (875)
71 Goserelin/ (1612)
72 ("ici 118630" or ici118630).ti,ab. (51)
73 ("ZD-9393" or ZD9393).ti,ab. (0)
74 zoladex.ti,ab. (379)
75 leuprorelin.ti,ab. (413)
76 carcinil.ti,ab. (0)
77 enanton*.ti,ab. (23)
78 ginecrin.ti,ab. (0)
79 leuplin.ti,ab. (13)
80 Leuprolide/ (2900)
81 leuprolide.ti,ab. (1743)
82 lucrin.ti,ab. (11)
83 lupron.ti,ab. (162)
84 provren.ti,ab. (0)
85 procrin.ti,ab. (3)
86 ("tap 144" or tap144).ti,ab. (40)
87 (a-43818 or a43818).ti,ab. (3)
88 Trenantone.ti,ab. (1)
89 staladex.ti,ab. (0)
90 prostap.ti,ab. (6)
91 Nafarelin/ (327)
92 nafarelin.ti,ab. (251)
93 ("76932-56-4" or "76932564").ti,ab. (0)
94 ("76932-60-0" or "76932600").ti,ab. (0)
95 ("86220-42-0" or "86220420").ti,ab. (0)
96 ("rs 94991 298" or rs94991298).ti,ab. (0)
97 synarel.ti,ab. (12)
98 deslorelin.ti,ab. (263)
99 gonadorelin.ti,ab. (201)
100 ("33515-09-2" or "33515092").ti,ab. (0)
101 ("51952-41-1" or "51952411").ti,ab. (0)
102 ("52699-48-6" or "52699486").ti,ab. (0)
103 cetrorelix.ti,ab. (463)
104 cetrotide.ti,ab. (41)
105 ("NS 75A" or NS75A).ti,ab. (0)
106 ("NS 75B" or NS75B).ti,ab. (0)

107 ("SB 075" or SB075).ti,ab. (0)
108 ("SB 75" or SB75).ti,ab. (63)
109 gonadoliberin.ti,ab. (143)
110 kryptocur.ti,ab. (6)
111 cetrorelix.ti,ab. (463)
112 cetrotide.ti,ab. (41)
113 antagon.ti,ab. (17)
114 ganirelix.ti,ab. (138)
115 ("ORG 37462" or ORG37462).ti,ab. (3)
116 orgalutran.ti,ab. (20)
117 ("RS 26306" or RS26306).ti,ab. (5)
118 ("AY 24031" or AY24031).ti,ab. (0)
119 factrel.ti,ab. (11)
120 fertagyl.ti,ab. (11)
121 lutrelef.ti,ab. (5)
122 lutrepulse.ti,ab. (3)
123 relefact.ti,ab. (10)
124 fertiral.ti,ab. (0)
125 (hoe471 or "hoe 471").ti,ab. (6)
126 relisorm.ti,ab. (4)
127 cystorelin.ti,ab. (18)
128 dirigestran.ti,ab. (5)
129 or/33-128 (42216)
130 32 and 129 (416)
131 limit 130 to english language (393)
132 limit 131 to (letter or historical article or comment or editorial or news or case reports) (36)
133 131 not 132 (357)
134 animals/ not humans/ (4686361)
135 133 not 134 (181)
136 limit 135 to yr="2000 -Current" (144)

Database: Medline in-process
Platform: Ovid
Version: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <1946 to July 21, 2020>
Search date: 23/7/2020
Number of results retrieved:
Search strategy: 42

1 Gender Dysphoria/ (0)
2 Gender Identity/ (0)
3 "Sexual and Gender Disorders"/ (0)
4 Transsexualism/ (0)
5 Transgender Persons/ (0)
6 Health Services for Transgender Persons/ (0)
7 exp Sex Reassignment Procedures/ (0)

8 (gender* adj3 (dysphori* or affirm* or incongruen* or identi* or disorder* or confus* or minorit* or queer*)).tw. (1645)
9 (transgend* or transex* or transsex* or transfem* or transwom* or transma* or transmen* or transperson* or transpeopl*).tw. (2333)
10 (trans or crossgender* or cross-gender* or crossex* or cross-sex* or genderqueer*).tw. (20884)
11 ((sex or gender*) adj3 (reassign* or chang* or transform* or transition*)).tw. (968)
12 (male-to-female or m2f or female-to-male or f2m).tw. (15513)
13 or/1-12 (39905)
14 exp Infant/ or Infant Health/ or Infant Welfare/ (0)
15 (prematur* or pre-matur* or preterm* or pre-term* or infan* or newborn* or new-born* or perinat* or peri-nat* or neonat* or neo-nat* or baby* or babies or toddler*).ti,ab,in,jn. (80723)
16 exp Child/ or exp Child Behavior/ or Child Health/ or Child Welfare/ (0)
17 Minors/ (0)
18 (child* or minor or minors or boy* or girl* or kid or kids or young*).ti,ab,in,jn. (321871)
19 exp pediatrics/ (0)
20 (pediatric* or paediatric* or peadiatric*).ti,ab,in,jn. (119783)
21 Adolescent/ or Adolescent Behavior/ or Adolescent Health/ (0)
22 Puberty/ (0)
23 (adolescen* or pubescen* or prepubescen* or pre-pubescen* or pubert* or prepubert* or pre-pubert* or teen* or preteen* or pre-teen* or juvenil* or youth* or under*age*).ti,ab,in,jn. (60264)
24 Schools/ (0)
25 Child Day Care Centers/ or exp Nurseries/ or Schools, Nursery/ (0)
26 (pre-school* or preschool* or kindergar* or daycare or day-care or nurser* or school* or pupil* or student*).ti,ab,jn. (69233)
27 (("eight" or "nine" or "ten" or "eleven" or "twelve" or "thirteen" or "fourteen" or "fifteen" or "sixteen" or "seventeen" or "eighteen" or "nineteen") adj2 (year or years or age or ages or aged)).ti,ab. (10319)
28 (("8" or "9" or "10" or "11" or "12" or "13" or "14" or "15" or "16" or "17" or "18" or "19") adj2 (year or years or age or ages or aged)).ti,ab. (112800)
29 or/14-28 (525529)
30 13 and 29 (9196)
31 (transchild* or transyouth* or transteen* or transadoles* or transgirl* or transboy*).tw. (3)
32 30 or 31 (9197)
33 Gonadotropin-Releasing Hormone/ (0)
34 (pubert* adj3 block*).ti,ab. (19)
35 ((gonadotrophin or gonadotropin) and releasing).ti,ab. (1425)
36 (GnRH adj2 analog*).ti,ab. (183)
37 GnRH*.ti,ab. (1695)
38 "GnRH agonist*".ti,ab. (379)
39 Triptorelin Pamoate/ (0)
40 triptorelin.ti,ab. (72)
41 arvekap.ti,ab. (0)
42 ("AY 25650" or AY25650).ti,ab. (0)
43 ("BIM 21003" or BIM21003).ti,ab. (0)
44 ("BN 52014" or BN52014).ti,ab. (0)
45 ("CL 118532" or CL118532).ti,ab. (0)

46 Debio.ti,ab. (11)
47 diphereline.ti,ab. (6)
48 moapar.ti,ab. (0)
49 pamorelin.ti,ab. (0)
50 trelstar.ti,ab. (0)
51 triptodur.ti,ab. (0)
52 ("WY 42422" or WY42422).ti,ab. (0)
53 ("WY 42462" or WY42462).ti,ab. (0)
54 gonapeptyl.ti,ab. (0)
55 decapeptyl.ti,ab. (8)
56 salvacyl.ti,ab. (0)
57 Buserelin/ (0)
58 buserelin.ti,ab. (59)
59 bigonist.ti,ab. (0)
60 ("hoe 766" or hoe-766 or hoe766).ti,ab. (3)
61 profact.ti,ab. (0)
62 receptal.ti,ab. (0)
63 suprecur.ti,ab. (1)
64 suprefact.ti,ab. (2)
65 tiloryth.ti,ab. (0)
66 histrelin.ti,ab. (9)
67 "LHRH-hydrogel implant".ti,ab. (0)
68 ("RL 0903" or RL0903).ti,ab. (0)
69 ("SPD 424" or SPD424).ti,ab. (0)
70 goserelin.ti,ab. (68)
71 Goserelin/ (0)
72 ("ici 118630" or ici118630).ti,ab. (0)
73 ("ZD-9393" or ZD9393).ti,ab. (0)
74 zoladex.ti,ab. (6)
75 leuprorelin.ti,ab. (47)
76 carcinil.ti,ab. (0)
77 enanton*.ti,ab. (1)
78 ginecrin.ti,ab. (0)
79 leuplin.ti,ab. (1)
80 Leuprolide/ (0)
81 leuprolide.ti,ab. (121)
82 lucrin.ti,ab. (4)
83 lupron.ti,ab. (10)
84 provren.ti,ab. (0)
85 procrin.ti,ab. (0)
86 ("tap 144" or tap144).ti,ab. (0)
87 (a-43818 or a43818).ti,ab. (0)
88 Trenantone.ti,ab. (1)
89 staladex.ti,ab. (0)
90 prostap.ti,ab. (0)
91 Nafarelin/ (0)
92 nafarelin.ti,ab. (5)
93 ("76932-56-4" or "76932564").ti,ab. (0)

94 ("76932-60-0" or "76932600").ti,ab. (0)
95 ("86220-42-0" or "86220420").ti,ab. (0)
96 ("rs 94991 298" or rs94991298).ti,ab. (0)
97 synarel.ti,ab. (0)
98 deslorelin.ti,ab. (14)
99 gonadorelin.ti,ab. (13)
100 ("33515-09-2" or "33515092").ti,ab. (0)
101 ("51952-41-1" or "51952411").ti,ab. (0)
102 ("52699-48-6" or "52699486").ti,ab. (0)
103 cetrorelix.ti,ab. (31)
104 cetrotide.ti,ab. (5)
105 ("NS 75A" or NS75A).ti,ab. (0)
106 ("NS 75B" or NS75B).ti,ab. (0)
107 ("SB 075" or SB075).ti,ab. (0)
108 ("SB 75" or SB75).ti,ab. (2)
109 gonadoliberin.ti,ab. (4)
110 kryptocur.ti,ab. (1)
111 cetrorelix.ti,ab. (31)
112 cetrotide.ti,ab. (5)
113 antagon.ti,ab. (0)
114 ganirelix.ti,ab. (8)
115 ("ORG 37462" or ORG37462).ti,ab. (0)
116 orgalutran.ti,ab. (3)
117 ("RS 26306" or RS26306).ti,ab. (0)
118 ("AY 24031" or AY24031).ti,ab. (0)
119 factrel.ti,ab. (2)
120 fertagyl.ti,ab. (1)
121 lutrelef.ti,ab. (0)
122 lutrepulse.ti,ab. (0)
123 relefact.ti,ab. (0)
124 fertiral.ti,ab. (0)
125 (hoe471 or "hoe 471").ti,ab. (0)
126 relisorm.ti,ab. (0)
127 cystorelin.ti,ab. (1)
128 dirigestran.ti,ab. (0)
129 or/33-128 (2332)
130 32 and 129 (45)
131 limit 130 to english language (45)
132 limit 131 to yr="2000 -Current" (42)

Database: Medline epubs ahead of print
Platform: Ovid
Version: Ovid MEDLINE(R) Epub Ahead of Print <July 21, 2020>
Search date: 23/7/2020
Number of results retrieved: 8
Search strategy:

1 Gender Dysphoria/ (0)

2 Gender Identity/ (0)
3 "Sexual and Gender Disorders"/ (0)
4 Transsexualism/ (0)
5 Transgender Persons/ (0)
6 Health Services for Transgender Persons/ (0)
7 exp Sex Reassignment Procedures/ (0)
8 (gender* adj3 (dysphori* or affirm* or incongruen* or identi* or disorder* or confus* or minorit* or queer*)).tw. (486)
9 (transgend* or transex* or transsex* or transfem* or transwom* or transma* or transmen* or transperson* or transpeopl*).tw. (640)
10 (trans or crossgender* or cross-gender* or crossex* or cross-sex* or genderqueer*).tw. (1505)
11 ((sex or gender*) adj3 (reassign* or chang* or transform* or transition*)).tw. (178)
12 (male-to-female or m2f or female-to-male or f2m).tw. (2480)
13 or/1-12 (4929)
14 exp Infant/ or Infant Health/ or Infant Welfare/ (0)
15 (prematur* or pre-matur* or preterm* or pre-term* or infan* or newborn* or new-born* or perinat* or peri-nat* or neonat* or neo-nat* or baby* or babies or toddler*).ti,ab,in,jn. (15496)
16 exp Child/ or exp Child Behavior/ or Child Health/ or Child Welfare/ (0)
17 Minors/ (0)
18 (child* or minor or minors or boy* or girl* or kid or kids or young*).ti,ab,in,jn. (53563)
19 exp pediatrics/ (0)
20 (pediatric* or paediatric* or peadiatric*).ti,ab,in,jn. (22796)
21 Adolescent/ or Adolescent Behavior/ or Adolescent Health/ (0)
22 Puberty/ (0)
23 (adolescen* or pubescen* or prepubescen* or pre-pubescen* or pubert* or prepubert* or pre-pubert* or teen* or preteen* or pre-teen* or juvenil* or youth* or under*age*).ti,ab,in,jn. (13087)
24 Schools/ (0)
25 Child Day Care Centers/ or exp Nurseries/ or Schools, Nursery/ (0)
26 (pre-school* or preschool* or kindergar* or daycare or day-care or nurser* or school* or pupil* or student*).ti,ab,jn. (12443)
27 (("eight" or "nine" or "ten" or "eleven" or "twelve" or "thirteen" or "fourteen" or "fifteen" or "sixteen" or "seventeen" or "eighteen" or "nineteen") adj2 (year or years or age or ages or aged)).ti,ab. (1416)
28 (("8" or "9" or "10" or "11" or "12" or "13" or "14" or "15" or "16" or "17" or "18" or "19") adj2 (year or years or age or ages or aged)).ti,ab. (20166)
29 or/14-28 (88366)
30 13 and 29 (1638)
31 (transchild* or transyouth* or transteen* or transadoles* or transgirl* or transboy*).tw. (1)
32 30 or 31 (1638)
33 Gonadotropin-Releasing Hormone/ (0)
34 (pubert* adj3 block*).ti,ab. (2)
35 ((gonadotrophin or gonadotropin) and releasing).ti,ab. (176)
36 (GnRH adj2 analog*).ti,ab. (30)
37 GnRH*.ti,ab. (223)
38 "GnRH agonist*".ti,ab. (49)
39 Triptorelin Pamoate/ (0)

40 triptorelin.ti,ab. (12)
41 arvekap.ti,ab. (0)
42 ("AY 25650" or AY25650).ti,ab. (0)
43 ("BIM 21003" or BIM21003).ti,ab. (0)
44 ("BN 52014" or BN52014).ti,ab. (0)
45 ("CL 118532" or CL118532).ti,ab. (0)
46 Debio.ti,ab. (2)
47 diphereline.ti,ab. (1)
48 moapar.ti,ab. (0)
49 pamorelin.ti,ab. (0)
50 trelstar.ti,ab. (0)
51 triptodur.ti,ab. (0)
52 ("WY 42422" or WY42422).ti,ab. (0)
53 ("WY 42462" or WY42462).ti,ab. (0)
54 gonapeptyl.ti,ab. (0)
55 decapeptyl.ti,ab. (0)
56 salvacyl.ti,ab. (0)
57 Buserelin/ (0)
58 buserelin.ti,ab. (7)
59 bigonist.ti,ab. (0)
60 ("hoe 766" or hoe-766 or hoe766).ti,ab. (0)
61 profact.ti,ab. (0)
62 receptal.ti,ab. (0)
63 suprecur.ti,ab. (0)
64 suprefact.ti,ab. (1)
65 tiloryth.ti,ab. (0)
66 histrelin.ti,ab. (2)
67 "LHRH-hydrogel implant".ti,ab. (0)
68 ("RL 0903" or RL0903).ti,ab. (0)
69 ("SPD 424" or SPD424).ti,ab. (0)
70 goserelin.ti,ab. (11)
71 Goserelin/ (0)
72 ("ici 118630" or ici118630).ti,ab. (0)
73 ("ZD-9393" or ZD9393).ti,ab. (0)
74 zoladex.ti,ab. (1)
75 leuprorelin.ti,ab. (13)
76 carcinil.ti,ab. (0)
77 enanton*.ti,ab. (1)
78 ginecrin.ti,ab. (0)
79 leuplin.ti,ab. (0)
80 Leuprolide/ (0)
81 leuprolide.ti,ab. (22)
82 lucrin.ti,ab. (0)
83 lupron.ti,ab. (2)
84 provren.ti,ab. (0)
85 procrin.ti,ab. (0)
86 ("tap 144" or tap144).ti,ab. (1)
87 (a-43818 or a43818).ti,ab. (0)

88 Trenantone.ti,ab. (0)
89 staladex.ti,ab. (0)
90 prostap.ti,ab. (0)
91 Nafarelin/ (0)
92 nafarelin.ti,ab. (4)
93 ("76932-56-4" or "76932564").ti,ab. (0)
94 ("76932-60-0" or "76932600").ti,ab. (0)
95 ("86220-42-0" or "86220420").ti,ab. (0)
96 ("rs 94991 298" or rs94991298).ti,ab. (0)
97 synarel.ti,ab. (0)
98 deslorelin.ti,ab. (3)
99 gonadorelin.ti,ab. (3)
100 ("33515-09-2" or "33515092").ti,ab. (0)
101 ("51952-41-1" or "51952411").ti,ab. (0)
102 ("52699-48-6" or "52699486").ti,ab. (0)
103 cetrorelix.ti,ab. (6)
104 cetrotide.ti,ab. (2)
105 ("NS 75A" or NS75A).ti,ab. (0)
106 ("NS 75B" or NS75B).ti,ab. (0)
107 ("SB 075" or SB075).ti,ab. (0)
108 ("SB 75" or SB75).ti,ab. (0)
109 gonadoliberin.ti,ab. (0)
110 kryptocur.ti,ab. (0)
111 cetrorelix.ti,ab. (6)
112 cetrotide.ti,ab. (2)
113 antagon.ti,ab. (1)
114 ganirelix.ti,ab. (1)
115 ("ORG 37462" or ORG37462).ti,ab. (0)
116 orgalutran.ti,ab. (0)
117 ("RS 26306" or RS26306).ti,ab. (0)
118 ("AY 24031" or AY24031).ti,ab. (0)
119 factrel.ti,ab. (0)
120 fertagyl.ti,ab. (0)
121 lutrelef.ti,ab. (0)
122 lutrepulse.ti,ab. (0)
123 relefact.ti,ab. (0)
124 fertiral.ti,ab. (0)
125 (hoe471 or "hoe 471").ti,ab. (0)
126 relisorm.ti,ab. (0)
127 cystorelin.ti,ab. (0)
128 dirigestran.ti,ab. (0)
129 or/33-128 (310)
130 32 and 129 (8)
131 limit 130 to english language (8)
132 limit 131 to yr="2000 -Current" (8)

Database: Medline daily update
Platform: Ovid

Version: Ovid MEDLINE(R) Daily Update <July 21, 2020>
Search date: 23/7/2020
Number of results retrieved: 1
Search strategy

1 Gender Dysphoria/ (4)
2 Gender Identity/ (38)
3 "Sexual and Gender Disorders"/ (0)
4 Transsexualism/ (2)
5 Transgender Persons/ (26)
6 Health Services for Transgender Persons/ (1)
7 exp Sex Reassignment Procedures/ (3)
8 (gender* adj3 (dysphori* or affirm* or incongruen* or identi* or disorder* or confus* or minorit* or queer*)).tw. (24)
9 (transgend* or transex* or transsex* or transfem* or transwom* or transma* or transmen* or transperson* or transpeopl*).tw. (39)
10 (trans or crossgender* or cross-gender* or crossex* or cross-sex* or genderqueer*).tw. (87)
11 ((sex or gender*) adj3 (reassign* or chang* or transform* or transition*)).tw. (15)
12 (male-to-female or m2f or female-to-male or f2m).tw. (181)
13 or/1-12 (358)
14 exp Infant/ or Infant Health/ or Infant Welfare/ (932)
15 (prematur* or pre-matur* or preterm* or pre-term* or infan* or newborn* or new-born* or perinat* or peri-nat* or neonat* or neo-nat* or baby* or babies or toddler*).ti,ab,in,jn. (981)
16 exp Child/ or exp Child Behavior/ or Child Health/ or Child Welfare/ (1756)
17 Minors/ (3)
18 (child* or minor or minors or boy* or girl* or kid or kids or young*).ti,ab,in,jn. (3672)
19 exp pediatrics/ (75)
20 (pediatric* or paediatric* or peadiatric*).ti,ab,in,jn. (1658)
21 Adolescent/ or Adolescent Behavior/ or Adolescent Health/ (2006)
22 Puberty/ (8)
23 (adolescen* or pubescen* or prepubescen* or pre-pubescen* or pubert* or prepubert* or pre-pubert* or teen* or preteen* or pre-teen* or juvenil* or youth* or under*age*).ti,ab,in,jn. (732)
24 Schools/ (56)
25 Child Day Care Centers/ or exp Nurseries/ or Schools, Nursery/ (5)
26 (pre-school* or preschool* or kindergar* or daycare or day-care or nurser* or school* or pupil* or student*).ti,ab,jn. (622)
27 (("eight" or "nine" or "ten" or "eleven" or "twelve" or "thirteen" or "fourteen" or "fifteen" or "sixteen" or "seventeen" or "eighteen" or "nineteen") adj2 (year or years or age or ages or aged)).ti,ab. (98)
28 (("8" or "9" or "10" or "11" or "12" or "13" or "14" or "15" or "16" or "17" or "18" or "19") adj2 (year or years or age or ages or aged)).ti,ab. (1301)
29 or/14-28 (6705)
30 13 and 29 (130)
31 (transchild* or transyouth* or transteen* or transadoles* or transgirl* or transboy*).tw. (0)
32 30 or 31 (130)
33 Gonadotropin-Releasing Hormone/ (11)

34 (pubert* adj3 block*).ti,ab. (0)
35 ((gonadotrophin or gonadotropin) and releasing).ti,ab. (10)
36 (GnRH adj2 analog*).ti,ab. (2)
37 GnRH*.ti,ab. (14)
38 "GnRH agonist*".ti,ab. (4)
39 Triptorelin Pamoate/ (1)
40 triptorelin.ti,ab. (1)
41 arvekap.ti,ab. (0)
42 ("AY 25650" or AY25650).ti,ab. (0)
43 ("BIM 21003" or BIM21003).ti,ab. (0)
44 ("BN 52014" or BN52014).ti,ab. (0)
45 ("CL 118532" or CL118532).ti,ab. (0)
46 Debio.ti,ab. (1)
47 diphereline.ti,ab. (0)
48 moapar.ti,ab. (0)
49 pamorelin.ti,ab. (0)
50 trelstar.ti,ab. (0)
51 triptodur.ti,ab. (0)
52 ("WY 42422" or WY42422).ti,ab. (0)
53 ("WY 42462" or WY42462).ti,ab. (0)
54 gonapeptyl.ti,ab. (0)
55 decapeptyl.ti,ab. (0)
56 salvacyl.ti,ab. (0)
57 Buserelin/ (0)
58 buserelin.ti,ab. (0)
59 bigonist.ti,ab. (0)
60 ("hoe 766" or hoe-766 or hoe766).ti,ab. (0)
61 profact.ti,ab. (0)
62 receptal.ti,ab. (0)
63 suprecur.ti,ab. (0)
64 suprefact.ti,ab. (0)
65 tiloryth.ti,ab. (0)
66 histrelin.ti,ab. (0)
67 "LHRH-hydrogel implant".ti,ab. (0)
68 ("RL 0903" or RL0903).ti,ab. (0)
69 ("SPD 424" or SPD424).ti,ab. (0)
70 goserelin.ti,ab. (1)
71 Goserelin/ (2)
72 ("ici 118630" or ici118630).ti,ab. (0)
73 ("ZD-9393" or ZD9393).ti,ab. (0)
74 zoladex.ti,ab. (0)
75 leuprorelin.ti,ab. (0)
76 carcinil.ti,ab. (0)
77 enanton*.ti,ab. (0)
78 ginecrin.ti,ab. (0)
79 leuplin.ti,ab. (0)
80 Leuprolide/ (0)
81 leuprolide.ti,ab. (0)

82 lucrin.ti,ab. (0)
83 lupron.ti,ab. (0)
84 provren.ti,ab. (0)
85 procrin.ti,ab. (0)
86 ("tap 144" or tap144).ti,ab. (0)
87 (a-43818 or a43818).ti,ab. (0)
88 Trenantone.ti,ab. (0)
89 staladex.ti,ab. (0)
90 prostap.ti,ab. (0)
91 Nafarelin/ (0)
92 nafarelin.ti,ab. (0)
93 ("76932-56-4" or "76932564").ti,ab. (0)
94 ("76932-60-0" or "76932600").ti,ab. (0)
95 ("86220-42-0" or "86220420").ti,ab. (0)
96 ("rs 94991 298" or rs94991298).ti,ab. (0)
97 synarel.ti,ab. (0)
98 deslorelin.ti,ab. (0)
99 gonadorelin.ti,ab. (0)
100 ("33515-09-2" or "33515092").ti,ab. (0)
101 ("51952-41-1" or "51952411").ti,ab. (0)
102 ("52699-48-6" or "52699486").ti,ab. (0)
103 cetrorelix.ti,ab. (0)
104 cetrotide.ti,ab. (0)
105 ("NS 75A" or NS75A).ti,ab. (0)
106 ("NS 75B" or NS75B).ti,ab. (0)
107 ("SB 075" or SB075).ti,ab. (0)
108 ("SB 75" or SB75).ti,ab. (0)
109 gonadoliberin.ti,ab. (0)
110 kryptocur.ti,ab. (0)
111 cetrorelix.ti,ab. (0)
112 cetrotide.ti,ab. (0)
113 antagon.ti,ab. (0)
114 ganirelix.ti,ab. (0)
115 ("ORG 37462" or ORG37462).ti,ab. (0)
116 orgalutran.ti,ab. (0)
117 ("RS 26306" or RS26306).ti,ab. (0)
118 ("AY 24031" or AY24031).ti,ab. (0)
119 factrel.ti,ab. (0)
120 fertagyl.ti,ab. (0)
121 lutrelef.ti,ab. (0)
122 lutrepulse.ti,ab. (0)
123 relefact.ti,ab. (0)
124 fertiral.ti,ab. (0)
125 (hoe471 or "hoe 471").ti,ab. (0)
126 relisorm.ti,ab. (0)
127 cystorelin.ti,ab. (0)
128 dirigestran.ti,ab. (0)
129 or/33-128 (23)

130 32 and 129 (1)
131 limit 130 to english language (1)
132 limit 131 to yr="2000 -Current" (1)

Database: Embase
Platform: Ovid
Version: Embase <1974 to 2020 July 22>
Search date: 23/7/2020
Number of results retrieved: 367
Search strategy:

1 exp Gender Dysphoria/ (5399)
2 Gender Identity/ (16820)
3 "Sexual and Gender Disorders"/ (24689)
4 Transsexualism/ (3869)
5 exp Transgender/ (6597)
6 Health Services for Transgender Persons/ (158848)
7 exp Sex Reassignment Procedures/ or sex transformation/ (3058)
8 (gender* adj3 (dysphori* or affirm* or incongru* or identi* or disorder* or confus* or minorit* or queer*)).tw. (13005)
9 (transgend* or transex* or transsex* or transfem* or transwom* or transma* or transmen* or transperson* or transpeopl*).tw. (22509)
10 (trans or crossgender* or cross-gender* or crossex* or cross-sex* or genderqueer*).tw. (154446)
11 ((sex or gender*) adj3 (reassign* or chang* or transform* or transition*)).tw. (10327)
12 (male-to-female or m2f or female-to-male or f2m).tw. (200166)
13 or/1-12 (582812)
14 exp juvenile/ or Child Behavior/ or Child Welfare/ or Child Health/ or infant welfare/ or "minor (person)"/ or elementary student/ (3437324)
15 (prematur* or pre-matur* or preterm* or pre-term* or infan* or newborn* or new-born* or perinat* or peri-nat* or neonat* or neo-nat* or baby* or babies or toddler*).ti,ab,in,jn. (1186161)
16 (child* or minor or minors or boy* or girl* or kid or kids or young*).ti,ab,in,jn. (3586795)
17 exp pediatrics/ (106214)
18 (pediatric* or paediatric* or peadiatric*).ti,ab,in,jn. (1491597)
19 exp adolescence/ or exp adolescent behavior/ or adolescent health/ or high school student/ or middle school student/ (105108)
20 (adolescen* or pubescen* or prepubescen* or pre-pubescen* or pubert* or prepubert* or pre-pubert* or teen* or preteen* or pre-teen* or juvenil* or youth* or under*age*).ti,ab,in,jn. (641660)
21 school/ or high school/ or kindergarten/ or middle school/ or primary school/ or nursery school/ or day care/ (103791)
22 (pre-school* or preschool* or kindergar* or daycare or day-care or nurser* or school* or pupil* or student*).ti,ab,jn. (687437)
23 (("eight" or "nine" or "ten" or "eleven" or "twelve" or "thirteen" or "fourteen" or "fifteen" or "sixteen" or "seventeen" or "eighteen" or "nineteen") adj2 (year or years or age or ages or aged)).ti,ab. (138908)
24 (("8" or "9" or "10" or "11" or "12" or "13" or "14" or "15" or "16" or "17" or "18" or "19") adj2 (year or years or age or ages or aged)).ti,ab. (1562903)

25 or/14-24 (7130881)
26 13 and 25 (182161)
27 (transchild* or transyouth* or transteen* or transadoles* or transgirl* or transboy*).tw.
(17)
28 26 or 27 (182161)
29 gonadorelin/ (37580)
30 (pubert* adj3 block*).ti,ab. (142)
31 ((gonadotrophin or gonadotropin) and releasing).ti,ab. (21450)
32 (GnRH adj2 analog*).ti,ab. (4013)
33 GnRH*.ti,ab. (29862)
34 "GnRH agonist*".ti,ab. (6719)
35 exp gonadorelin agonist/ or gonadorelin derivative/ or gonadorelin acetate/ (23304)
36 Triptorelin/ (5427)
37 triptorelin.ti,ab. (1182)
38 arvekap.ti,ab. (3)
39 ("AY 25650" or AY25650).ti,ab. (1)
40 ("BIM 21003" or BIM21003).ti,ab. (0)
41 ("BN 52014" or BN52014).ti,ab. (0)
42 ("CL 118532" or CL118532).ti,ab. (0)
43 Debio.ti,ab. (185)
44 diphereline.ti,ab. (51)
45 moapar.ti,ab. (0)
46 pamorelin.ti,ab. (0)
47 trelstar.ti,ab. (5)
48 triptodur.ti,ab. (1)
49 ("WY 42422" or WY42422).ti,ab. (0)
50 ("WY 42462" or WY42462).ti,ab. (0)
51 gonapeptyl.ti,ab. (10)
52 decapeptyl.ti,ab. (307)
53 salvacyl.ti,ab. (1)
54 buserelin acetate/ or buserelin/ (5164)
55 buserelin.ti,ab. (1604)
56 bigonist.ti,ab. (1)
57 ("hoe 766" or hoe-766 or hoe766).ti,ab. (89)
58 profact.ti,ab. (4)
59 receptal.ti,ab. (37)
60 suprecur.ti,ab. (8)
61 suprefact.ti,ab. (30)
62 tiloryth.ti,ab. (0)
63 histrelin/ (446)
64 histrelin.ti,ab. (107)
65 "LHRH-hydrogel implant".ti,ab. (1)
66 ("RL 0903" or RL0903).ti,ab. (1)
67 ("SPD 424" or SPD424).ti,ab. (1)
68 goserelin.ti,ab. (1487)
69 Goserelin/ (7128)
70 ("ici 118630" or ici118630).ti,ab. (49)
71 ("ZD-9393" or ZD9393).ti,ab. (0)

72 zoladex.ti,ab. (501)
73 leuprorelin/ (11312)
74 leuprorelin.ti,ab. (727)
75 carcinil.ti,ab. (0)
76 enanton*.ti,ab. (38)
77 ginecrin.ti,ab. (1)
78 leuplin.ti,ab. (26)
79 leuprolide.ti,ab. (2788)
80 lucrin.ti,ab. (47)
81 lupron.ti,ab. (361)
82 provren.ti,ab. (0)
83 procrin.ti,ab. (11)
84 ("tap 144" or tap144).ti,ab. (63)
85 (a-43818 or a43818).ti,ab. (3)
86 Trenantone.ti,ab. (7)
87 staladex.ti,ab. (0)
88 prostap.ti,ab. (11)
89 nafarelin acetate/ or nafarelin/ (1441)
90 nafarelin.ti,ab. (324)
91 ("76932-56-4" or "76932564").ti,ab. (0)
92 ("76932-60-0" or "76932600").ti,ab. (0)
93 ("86220-42-0" or "86220420").ti,ab. (0)
94 ("rs 94991 298" or rs94991298).ti,ab. (0)
95 synarel.ti,ab. (28)
96 deslorelin/ (452)
97 deslorelin.ti,ab. (324)
98 gonadorelin.ti,ab. (338)
99 ("33515-09-2" or "33515092").ti,ab. (0)
100 ("51952-41-1" or "51952411").ti,ab. (0)
101 ("52699-48-6" or "52699486").ti,ab. (0)
102 cetrorelix/ (2278)
103 cetrorelix.ti,ab. (717)
104 cetrotide.ti,ab. (113)
105 ("NS 75A" or NS75A).ti,ab. (0)
106 ("NS 75B" or NS75B).ti,ab. (0)
107 ("SB 075" or SB075).ti,ab. (1)
108 ("SB 75" or SB75).ti,ab. (76)
109 gonadoliberin.ti,ab. (152)
110 kryptocur.ti,ab. (6)
111 cetrorelix.ti,ab. (717)
112 cetrotide.ti,ab. (113)
113 antagon.ti,ab. (32)
114 ganirelix/ (1284)
115 ganirelix.ti,ab. (293)
116 ("ORG 37462" or ORG37462).ti,ab. (4)
117 orgalutran/ (1284)
118 orgalutran.ti,ab. (68)
119 ("RS 26306" or RS26306).ti,ab. (6)

120 ("AY 24031" or AY24031).ti,ab. (0)
121 factrel.ti,ab. (14)
122 fertagyl.ti,ab. (20)
123 lutrelef.ti,ab. (7)
124 lutrepulse.ti,ab. (6)
125 relefact.ti,ab. (10)
126 fertiral.ti,ab. (0)
127 (hoe471 or "hoe 471").ti,ab. (4)
128 relisorm.ti,ab. (6)
129 cystorelin.ti,ab. (26)
130 dirigestran.ti,ab. (5)
131 or/29-130 (80790)
132 28 and 131 (988)
133 limit 132 to english language (940)
134 133 not (letter or editorial).pt. (924)
135 134 not (conference abstract or conference paper or conference proceeding or "conference review").pt. (683)
136 nonhuman/ not (human/ and nonhuman/) (4649157)
137 135 not 136 (506)
138 limit 137 to yr="2000 -Current" (420)
139 elsevier.cr. (25912990)
140 138 and 139 (372)
141 remove duplicates from 140 (367)

Database: Cochrane Library – incorporating Cochrane Database of Systematic Reviews (CDSR); CENTRAL
Platform: Wiley
Version:
CDSR – Issue 7 of 12, July 2020
CENTRAL – Issue 7 of 12, July 2020
Search date: 23/7/2020
Number of results retrieved: CDSR – 1; CENTRAL - 8.

#1 [mh ^"Gender Dysphoria"] 3
#2 [mh ^"gender identity"] 227
#3 [mh ^"sexual and gender disorders"] 2
#4 [mh ^transsexualism] 27
#5 [mh ^"transgender persons"] 36
#6 [mh ^"health services for transgender persons"] 0
#7 [mh "sex reassignment procedures"] 4
#8 (gender* NEAR/3 (dysphori* or affirm* or incongruen* or identi* or disorder* or confus* or minorit* or queer*)):ti,ab 308
#9 (transgend* or transex* or transsex* or transfem* or transwom* or transma* or transmen* or transperson* or transpeopl*):ti,ab 929
#10 (trans or crossgender* or cross-gender* or crossex* or cross-sex* or genderqueer*):ti,ab 3915
#11 ((sex or gender*) NEAR/3 (reassign* or chang* or transform* or transition*)):ti,ab 493
#12 (male-to-female or m2f or female-to-male or f2m):ti,ab 489

#13 {or #1-#12} 6142
#14 [mh infant] or [mh ^"infant health"] or [mh ^"infant welfare"] 27769
#15 (prematur* or pre-matur* or preterm* or pre-term* or infan* or newborn* or new-born* or perinat* or peri-nat* or neonat* or neo-nat* or baby* or babies or toddler*):ti,ab 69476
#16 [mh child] or [mh "child behavior"] or [mh ^"child health"] or [mh ^"child welfare"] 42703
#17 [mh ^minors] 8
#18 (child* or minor or minors or boy* or girl* or kid or kids or young*):ti,ab 175826
#19 [mh pediatrics]661
#20 (pediatric* or paediatric* or peadiatric*):ti,ab 30663
#21 [mh ^adolescent] or [mh ^"adolescent behavior"] or [mh ^"adolescent health"] 102154
#22 [mh ^puberty] 295
#23 (adolescen* or pubescen* or prepubescen* or pre-pubescen* or pubert* or prepubert* or pre-pubert* or teen* or preteen* or pre-teen* or juvenil* or youth* or under*age*):ti,ab 34139
#24 [mh ^schools] 1914
#25 [mh ^"Child Day Care Centers"] or [mh nurseries] or [mh ^"schools, nursery"] 277
#26 (pre-school* or preschool* or kindergar* or daycare or day-care or nurser* or school* or pupil* or student*):ti,ab 54723
#27 (("eight" or "nine" or "ten" or "eleven" or "twelve" or "thirteen" or "fourteen" or "fifteen" or "sixteen" or "seventeen" or "eighteen" or "nineteen") NEAR/2 (year or years or age or ages or aged)):ti,ab 6710
#28 (("8" or "9" or "10" or "11" or "12" or "13" or "14" or "15" or "16" or "17" or "18" or "19") NEAR/2 (year or years or age or ages or aged)):ti,ab 196881
#29 {or #14-#28} 469351
#30 #13 and #29 2146
#31 (transchild* or transyouth* or transteen* or transadoles* or transgirl* or transboy*):ti,ab 0
#32 #30 or #31 2146
#33 [mh ^"Gonadotropin-Releasing Hormone"] 1311
#34 (pubert* NEAR/3 block*):ti,ab 1
#35 ((gonadotrophin or gonadotropin) and releasing):ti,ab 2095
#36 (GnRH NEAR/2 analog*):ti,ab 493
#37 GnRH*:ti,ab 3764
#38 "GnRH agonist*":ti,ab 1399
#39 [mh ^"Triptorelin Pamoate"] 451
#40 triptorelin:ti,ab 451
#41 arvekap:ti,ab 4
#42 ("AY 25650" or AY25650):ti,ab 0
#43 ("BIM 21003" or BIM21003):ti,ab 0
#44 ("BN 52014" or BN52014):ti,ab 0
#45 ("CL 118532" or CL118532):ti,ab 0
#46 Debio:ti,ab 301
#47 diphereline:ti,ab 25
#48 moapar:ti,ab 0
#49 pamorelin:ti,ab 5
#50 trelstar:ti,ab 3

#51 triptodur:ti,ab 0
#52 ("WY 42422" or WY42422):ti,ab 0
#53 ("WY 42462" or WY42462):ti,ab 0
#54 gonapeptyl:ti,ab 11
#55 decapeptyl:ti,ab 135
#56 salvacyl:ti,ab 0
#57 [mh ^Buserelin] 290
#58 Buserelin:ti,ab 339
#59 bigonist:ti,ab 0
#60 ("hoe 766" or hoe-766 or hoe766):ti,ab 11
#61 profact:ti,ab 1
#62 receptal:ti,ab 4
#63 suprecur:ti,ab 0
#64 suprefact:ti,ab 28
#65 tiloryth:ti,ab 0
#66 histrelin:ti,ab 5
#67 "LHRH-hydrogel implant":ti,ab 0
#68 ("RL 0903" or RL0903):ti,ab 0
#69 ("SPD 424" or SPD424):ti,ab 0
#70 goserelin:ti,ab 761
#71 [mh ^goserelin] 568
#72 ("ici 118630" or ici118630):ti,ab 7
#73 ("ZD-9393" or ZD9393):ti,ab 1
#74 zoladex:ti,ab 318
#75 leuprorelin:ti,ab 248
#76 carcinil:ti,ab 0
#77 enanton*:ti,ab 21
#78 ginecrin:ti,ab 1
#79 leuplin:ti,ab 7
#80 [mh ^Leuprolide] 686
#81 leuprolide:ti,ab696
#82 lucrin:ti,ab 21
#83 lupron:ti,ab 77
#84 provren:ti,ab 0
#85 procrin:ti,ab 2
#86 ("tap 144" or tap144):ti,ab 24
#87 (a-43818 or a43818):ti,ab 0
#88 Trenantone:ti,ab 3
#89 staladex:ti,ab 0
#90 prostap:ti,ab 9
#91 [mh ^Nafarelin] 77
#92 nafarelin:ti,ab 114
#93 ("76932-56-4" or "76932564"):ti,ab 0
#94 ("76932-60-0" or "76932600"):ti,ab 2
#95 ("86220-42-0" or "86220420"):ti,ab 0
#96 ("rs 94991 298" or rs94991298):ti,ab 0
#97 synarel:ti,ab 10
#98 deslorelin:ti,ab16

#99 gonadorelin:ti,ab 11
#100 ("33515-09-2" or "33515092"):ti,ab 0
#101 ("51952-41-1" or "51952411"):ti,ab 0
#102 ("52699-48-6" or "52699486"):ti,ab 0
#103 cetrorelix:ti,ab 221
#104 cetrotide:ti,ab 111
#105 ("NS 75A" or NS75A):ti,ab 0
#106 ("NS 75B" or NS75B):ti,ab 0
#107 ("SB 075" or SB075):ti,ab 0
#108 ("SB 75" or SB75):ti,ab 10
#109 gonadoliberin:ti,ab 5
#110 kryptocur:ti,ab 0
#111 cetrorelix:ti,ab 221
#112 cetrotide:ti,ab 111
#113 antagon:ti,ab 12
#114 ganirelix:ti,ab 142
#115 ("ORG 37462" or ORG37462):ti,ab 4
#116 orgalutran:ti,ab 45
#117 ("RS 26306" or RS26306):ti,ab 0
#118 ("AY 24031" or AY24031):ti,ab 0
#119 factrel:ti,ab 1
#120 fertagyl:ti,ab 0
#121 lutrelef:ti,ab 0
#122 lutrepulse:ti,ab 1
#123 relefact:ti,ab 1
#124 fertiral:ti,ab 0
#125 (hoe471 or "hoe 471"):ti,ab 3
#126 relisorm:ti,ab 0
#127 cystorelin:ti,ab 0
#128 dirigestran:ti,ab 0
#129 {or #33-#128} 6844
#130 #32 and #129 27
#131 #130 with Cochrane Library publication date Between Jan 2000 and Jul 2020, in Cochrane Reviews 1
#132 #130 27
#133 "conference":pt or (clinicaltrials or trialsearch):so 492465
#134 #132 not #133 9
#135 #134 with Publication Year from 2000 to 2020, in Trials 8

Database: HTA
Platform: CRD
Version: HTA
Search date: 23/7/2020
Number of results retrieved: 26
Search strategy:

1 MeSH DESCRIPTOR Gender Dysphoria EXPLODE ALL TREES 0
2 MeSH DESCRIPTOR Gender Identity EXPLODE ALL TREES 14

3 MeSH DESCRIPTOR Sexual and Gender Disorders EXPLODE ALL TREES 2

4 MeSH DESCRIPTOR Transsexualism EXPLODE ALL TREES 12
5 MeSH DESCRIPTOR Transgender Persons EXPLODE ALL TREES 3
6 MeSH DESCRIPTOR Health Services for Transgender Persons EXPLODE ALL TREES 0
7 MeSH DESCRIPTOR Sex Reassignment Procedures EXPLODE ALL TREES 1

8 ((gender* adj3 (dysphori* or affirm* or incongruen* or identi* or disorder* or confus* or minorit* or queer*))) 28
9 ((transgend* or transex* or transsex* or transfem* or transwom* or transma* or transmen* or transperson* or transpeopl*)) 76
10 ((trans or crossgender* or cross-gender* or crossex* or cross-sex* or genderqueer*)) 83
11 (((sex or gender*) adj3 (reassign* or chang* or transform* or transition*))) 24
12 (male-to-female or m2f or female-to-male or f2m) 86
13 ((transchild* or transyouth* or transteen* or transadoles* or transgirl* or transboy*)) 0
14 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 262
15 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13) IN HTA 30

*26 results are from 200 onwards. Downloaded as a set to sift for drug terms rather than continuing with search strategy.

Database: APA PsycInfo
Search date: July 2020 (Week 2)
Search Strategy:
---
1 Gender Dysphoria/ (936)
2 Gender Identity/ (8648)
3 Transsexualism/ (2825)
4 Transgender/ (5257)
5 exp Gender Reassignment/ (568)
6 (gender* adj3 (dysphori* or affirm* or incongruen* or identi* or disorder* or confus* or minorit* or queer*)).tw. (15471)
7 (transgend* or transex* or transsex* or transfem* or transwom* or transma* or transmen* or transperson* or transpeopl*).tw. (13028)
8 (trans or crossgender* or cross-gender* or crossex* or cross-sex* or genderqueer*).tw. (7679)
9 ((sex or gender*) adj3 (reassign* or chang* or transform* or transition*)).tw. (5796)
10 (male-to-female or m2f or female-to-male or f2m).tw. (63688)
11 or/1-10 (99560)
12 exp Infant Development/ (21841)
13 (prematur* or pre-matur* or preterm* or pre-term* or infan* or newborn* or new-born* or perinat* or peri-nat* or neonat* or neo-nat* or baby* or babies or toddler*).ti,ab,in,jn. (150219)

14 Child Characteristics/ or exp Child Behavior/ or Child Psychology/ or exp Child Welfare/ or Child Psychiatry/ (23423)
15 (child* or minor or minors or boy* or girl* or kid or kids or young*).ti,ab,in,jn. (984230)
16 (pediatric* or paediatric* or peadiatric*).ti,ab,in,jn. (78962)
17 Adolescent Psychiatry/ or Adolescent Behavior/ or Adolescent Development/ or Adolescent Psychology/ or Adolescent Characteristics/ or Adolescent Health/ (62142)
18 Puberty/ (2753)
19 (adolescen* or pubescen* or prepubescen* or pre-pubescen* or pubert* or prepubert* or pre-pubert* or teen* or preteen* or pre-teen* or juvenil* or youth* or under*age*).ti,ab,in,jn. (347604)
20 Schools/ or exp elementary school students/ or high school students/ or junior high school students/ or middle school students/ (113053)
21 Child Day Care/ or Nursery Schools/ (2836)
22 (pre-school* or preschool* or kindergar* or daycare or day-care or nurser* or school* or pupil* or student*).ti,ab,jn. (772814)
23 (("eight" or "nine" or "ten" or "eleven" or "twelve" or "thirteen" or "fourteen" or "fifteen" or "sixteen" or "seventeen" or "eighteen" or "nineteen") adj2 (year or years or age or ages or aged)).ti,ab. (21475)
24 (("8" or "9" or "10" or "11" or "12" or "13" or "14" or "15" or "16" or "17" or "18" or "19") adj2 (year or years or age or ages or aged)).ti,ab. (285697)
25 or/12-24 (1772959)
26 11 and 25 (49612)
27 (transchild* or transyouth* or transteen* or transadoles* or transgirl* or transboy*).tw. (14)
28 26 or 27 (49613)
29 exp Gonadotropic Hormones/ (4226)
30 (pubert* adj3 block*).ti,ab. (29)
31 ((gonadotrophin or gonadotropin) and releasing).ti,ab. (1060)
32 (GnRH adj2 analog*).ti,ab. (49)
33 GnRH*.ti,ab. (998)
34 "GnRH agonist*".ti,ab. (72)
35 triptorelin.ti,ab. (25)
36 arvekap.ti,ab. (0)
37 ("AY 25650" or AY25650).ti,ab. (0)
38 ("BIM 21003" or BIM21003).ti,ab. (0)
39 ("BN 52014" or BN52014).ti,ab. (0)
40 ("CL 118532" or CL118532).ti,ab. (0)
41 Debio.ti,ab. (7)
42 diphereline.ti,ab. (0)
43 moapar.ti,ab. (0)
44 pamorelin.ti,ab. (0)
45 trelstar.ti,ab. (0)
46 triptodur.ti,ab. (0)
47 ("WY 42422" or WY42422).ti,ab. (0)
48 ("WY 42462" or WY42462).ti,ab. (0)
49 gonapeptyl.ti,ab. (0)
50 decapeptyl.ti,ab. (3)
51 salvacyl.ti,ab. (1)

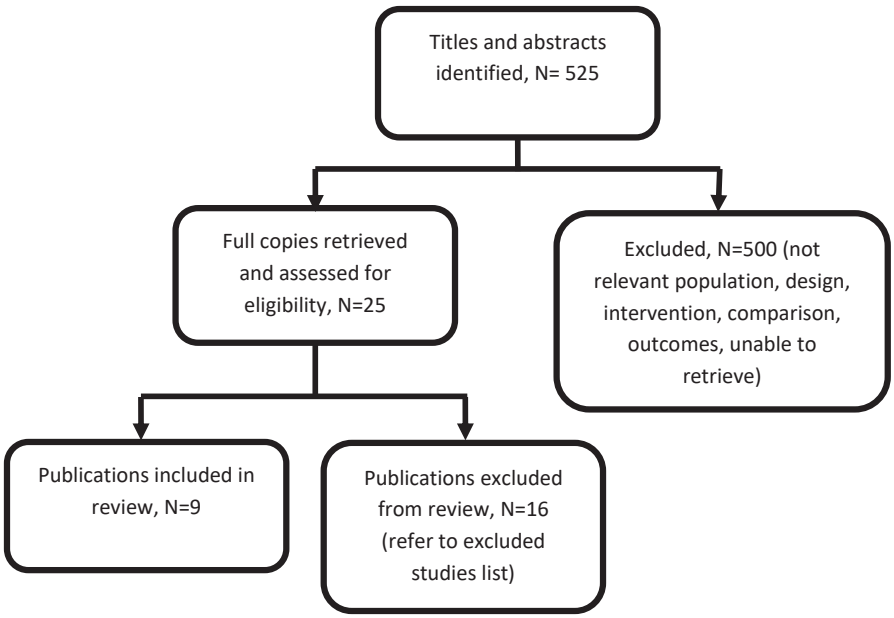
52 buserelin.ti,ab. (6)
53 bigonist.ti,ab. (0)
54 ("hoe 766" or hoe-766 or hoe766).ti,ab. (0)
55 profact.ti,ab. (0)
56 receptal.ti,ab. (0)
57 suprecur.ti,ab. (0)
58 suprefact.ti,ab. (0)
59 tiloryth.ti,ab. (0)
60 histrelin.ti,ab. (1)
61 "LHRH-hydrogel implant".ti,ab. (0)
62 ("RL 0903" or RL0903).ti,ab. (0)
63 ("SPD 424" or SPD424).ti,ab. (0)
64 goserelin.ti,ab. (30)
65 ("ici 118630" or ici118630).ti,ab. (0)
66 ("ZD-9393" or ZD9393).ti,ab. (0)
67 zoladex.ti,ab. (3)
68 leuprorelin.ti,ab. (12)
69 carcinil.ti,ab. (0)
70 enanton*.ti,ab. (1)
71 ginecrin.ti,ab. (0)
72 leuplin.ti,ab. (0)
73 leuprolide.ti,ab. (79)
74 lucrin.ti,ab. (1)
75 lupron.ti,ab. (18)
76 provren.ti,ab. (0)
77 procrin.ti,ab. (0)
78 ("tap 144" or tap144).ti,ab. (1)
79 (a-43818 or a43818).ti,ab. (0)
80 Trenantone.ti,ab. (0)
81 staladex.ti,ab. (0)
82 prostap.ti,ab. (0)
83 nafarelin.ti,ab. (1)
84 ("76932-56-4" or "76932564").ti,ab. (0)
85 ("76932-60-0" or "76932600").ti,ab. (0)
86 ("86220-42-0" or "86220420").ti,ab. (0)
87 ("rs 94991 298" or rs94991298).ti,ab. (0)
88 synarel.ti,ab. (0)
89 deslorelin.ti,ab. (8)
90 gonadorelin.ti,ab. (3)
91 ("33515-09-2" or "33515092").ti,ab. (0)
92 ("51952-41-1" or "51952411").ti,ab. (0)
93 ("52699-48-6" or "52699486").ti,ab. (0)
94 cetrorelix.ti,ab. (9)
95 cetrotide.ti,ab. (0)
96 ("NS 75A" or NS75A).ti,ab. (0)
97 ("NS 75B" or NS75B).ti,ab. (0)
98 ("SB 075" or SB075).ti,ab. (0)
99 ("SB 75" or SB75).ti,ab. (1)

100 gonadoliberin.ti,ab. (1)
101 kryptocur.ti,ab. (0)
102 cetrorelix.ti,ab. (9)
103 cetrotide.ti,ab. (0)
104 antagon.ti,ab. (0)
105 ganirelix.ti,ab. (0)
106 ("ORG 37462" or ORG37462).ti,ab. (0)
107 orgalutran.ti,ab. (0)
108 ("RS 26306" or RS26306).ti,ab. (0)
109 ("AY 24031" or AY24031).ti,ab. (0)
110 factrel.ti,ab. (0)
111 fertagyl.ti,ab. (0)
112 lutrelef.ti,ab. (0)
113 lutrepulse.ti,ab. (0)
114 relefact.ti,ab. (0)
115 fertiral.ti,ab. (0)
116 (hoe471 or "hoe 471").ti,ab. (0)
117 relisorm.ti,ab. (0)
118 cystorelin.ti,ab. (0)
119 dirigestran.ti,ab. (0)
120 or/29-119 (4869)
121 28 and 120 (130)
122 limit 121 to english language (120)
123 limit 122 to yr="2000 -Current" (93)

Appendix C Evidence selection

The literature searches identified 525 references. These were screened using their titles and abstracts and 25 references were obtained and assessed for relevance. Of these, 9 references are included in the evidence review. The remaining 16 references were excluded and are listed in appendix D.

Figure 1 – Study selection flow diagram



References submitted with Preliminary Policy Proposal

There is no preliminary policy proposal for this policy.

Appendix D Excluded studies table

Study reference	Reason for exclusion
Achille, C., Taggart, T., Eaton, N.R. et al. (2020) Longitudinal impact of gender-affirming endocrine intervention on the mental health and well-being of transgender youths: Preliminary results. International Journal of Pediatric Endocrinology 2020(1): 8	Intervention – data for GnRH analogues not reported separately from other interventions
Bechard, Melanie, Vanderlaan, Doug P, Wood, Hayley et al. (2017) Psychosocial and Psychological Vulnerability in Adolescents with Gender Dysphoria: A "Proof of Principle" Study. Journal of sex & marital therapy 43(7): 678-688	Population – no GnRH analogues at time of study
Chew, Denise, Anderson, Jemma, Williams, Katrina et al. (2018) Hormonal Treatment in Young People With Gender Dysphoria: A Systematic Review. Pediatrics 141(4)	All primary studies included apart from 1 conference abstract
de Vries, Annelou L C, McGuire, Jenifer K et al. (2014) Young adult psychological outcome after puberty suppression and gender reassignment. Pediatrics 134(4): 696-704	Population – relevant population included in de Vries et al. 2011
Ghelani, Rahul, Lim, Cheryl, Brain, Caroline et al. (2020) Sudden sex hormone withdrawal and the effects on body composition in late pubertal adolescents with gender dysphoria. Journal of pediatric endocrinology & metabolism: JPEM 33(1): 107-112	Outcomes – not in the PICO

Study reference	Reason for exclusion
Giovanardi, G, Morales, P, Mirabella, M et al. (2019) Transition memories: experiences of trans adult women with hormone therapy and their beliefs on the usage of hormone blockers to suppress puberty. Journal of endocrinological investigation 42(10): 1231-1240	Population – adults only
Hewitt, Jacqueline K, Paul, Campbell, Kasiannan, Porpavai et al. (2012) Hormone treatment of gender identity disorder in a cohort of children and adolescents. The Medical journal of Australia 196(9): 578-81	Outcomes – no data reported for relevant outcomes
Jensen, R.K., Jensen, J.K., Simons, L.K. et al. (2019) Effect of Concurrent Gonadotropin-Releasing Hormone Agonist Treatment on Dose and Side Effects of Gender-Affirming Hormone Therapy in Adolescent Transgender Patients. Transgender Health 4(1): 300-303	Outcomes – not in the PICO
Klaver, Maartje, de Mutsert, Renee, Wiepjes, Chantal M et al. (2018) Early Hormonal Treatment Affects Body Composition and Body Shape in Young Transgender Adolescents. The journal of sexual medicine 15(2): 251-260	Outcomes – not in the PICO
Klaver, Maartje, de Mutsert, Renee van der Loos, Maria A T C et al. (2020) Hormonal Treatment and Cardiovascular Risk Profile in Transgender Adolescents. Pediatrics 145(3)	Outcomes – not in the PICO
Lopez, Carla Marisa, Solomon, Daniel, Boulware, Susan D et al. (2018) Trends in the use of puberty blockers among transgender children in the United States. Journal of pediatric endocrinology & metabolism : JPEM 31(6): 665-670	Outcomes – not in the PICO
Schagen, Sebastian E E, Lustenhouwer, Paul, Cohen-Kettenis, Peggy T et al. (2018) Changes in Adrenal Androgens During Puberty Suppression and Gender-Affirming Hormone Treatment in Adolescents With Gender Dysphoria. The journal of sexual medicine 15(9): 1357-1363	Outcomes – not in the PICO
Swendiman, Robert A, Vogiatzi, Maria G, Alter, Craig A et al. (2019) Histrelin implantation in the pediatric population: A 10-year institutional experience. Journal of pediatric surgery 54(7): 1457-1461	Population – less than 10% of participants had gender dysphoria; data not reported separately
Turban, Jack L, King, Dana, Carswell, Jeremi M et al. (2020) Pubertal Suppression for Transgender Youth and Risk of Suicidal Ideation. Pediatrics 145(2)	Intervention – data for GnRH analogues not reported separately from other interventions
Vrouenraets, Lieke Josephina Jeanne Johanna, Fredriks, A Miranda, Hannema, Sabine E et al. (2016) Perceptions of Sex, Gender, and Puberty Suppression: A Qualitative Analysis of Transgender Youth. Archives of sexual behavior 45(7): 1697-703	Outcomes – not in the PICO
Zucker, Kenneth J, Bradley, Susan J, Owen-Anderson, Allison et al. (2010) Puberty-blocking hormonal therapy for adolescents with gender identity disorder: A descriptive clinical study. Journal of Gay & Lesbian Mental Health 15(1): 58-82	Intervention – data for GnRH analogues not reported separately from other interventions

Appendix E Evidence tables

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
Brik T, Vrouenraets L, de Vries M, et al. (2020) Trajectories of adolescents treated with gonadotropin-releasing hormone analogues for gender dysphoria. Archives of Sexual Behaviour https://doi.org/10.1007/s10508-020-01660-8 Netherlands Retrospective observational single-centre study To document trajectories after the initiation of GnRH analogue and explore reasons for extended use and discontinuation of GnRH analogues. Includes participants seen between November 2010 and January 1, 2018.	Inclusion criteria were adolescents with gender dysphoria, according to the DSM-5 criteria, seen at the single centre and treated with GnRH analogues between November 2010 and January 1, 2018. The study excluded adolescents without a diagnosis of gender dysphoria, those who had coexisting problems that interfered with the diagnostic process and/or might interfere with successful treatment (not further defined), those adolescents not wanting hormones, those with ongoing diagnostic evaluation and those who did not attend appointments. The sample consisted of 143 adolescents meeting the inclusion/exclusion criteria, 38 transfemales, 105 transmales, with median ages of 15.0 years (range 11.1 to 18.6 years) and 16.1 years (range 10.1 to 17.9	The study only reports that GnRH analogues were given, no specific drug, dose, route, or frequency of administration are reported. No comparator cohort was used in the study. Follow-up was at (up to) 9 years (last follow-up July 2019).	**Critical outcomes** No critical outcomes assessed. **Important outcomes** ***Psychosocial impact*** Not assessed. ***Engagement with health care services*** Not formally assessed but the study reported that out of 214 age and developmentally appropriate adolescents for potential inclusion in the study, 9 were excluded as they stopped attending appointments (4.2%). ***Stopping treatment*** Of the 143 adolescents, 9 (6.2%, 1 transfemale and 8 transmales) stopped taking GnRH analogues after a median duration of 0.8 years (range 0.1 to 3.0). Four adolescents (2.8%) discontinued GnRH analogues although they wanted to continue endocrine treatments for gender dysphoria: • 1 transmale stopped due to increase in mood problems, suicidal thoughts and confusion attributed to GnRH analogues (later had gender-affirming hormones at an adult gender clinic)[1] • 1 transmale experienced hot flushes, increased migraines, had a fear of injections, stress at school and unrelated medical issues, and temporarily discontinued treatment (after 4 months)[2]	This study was appraised using the Newcastle-Ottawa tool for cohort studies. **Domain 1: Selection** 1. somewhat representative 2. no-non exposed cohort 3. secure record 4. yes **Domain 2: Comparability** 1. no comparator **Domain 3: Outcome** 1. record linkage 2. yes 3. complete follow-up **Overall quality is assessed as poor.** Other comments: Physical and psychological comorbidity was poorly reported, concomitant use of other medicines was not reported. Source of funding: not reported.

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
	years), respectively at commencement of GnRH analogues. Of the 143 adolescents in the study, 125 (87%, 36 transfemales and 89 transmales) subsequently started treatment with gender-affirming hormones after median 1.0 (range 0.5 to 3.8) years and 0.8 (0.3 to 3.7) years, respectively. Median age at the start of gender-affirming hormones was 16.2 years (range 14.5 to 18.6 years) in transfemales and 17.1 years (range 14.9 to 18.8 years) in transmales. Five adolescents who used GnRH analogues had not started gender-affirming hormones at the time of data collection as they were not yet eligible for this treatment due to age. At the time of data collection, they had used GnRH analogues for a median duration of 2.1 years (range 1.6 to 2.8). Tanner stage was not reported. Six adolescents had been referred to a gender clinic elsewhere for further		• 1 transmale experienced mood swings 4 months after commencing GnRH analogues. After 2.2 years he developed unexplained severe nausea and rapid weight loss and due to his general condition discontinued GnRH analogues after 2.4 years[3] • 1 transmale stopped GnRH analogues as his parents were unable to regularly collect medication from the pharmacy and take him to appointments for the injections[4] Five adolescents (3.5%) stopped treatment as they no longer wished to continue with gender-affirming treatment. • 1 adolescent had been very distressed about breast development at the start of GnRH analogues and later thought that she might want to live as a woman without breasts. She did not want to live as a boy and discontinued GnRH analogues, although dreaded breast development and menstruation. • 1 adolescent experienced concurrent psychosocial problems interfering with the exploration of gender identity and did not currently want treatment.[5] • 1 adolescent felt more in between male and female and therefore did not want to continue with GnRH analogues.[6] • 1 adolescent made a social transition while using GnRH analogues and shortly after decided to discontinue treatment.[7]	

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
	treatment, including 1 who had prolonged use.		• 1 adolescent discontinued after using GnRH analogues as the treatment allowed them to feel who they were.[8]	

[1] The adolescent later indicated "I was already fully matured when I started GnRH analogues, menstruations were already suppressed by contraceptives. For me, it had no added value" (transmale, age 19 years).
[2] The adolescent restarted endocrine treatment (testosterone) 5 months later.
[3] The adolescent recovered over the next 2 years and subsequently started lynestrenol and testosterone treatment.
[4] The adolescent subsequently started lynestrenol to suppress menses, he was not yet eligible for testosterone treatment.
[5] The adolescent later reflected that "The decision to stop GnRH analogues to my mind was made by the gender team, because they did not think gender dysphoria was the right diagnosis. I do still feel like a man, but for me it is okay to be just me instead of a he or a she, so for now I do not want any further treatment" (adolescent assigned female sex at birth, age 16 years).
[6] The adolescent stated "At the moment, I feel more like 'I am' instead of 'I am a woman' or 'I am a man'" (adolescent assigned female sex at birth, age 16 years).
[7] The adolescent stated that "he had fallen in love with a girl and had never had such feelings, which made him question his gender identity. At subsequent visits, he indicated that he was happy living as a man.
[8] The adolescent stated "After using GnRH analogues for the first time, I could feel who I was without the female hormones, this gave me peace of mind to think about my future. It was an inner feeling that said I am a woman" (adolescent assigned female sex at birth, age 18 years).

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
Costa R, Dunsford M, Skagerberg E, et al. (2015) Psychological support, puberty suppression, and psychosocial functioning in adolescents with gender dysphoria. Journal of Sexual Medicine 12(11):2206-14. United Kingdom Prospective longitudinal observational single centre cohort study Includes participants referred to the service between 2010 and 2014.	Adolescents with gender dysphoria who completed a 6-month diagnostic process using DSM-IV-TR criteria for gender dysphoria (comprising the gender dysphoria assessment and psychological interventions) either immediately eligible for treatment with GnRH analogues or delayed eligible for treatment with GnRH analogues (received psychological support without any physical intervention). No exclusion criteria were reported. The sample consisted of 201 adolescents (sex assigned at birth male to female ratio 1:1.6) mean (±SD) age 15.52±1.41 years) from a sampling frame of	**Intervention** 101 individuals were assessed as being immediately eligible for use of GnRH analogues (no specific treatment, dose or route, or frequency of administration reported but all received psychological support). **Comparison** The analyses were between the immediately eligible and delayed eligible (n=100) adolescents,	**Critical outcomes** ***Impact on gender dysphoria*** The Utrecht gender dysphoria scale (UGDS) was used to assess adolescents' gender dysphoria related discomfort. The Cronbach's alpha (α) for the study was reported as 0.76 to 0.88, suggesting good internal consistency. UGDS was only reported once, for 160 adolescents (50 sex assigned at birth males and 110 sex assigned at birth females). The assessment time point is not reported (baseline or follow-up) and the comparison for gender related discomfort was between sex assigned at birth males and sex assigned at birth females. Sex assigned at birth males had a mean (±SD) UGDS score of 51.6 [±9.7] versus sex assigned at birth females score of 56.1 [±4.3], *t*-test 4.07; p<0.001.	This study was appraised using the Newcastle-Ottawa tool for cohort studies. **Domain 1: Selection** 1. somewhat representative 2. drawn from the same community as the exposed cohort. 3. secure record 4. no **Domain 2: Comparability** 1. partial comparator **Domain 3: Outcome** 1. independent assessment (unclear if blinded) 2. yes 3. incomplete follow-up **Overall quality is assessed as poor.**

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
	436 consecutive adolescents referred to the service between 2010 and 2014. The mean (±SD) age (n=201) at the start of GnRH analogues was 16.48 [±1.26], range 13 to 17 years. The interval from the start of the diagnostic procedure to the start of puberty suppression took approximately 1.5 years [±0.63] from baseline. None of the delayed eligible individuals received puberty suppression at the time of this study. Tanner stage was not reported.	Baseline assessment (following diagnostic procedure) was followed by follow-up at 6 months from baseline (T1), 12 months from baseline (T2) and 18 months from baseline (T3).	***Impact on mental health*** Not assessed. ***Impact on quality of life*** Not assessed. **Important outcomes** ***Psychosocial impact*** The Children's Global Assessment Scale (CGAS) was used to assess adolescents' psychosocial functioning. The CGAS was administered by psychologists, psychotherapists, and psychiatrists (intra-class correlation assessment was 0.76 ≤ Cronbach's α ≤0.94). At baseline, CGAS scores were not associated with any demographic variable, in both sex assigned at birth males and sex assigned at birth females (all p>0.1). In comparison with sex assigned at birth females, sex assigned at birth males had statistically significantly lower mean (±SD) baseline CGAS scores (55.4 [±12.7] versus 59.2 [11.8]; *t*-test 2.15; p=0.03). There was no statistically significant difference in mean (±SD) CGAS scores at baseline (T0) between immediately eligible adolescents and delayed eligible adolescents (n=201, 58.72 [±11.38] versus 56.63 [±13.14]; *t*-test 1.21; p=0.23). **Immediately eligible compared with delayed eligible participants** At follow-up, there was no statistically significant difference in mean (±SD) CGAS scores at any follow-up time point (T1, T2 or T3) between immediately	Other comments: Physical and psychological comorbidity was poorly reported, concomitant use of other medicines was not reported. Large unexplained loss to follow-up (64.7%) at T3. Source of funding: not reported.

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
			eligible adolescents and delayed eligible adolescents: • T1, n=201, 60.89 [±12.17] versus 60.29 [±12.81]; *t*-test 0.34; p=0.73 • T2, n=121, 64.70 [±13.34] versus 62.97 [±14.10]; *t*-test 0.69; p=0.49 • T3, n=71, 67.40 [±13.93] versus 62.53 [±13.54]; *t*-test 1.49; p=0.14. **All participants** There was a statistically significant increase in mean (±SD) CGAS scores at any follow-up time point (T1, T2 or T3) compared with baseline (T0) for the all adolescents group: • T0 (n=201) versus T1 (n=201), 57.73 [±12.27] versus 60.68 [±12.47]; *t*-test 4.87; p<0.001 • T0 (n=201) versus T2 (n=121), 57.73 [±12.27] versus 63.31 [±14.41]; *t*-test 3.70; p<0.001 • T0 (n=201) versus T3 (n=71), 57.73 [±12.27] versus 64.93 [±13.85]; *t*-test 4.11; p<0.001 There was a statistically significant increase in mean (±SD) CGAS scores when comparing the follow-up period T1 to T3 but not for the periods T1 to T2 and T2 to T3, for all adolescents: • T1 (n=201) versus T2 (n=121), 60.68 [±12.47] versus 63.31 [±14.41]; *t*-test 1.73; p<0.08 • T1 (n=201) versus T3 (n=71), 60.68 [±12.47] versus 64.93 [±13.85], *t*-test 2.40; p<0.02 • T2 (n=121) versus T3 (n=71), 63.31 [±14.41] versus 64.93 [±13.85], *t*-test 0.76; p=0.45 There were no statistically significant differences in CGAS scores between sex assigned at birth males and sex	

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
			assigned at birth females with gender dysphoria in all the follow-up evaluations (all p>0.1). Delayed eligible and immediately eligible adolescents with gender dysphoria were not statistically significantly different for demographic variables (all p>0.1). **Immediately eligible participants** There was a statistically significant increase in mean (±SD) CGAS scores at follow-up times T2 and T3 compared with baseline (T0) but not for T0 versus T1, for the immediately eligible adolescents: • T0 (n=101) versus T1 (n=101), 58.72 [±11.38] versus 60.89 [±12.17]; *t*-test 1.31; p=0.19 • T0 (n=101) versus T2 (n=60), 58.72 [±11.38] versus 64.70 [±13.34]; *t*-test 3.02; p=0.003 • T0 (n=101) versus T3 (n=35), 58.72 [±11.38] versus 67.40 [±13.93]; *t*-test 3.66; p<0.001 There was a statistically significant increase in mean (±SD) CGAS scores when comparing the follow-up period T1 to T3 with each other but not for the periods T1 to T2 and T2 to T3, for the immediately eligible adolescents: • T1 (n=101) versus T2 (n=60), 60.89 [±12.17] versus 64.70 [±13.34]; *t*-test 1.85; p=0.07 • T1 (n=101) versus T3 (n=35), 60.89 [±12.17] versus 67.40 [±13.93], *t*-test 2.63; p<0.001 • T2 (n=60) versus T3 (n=35), 64.70 [±13.34] versus 67.40 [±13.93], *t*-test 0.94; p=0.35 The immediately eligible adolescents had a CGAS score which was not	

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
			statistically significantly different compared to the sample of children/ adolescents without observed psychological /psychiatric symptoms after 12 months of puberty suppression (T3, *t*=0.01, *p*=0.99).	

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
de Vries A, Steensma T, Doreleijers T, et al. (2011) Puberty suppression in adolescents with gender identity disorder: a prospective follow-up study. The Journal of Sexual Medicine 8 (8):2276-83. Netherlands Prospective longitudinal observational single centre before and after study.	The sample size was 70 adolescents receiving GnRH analogues (mean age [±SD] at assessment 13.6±1.8 years) from a sampling frame of 196 consecutive adolescents referred to the service between 2000 and 2008. Inclusion criteria were if they subsequently started gender-affirming hormones between 2003 and 2009 (mean [±SD] age at start of GnRH analogues was 14.75 [±1.92] years)[1]. No specific exclusion criteria were described. No diagnostic criteria or concomitant treatments were reported. Tanner stage of the included adolescents was not reported.	**Intervention** 70 adolescents were assessed at baseline (T0) before the start of GnRH analogues (no specific treatment, dose or route of administration reported). **Comparison** The same 70 adolescents were assessed again at follow-up (T1), shortly before starting gender-affirming hormones. Not all adolescents completed all assessments for all items[2].	**Critical outcomes** ***Impact on gender dysphoria*** Impact on gender dysphoria was assessed using the Utrecht Gender Dysphoria Scale (UGDS). • There was no statistically significant difference in UGDS scores between T0 and T1 (n=41). There was a statistically significant difference between sex assigned at birth males and sex assigned at birth females, with sex assigned at birth females reporting more gender dysphoria, *F* (*df, errdf*), *P*: 15.98 (1,39), p<0.001. ***Impact on mental health*** Depressive symptoms were assessed using the Beck Depression Inventory (BDI-II). • There was a statistically significant reduction in BDI score between T0 and T1, n=41, 8.31 [±7.12] versus 4.95 [±6.72], *F* (*df, errdf*), *P*: 9.28 (1,39), p=0.004. • There was no statistically significant difference between sex assigned at birth males and sex assigned at birth females, *F* (*df, errdf*), *P*: 3.85 (1,39), p=0.057.	This study was appraised using the Newcastle-Ottawa tool for cohort studies. **Domain 1: Selection** 1. somewhat representative of children and adolescents who have gender dysphoria 2. no non-exposed cohort 3. no description 4. no **Domain 2: Comparability** 1. study controls for age, age at start of treatment, IQ, and parental factors **Domain 3: Outcome** 1. no description 2. no/unclear 3. complete **Overall quality is assessed as poor**. Other comments: Physical and psychological comorbidity was not reported, concomitant use of other medicines was not reported. Source of funding: This study was supported by a personal

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
			Anger and anxiety were assessed using Trait Anger and Anxiety (TPI and STAI, respectively) Scales of the State-Trait Personality Inventory. • There was no statistically significant difference in anger (TPI) scale scores between T0 and T1 (n=41). There was a statistically significant difference between sex assigned at birth males and sex assigned at birth females, with sex assigned at birth females reporting increased anger compared with sex assigned at birth males, *F* (*df, errdf*), *P*: 5.70 (1,39), p=0.022. • Similarly, there was no statistically significant difference in anxiety (STAI) scale scores between T0 and T1 (n=41). There was a statistically significant difference between sex assigned at birth males and sex assigned at birth females, with sex assigned at birth females reporting increased anxiety compared with sex assigned at birth males, *F* (*df, errdf*), *P*: 16.07 (1,39), p<0.001. ***Impact on quality of life*** Not assessed. **Important outcomes** ***Impact on body image*** Impact on body image was assessed using the Body Image Scale to measure body satisfaction (BIS). There was no statistically significant difference between T0 and T1 for any of the 3 BIS scores (primary sex characteristics, secondary sex characteristics or neutral characteristics,	grant awarded to the first author by the Netherlands Organization for Health Research and Development.

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
			n=57). There were statistically significant differences between sex assigned at birth males and sex assigned at birth females, with sex assigned at birth females reporting more dissatisfaction, for: • primary sexual characteristics, *F* (*df, errdf*), *P*: 4.11 (1,55), p=0.047. • secondary sexual characteristics, *F* (*df, errdf*), *P*: 11.57 (1,55), p=0.001. But no statistically significant difference between sex assigned at birth males and sex assigned at birth females was found for neutral characteristics. However, there was a significant interaction effect between sex assigned at birth sex and the changes of gender dysphoria between T0 and T1; sex assigned at birth females became more dissatisfied with their secondary sex characteristics compared with sex assigned at birth males, *F* (*df, errdf*), *P*: 14.59 (1,55), p<0.001) and neutral characteristics, *F* (*df, errdf*), *P*: 15.26 (1,55), p<0.001). ***Psychosocial impact*** Psychosocial impact was assessed using both the Child Behaviour Checklist (CBCL) and the Youth Self-Report (YSR) to parents and adolescents, respectively. The Children's Global Assessment Scale was also reported. There was a statistically significant decrease in mean (±SD) total, internalising, and externalising[3] parental CBCL scores between T0 and T1[4] for all adolescents (n=54): • Total score (T0 – T1) 60.70 [±12.76] versus 54.46 [±11.23], *F* (*df, errdf*), *P*: 26.17 (1,52), p<0.001.	

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
			• Internalising score (T0 – T1) 61.00 [±12.21] versus 54.56 [±10.22], *F* (*df, errdf*), *P*: 22.93 (1,52), p<0.001. • Externalising score (T0 – T1) 58.04 [±12.99] versus 53.81 [±11.86], *F* (*df, errdf*), *P*: 12.04 (1,52), p=0.001. There was no statistically significant difference between sex assigned at birth males and sex assigned at birth females for total and internalising CBCL score but there was a significant difference for the externalising score: • Externalising score, *F* (*df, errdf*), *P*: 6.29 (1,52), p=0.015. There was a statistically significant decrease in mean (±SD) total, internalising, and externalising[3] YSR scores between T0 and T1 for all adolescents (n=54): • Total score (T0 – T1) 55.46 [±11.56] versus 50.00 [±10.56], *F* (*df, errdf*), *P*: 16.24 (1,52), p<0.001. • Internalising score (T0 – T1) 56.04 [±12.49] versus 49.78 [±11.63], *F* (*df, errdf*), *P*: 15.05 (1,52), p<0.001. • Externalising score (T0 – T1) 53.30 [±11.87] versus 49.98 [±9.35], *F* (*df, errdf*), *P*: 7.26 (1,52), p=0.009. There was no statistically significant difference between sex assigned at birth males and sex assigned at birth females for total and internalising YSR score but there was a significant difference for the externalising score: • Externalising score, *F* (*df, errdf*), *P*: 9.14 (1,52), p=0.004. There was a statistically significant increase in CGAS mean (±SD) score between T0 and T1 (n=41), 70.24 [±10.12] versus 73.90 [±9.63], *F* (*df, errdf*), *P*: 8.76	

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
			(1,39), p=0.005. There was a statistically significant difference between sex assigned at birth males and sex assigned at birth females, with sex assigned at birth females reporting lower score for global functioning compared with sex assigned at birth males, *F* (*df, errdf*), *P*: 5.77 (1,52), p=0.021. The proportion of adolescents scoring in the clinical range significantly decreased between T0 and T1, on the CBCL total problem scale (44.4% versus 22.2%, X^2[1] = 6.00, p=0.001), and the internalising scale (29.6% versus 11.1%, X^2[1] = 5.71, p=0.017) of the YSR.	

[1] There were statistically significant mean age [±SD] differences between sex assigned at birth males and sex assigned at birth females for age at assessment (13.14 [±1.55] versus 14.10 [±1.99] years, p=0.028), age at start of GnRH analogues (14.25 [±1.79] versus 15.21 [±1.95] years, p=0.036) and age at the start of gender-affirming hormones (16.24 [±1.21] versus 16.99 [±1.09] years, p=0.008). No statistically significant differences were seen for other baseline characteristics, time between GnRH analogue and gender-affirming hormones, full scale IQ, parental marital status, education, and sexual attraction to own, other or both sexes.
[2] Independent t-tests between mean scores on the CBCL, YSR, BDI, TPI, STAI, CGAS, UGS, and BIS of adolescents who completed both assessments and mean scores of adolescents who completed only one of the assessments revealed no significant differences on all used measures, at neither T0 or at T1.
[3] The CBCL/YSR has 2 components: Internalising score which sums the anxious/depressed, withdrawn-depressed, and somatic complaints scores; externalising score which sums rule-breaking and aggressive behaviour. The total problems score is the sum of the scores of all the problem items. The YSR is a child self-report version of the CBCL.
[4] A repeated measures ANOVA (analysis of variance) was used.

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
Joseph T, Ting J, Butler G. (2019) The effect of GnRH analogue treatment on bone mineral density in young adolescents with gender dysphoria: findings from a large national cohort. Journal of pediatric endocrinology & metabolism 32(10): 1077-1081 United Kingdom	Adolescents (12 to 14 years) with gender dysphoria (no diagnostic criteria described), n=70, including 31 transfemales and 39 transmales. All had been seen and assessed by a Gender Identity Development Service multi-disciplinary psychosocial health team for at least 4 assessments over a minimum of 6 months. All participants had entered puberty	Treatment with a GnRH analogue for at least 1 year or ongoing until they reached 16 years. No specific treatment, dose or route of administration reported. No concomitant treatments were reported.	**Critical outcomes** No critical outcomes assessed. **Important outcomes** ***Bone density: lumbar[1]*** **Lumbar spine bone mineral apparent density (BMAD)[2] 0 to 1 year** Transfemales (mean [±SD]): 0.235 (0.030) g/cm3 at baseline, 0.233 g/cm3 (0.029) at 1 year (p=0.459); z-score 0.859 (0.154) at baseline, −0.228 (1.027) at 1 year (p=0.000) Transmales (mean [±SD]):	This study was appraised using the Newcastle-Ottawa quality assessment checklist for cohort studies. **Domain 1: Selection** 1. Somewhat representative of children and adolescents who have gender dysphoria 2. Not applicable 3. Via routine clinical records 4. No

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
Retrospective longitudinal observational single centre study To investigate whether there is any significant loss of bone mineral density (BMD) and bone mineral apparent density (BMAD) for up to 3 years of GnRH analogues. To investigate whether there was a significant drop after 1 year of treatment following abrupt withdrawal. 2011 to 2016	and all but 2 of the transmales were postmenarchal. 57% of the transfemales were in early puberty (G2–3 and testicular volume >4 mL) and 43% were in late puberty (G4–5). Details of the sampling frame were not reported. Further details of how the sample was drawn are not reported.	No comparator.	0.196 (0.035) g/cm3 at baseline, 0.201 (0.033) g/cm3 at 1 year (p=0.074); z-score −0.186 (1.230) at baseline, −0.541 (1.396) at 1 year (p=0.006) **Lumbar spine BMAD 0 to 2 years** Transfemales (mean [±SD]): 0.240 (0.027) g/cm3 at baseline, 0.240 (0.030) g/cm3 at 2 years (p=0.865); z-score 0.486 (0.809) at baseline, −0.279 (0.930) at 2 years (p=0.000) Transmales (mean [±SD]): 0.195 (0.058) g/cm3 at baseline, 0.198 (0.055) at 2 years (p=0.433); z-score −0.361 (1.439) at baseline, −0.913 (1.318) at 2 years (p=0.001) **Lumbar spine bone mineral density (BMD) 0 to 1 year** Transfemales (mean [±SD]): 0.860 (0.154) kg/m2 at baseline, 0.859 (0.129) kg/m2 at 1 year (p=0.962); z-score −0.016 (1.106) at baseline, −0.461 (1.121) at 1 year (p=0.003) Transmales (mean [±SD]): 0.694 (0.149) kg/m2 at baseline, 0.718 (0.124) kg/m2 at 1 year (p=0.006); z-score −0.395 (1.428) at baseline, −1.276 (1.410) at 1 year (p=0.000) **Lumbar spine BMD 0 to 2 years** Transfemales (mean [±SD]): 0.867 (0.141) kg/m2 at baseline, 0.878 (0.130) kg/m2 at 2 years (p=0.395); z-score 0.130 (0.972) at baseline, −0.890 (1.075) at 2 years (p=0.000) Transmales (mean [±SD]): 0.695 (0.220) kg/m2 at baseline, 0.731 (0.209) kg/m2 at 2 years (p=0.058); z-score −0.715 (1.406) at baseline, −2.000 (1.384) at 2 years (p=0.000) ***Bone density: femoral***	**Domain 2: Comparability** 1. No control group **Domain 3: Outcome** 1. Via routine clinical records 2. Yes 3. No statement **Overall quality is assessed as poor**. Other comments: although the evidence is of poor quality, the results suggest a possible association between GnRH analogues and BMAD. However, the results are not reliable and could be due to bias or chance. Further details of how the sample was drawn are not reported. No concomitant treatments were reported. Source of funding: None disclosed

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
			Femoral neck (hip) BMD 0 to 1 year Transfemales (mean [±SD]): 0.894 (0.118) kg/m2 at baseline, 0.905 (0.104) kg/m2 at 1 year (p=0.571); z-score 0.157 (0.905) at baseline, −0.340 (0.816) at 1 year (p=0.002) Transmales (mean [±SD]): 0.772 (0.137) kg/m2 at baseline, 0.785 (0.120) kg/m2 at 1 year (p=0.797); z-score −0.863 (1.215) at baseline, −1.440 (1.075) at 1 year (p=0.000) **Femoral neck (hip) BMD 0 to 2 years** Transfemales (mean [±SD]): 0.920 (0.116) kg/m2 at baseline, 0.910 (0.125) kg/m2 at 2 years (p=0.402); z-score 0.450 (0.781) at baseline, −0.600 (1.059) at 2 years (p=0.002) Transmales (mean [±SD]): 0.766 (0.215) kg/m2 at baseline, 0.773 (0.197) at 2 years (p=0.604); z-score −1.075 (1.145) at baseline, −1.779 (0.816) at 2 years (p=0.001)	

[1] Lumbar spine (L1-L4) BMD was measured by yearly dual energy X-ray absorptiometry (DXA) scans at baseline (n=70), 1 year (n=70), and 2 years (n=31).
[2] BMAD is a size adjusted value of BMD incorporating body size measurements using UK norms in growing adolescents. Reported as g/cm3 and z-scores. Hip BMAD z-scores were not calculated as there were no available reference ranges.

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
Khatchadourian K, Shazhan A, Metzger D. (2014) Clinical management of youth with gender dysphoria in Vancouver. The Journal of Pediatrics 164 (4): 906-11. Canada Retrospective observational chart review single centre study	27 young people with gender dysphoria who started GnRH analogues (at mean age [±SD] 14.7±1.9 years) out of 84 young people seen at the unit between 1998 and 2011. Note: the transmale and transfemale subgroups reported in the paper is discrepant, 15 transmales and 11 transfemales (n=26) reported in the outcomes section rather than the n=27	**Intervention** 84 young people with gender dysphoria were included. For GnRH analogues no specific treatment, dose or route of administration reported. **Comparison** No comparator.	**Critical Outcomes** No critical outcomes assessed. **Important outcomes** ***Stopping treatment*** The authors report that of 15 transmales taking GnRH analogues: • 14 transitioned to testosterone treatment during the observation period • 7 continued taking GnRH analogues after starting testosterone	This study was appraised using the Newcastle-Ottawa tool for cohort studies. **Domain 1: Selection** 1. not reported 2. no non-exposed cohort 3. secure record 4. no **Domain 2: Comparability** 1. not applicable **Domain 3: Outcome**

Study details	Population	Interventions	Study outcomes	Appraisal and Funding

	stated in the paper; complete outcome reporting is also incomplete for the transfemale group.
	Inclusion criteria were at least Tanner stage 2 pubertal development, previous assessment by a mental health professional and a confirmed diagnosis of gender dysphoria (diagnostic criteria not specified). No exclusion criteria are specified.
			• 7 discontinued GnRH analogues after a median of 3.0 years (range 0.2 to 9.2 years), of which:
			  ○ 5 discontinued after hysterectomy and salpingo-oophorectomy
			  ○ 1 discontinued after 2.2 years (transitioned to gender-affirming hormone)
			  ○ 1 discontinued after <2 months due to mood and emotional lability
			The authors report that of 11 transfemales taking GnRH analogues:
			• 5 received oestrogen treatment during the observation period
			• 4 continued taking GnRH analogues during oestrogen treatment
			• 1 discontinued GnRH analogues during oestrogen treatment (no reason reported)
			• 1 stopped GnRH analogues after a few months due to emotional lability
			• 1 stopped GnRH analogues before oestrogen treatment (the following year delayed due to heavy smoking)
			• 1 discontinued GnRH analogues after 13 months due to choosing not to pursue transition
			
			Safety
			Of the 27 patients treated with GnRH analogues:
			• 1 transmale participant developed sterile abscesses; they were switched from leuprolide acetate to triptorelin, and this was well tolerated.
			• 1 transmale participant developed leg pains and headaches on GnRH analogues, which eventually resolved without treatment.
				1. record linkage
				2. yes
				3. in complete missing data
				
				Overall quality is assessed as poor.
				
				Other comments: mental health comorbidity was reported for all participants but not for the GnRH analogue cohort separately. Concomitant use of other medicines was not reported.
				
				Source of funding: No source of funding identified.

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
			• 1 participant gained 19 kg within 9 months of initiating GnRH analogues, although their body mass index was >85 percentile before GnRH analogues.	

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
Klink D, Caris M, Heijboer A et al. (2015) Bone mass in young adulthood following gonadotropin-releasing hormone analog treatment and cross-sex hormone treatment in adolescents with gender dysphoria. The Journal of clinical endocrinology and metabolism 100(2): e270-5 Netherlands Retrospective longitudinal observational single centre study To assess BMD development during GnRH analogues and at age 22 years in adolescents with gender dysphoria who started treatment for gender dysphoria during adolescence. 1998 to 2012	34 adolescents (mean age ±SD 14.9±1.9 for transfemales and 15.0±2.0 for transmales at start of GnRH analogues). Participants were included if they met DSM-IV-TR criteria for gender identity disorder of adolescence and had been treated with GnRH analogues and gender-affirming hormones during their pubertal years. No concomitant treatments were reported.	The intervention was GnRH analogue monotherapy (triptorelin pamoate 3.75 mg subcutaneously every 4 weeks) followed by gender-affirming hormones from 16 years with discontinuation of GnRH analogue after gonadectomy. Median duration of GnRH analogue monotherapy in transfemales was 1.3 years (range, 0.5 to 3.8 years), and in transmales was 1.5 years (range, 0.25 to 5.2 years).	**Critical outcomes** No critical outcomes assessed. **Important outcomes** ***Bone density: lumbar*** **Lumbar spine bone mineral apparent density (BMAD)[1]** Change from starting GnRH analogue (mean age 14.9±1.9) to starting gender-affirming hormones (mean age 16.6±1.4) in transfemales (mean [±SD]): GnRH analogue: 0.22 (0.03) g/cm3, gender-affirming hormones: 0.22 (0.02) g/cm3 (NS); z-score GnRH analogue: −0.44 (1.10), gender-affirming hormones: −0.90 (0.80) (p=NS) Change from starting GnRH analogue (mean age 15.0±2.0) to starting gender-affirming hormones (mean age 16.4±2.3) in transmales (mean [±SD]: GnRH analogue: 0.25 (0.03) g/cm3, gender-affirming hormones: 0.24 (0.02) g/cm3 (NS); z-score GnRH analogue: 0.28 (0.90), gender-affirming hormones: −0.50 (0.81) (p=0.004) **Lumbar spine bone mineral density (BMD)[1]** Change from starting GnRH analogue (mean age 14.9±1.9) to starting gender-affirming hormones (mean age	This study was appraised using the Newcastle-Ottawa quality assessment checklist for cohort studies. **Domain 1: Selection** 1. somewhat representative of children and adolescents who have gender dysphoria 2. not applicable 3. via routine clinical records 4. no **Domain 2: Comparability** 1. no control group **Domain 3: Outcome** 1. via routine clinical records 2. yes 3. follow-up rate variable across timepoints and no description of those lost **Overall quality is assessed as poor**. Other comments: Within person comparison. Small numbers of participants in each subgroup. No concomitant treatments or comorbidities were reported. Source of funding: None disclosed

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
			16.6±1.4) in transfemales (mean [±SD]): GnRH analogue: 0.84 (0.13) g/m2, gender-affirming hormones: 0.84 (0.11) g/m2 (NS); z-score GnRH analogue: −0.77 (0.89), gender-affirming hormones: −1.01 (0.98) (NS) Change from starting GnRH analogue (mean age 15.0±2.0) to starting gender-affirming hormones (mean age 16.4±2.3) in transmales (mean [±SD]): GnRH analogue: 0.95 (0.12) g/m2, gender-affirming hormones: 0.91 (0.10) g/m2 (p=0.006); z-score GnRH analogue: 0.17 (1.18), gender-affirming hormones: −0.72 (0.99) (p<0.001) ***Bone density; femoral*** **Femoral area BMAD[1]** Change from starting GnRH analogue (mean age 14.9±1.9) to starting gender-affirming hormones (mean age 16.6±1.4) in transfemales (mean [±SD]), GnRH analogue: 0.28 (0.04) g/cm3, gender-affirming hormones: 0.26 (0.04) g/cm3 (NS); z-score GnRH analogue: −0.93 (1.22), gender-affirming hormones: −1.57 (1.74) (p=NS) Change from starting GnRH analogue (mean age 15.0±2.0) to starting gender-affirming hormones (mean age 16.4±2.3) in transmales (mean [±SD]), GnRH analogue: 0.32 (0.04) g/cm3, gender-affirming hormones: 0.31 (0.04) (NS); z-score GnRH analogue: 0.01 (0.70), gender-affirming hormones: −0.28 (0.74) (NS)	

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
			Femoral area BMD[1] Change from starting GnRH analogue (mean age 14.9±1.9) to starting gender-affirming hormones (mean age 16.6±1.4) in transfemales (mean [±SD]), GnRH analogue: 0.88 (0.12) g/m2, gender-affirming hormones: 0.87 (0.08) (NS); z-score GnRH analogue: −0.66 (0.77), gender-affirming hormones: −0.95 (0.63) (NS) Change from starting GnRH analogue (mean age 15.0±2.0) to starting gender-affirming hormones (mean age 16.4±2.3) in transmales (mean [±SD]), GnRH analogue: 0.92 (0.10) g/m2, gender-affirming hormones: 0.88 (0.09) (p=0.005); z-score GnRH analogue: 0.36 (0.88), gender-affirming hormones: −0.35 (0.79) (p=0.001)	

[1] BMD and BMAD of the lumbar spine and femoral region (nondominant side) measured by DXA scans at start of GnRH analogues, (n=32), start of gender-affirming hormones (n=34), and at 22 years (n=34).

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
Schagen SEE, Cohen-Kettenis PT, Delemarre-van de Waal HA et al. (2016) Efficacy and Safety of Gonadotropin-Releasing Hormone Agonist Treatment to Suppress Puberty in Gender Dysphoric Adolescents. The journal of sexual medicine 13(7): 1125-32	Adolescents with gender dysphoria (n=116), median age (range) 13.6 years (11.6 to 17.9) in transfemales and 14.2 years (11.1 to 18.6) in transmales during first year of GnRH analogues. Participants were included if they met DSM-IV-TR criteria for gender dysphoria, had lifelong extreme gender dysphoria, were psychologically stable and were living in a supportive environment. No concomitant treatments were	GnRH analogue monotherapy (triptorelin pamoate 3.75 mg at 0, 2 and 4 weeks followed by injections every 4 weeks, route of administration not described) for at least 3 months.	**Critical outcomes** No critical outcomes assessed. **Important outcomes** ***Other safety outcomes: liver function*** Glutamyl transferase was not elevated at baseline or during treatment in any subject. Mild elevations of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) above the reference range were present at baseline but were not more prevalent during treatment than at baseline. Glutamyl transferase, AST, and ALT	This study was appraised using the Newcastle-Ottawa quality assessment checklist for cohort studies. **Domain 1: Selection** 1. somewhat representative of children and adolescents who have gender dysphoria 2. not applicable 3. via routine clinical records 4. no **Domain 2: Comparability** 1. no control group

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
Netherlands Prospective longitudinal study To describe the changes in Tanner stage, testicular volume, gonadotropins, and sex steroids during GnRH analogues of adolescents with gender dysphoria to evaluate the efficacy. To report on liver enzymes, renal function and changes in body composition. 1998 to 2009	reported.		levels did not significantly change from baseline to 12 months of treatment. No values or statistical analyses were reported. ***Other safety outcomes: kidney function*** **Change in serum creatinine between 0 and 1 year** Transfemales (mean [±SD]): 70 (12) micromol/l at baseline, 66 (13) micromol/l at 1 year (p=0.20) Transmales (mean [±SD]): 73 (8) micromol/l at baseline, 68 (13) micromol/l at 1 year (p=0.01)	**Domain 3: Outcome** 1. via routine clinical records 2. yes 3. no statement **Overall quality is assessed as poor**. Other comments: Within person comparison. No concomitant treatments or comorbidities were reported. Source of funding: Ferring pharmaceuticals (triptorelin manufacturer)

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
Staphorsius A, Baudewijntje P, Kreukels P, et al. (2015) Puberty suppression and executive functioning: an fMRI-study in adolescents with gender dysphoria. Psychoneuroendocrinology 565:190-9. Netherlands Cross-sectional (single time point) assessment single centre study	The inclusion criteria were diagnosed with Gender Identity Disorder according to the DSM-IV-TR and at least 12 years old and Tanner stage of at least B2 or G2 to G3 with measurable oestradiol and testosterone levels in girls and boys, respectively. For all group's exclusion criteria were an insufficient command of the Dutch language (how assessed not reported), unadjusted endocrine disorders, neurological or psychiatric disorders that could lead to deviant test results (details not reported) use	**Intervention** GnRH analogues (triptorelin pamoate 3.75 mg every 4 weeks subcutaneously or intramuscularly). **Comparison** The comparison was between adolescents with gender dysphoria receiving GnRH analogues and those without GnRH	**Critical Outcomes** No critical outcomes assessed. **Important outcomes** ***Psychosocial impact*** The Child Behaviour Checklist (CBCL) was used to assess psychosocial impact. The CBCL was administered once during the study. The reported outcomes for each group were (n, mean [±SD]): • Transfemales (all, n=18) 57.8 [±9.2] • Transfemales on GnRH analogues (n=8) 57.4 [±9.8] • Transfemales without GnRH analogues (n=10) 58.2 [±9.3]	This study was appraised using the Newcastle-Ottawa tool for cohort studies. **Domain 1: Selection domain** 1. somewhat representative of children and adolescents who have gender dysphoria 2. drawn from the same community as the exposed cohort 3. via routine clinical records 4. no **Domain 2: Comparability** 1. study controls for age and diagnosis

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
	of psychotropic medication, and contraindications for an MRI scan. Additionally, adolescents receiving puberty delaying medication or any form of hormones besides oral contraceptives were excluded as controls. The sample size was 85 of whom 41 were adolescents (the numbers are discrepant with the number for whom outcomes are reported n=40) with gender dysphoria (20 of whom were being treated with GnRH analogues); 24 girls and 21 boys without gender dysphoria acted as controls (not further reported here). Details of the sampling frame are not reported. The ages at which GnRH analogues were started was not reported. The mean duration of treatment was 1.6 years (SD 1.0) Mean (±SD) Tanner stage for each group was reported: • Transfemales 3.9 [±1.1] • Transfemales on GnRH analogues 4.1 [±1.0] • Transfemales without GnRH analogues 3.8 [±1.1] • Transmales 4.5 [±0.9] • Transmales on GnRH analogues 4.1 [±1.1] Transmales without GnRH analogues 4.9 [±0.3]	analogues.	• Transmales (all, n=22) 60.4 [±10.2] • Transmales on GnRH analogues (n=12) 57.5 [±9.4] • Transmales without GnRH analogues (n=10) 63.9 [±10.5] The analysis of the CBCL data is not discussed, and statistical analysis is unclear. ***Cognitive development or functioning*** **IQ[1]** • Transfemales (mean [±SD]) on GnRH analogues: 94.0 (10.3) • Transfemales (mean [±SD]) without GnRH analogues: 109.4 (21.2) • Transmales (mean [±SD]) on GnRH analogues: 95.8 (15.6) • Transmales (mean [±SD]) without GnRH analogues: 98.5 (15.9) **Reaction time[2]** • Transfemales (mean [±SD]) on GnRH analogues: 10.9 (4.1) • Transfemales (mean [±SD]) without GnRH analogues: 9.9 (3.1) • Transmales (mean [±SD]) on GnRH analogues: 9.9 (3.1) • Transmales (mean [±SD]) without GnRH analogues: 10.0 (2.0) **Accuracy[3]** • Transfemales (mean [±SD]) on GnRH analogues: 73.9 (9.1) • Transfemales (mean [±SD]) without GnRH analogues: 83.4 (9.5) • Transmales (mean [±SD]) on GnRH analogues: 85.7 (10.5) • Transmales (mean [±SD]) without	**Domain 3: Outcome** 1. via clinical assessment 2. yes 3. unclear **Overall quality is assessed as poor.** Other comments: Physical and psychological comorbidity was not reported, concomitant use of other medicines was not reported. Source of funding: This work was supported by an educational grant from the pharmaceutical firm Ferring BV, and by a VICI grant (453-08-003) from the Dutch Science Foundation. The authors state that funding sources did not play a role in any component of this study.

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
			GnRH analogues: 88.8 (9.7)	

[1] Estimated with 4 subscales (arithmetic, vocabulary, picture arrangement, and block design) of the Wechsler Intelligence Scale for Children, third edition (WISC-III®, Wechsler 1991) or the Wechsler Adult Intelligence Scale, third edition (WAIS-III®, Wechsler 1997), depending on the participant's age.
[2] Reaction time in seconds in the Tower of London task
[3] Percentage of correct trials in the Tower of London task

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
Vlot, Mariska C, Klink, Daniel T, den Heijer, Martin et al. (2017) Effect of pubertal suppression and cross-sex hormone therapy on bone turnover markers and bone mineral apparent density (BMAD) in transgender adolescents. Bone 95: 11-19 Netherlands Retrospective observational data analysis study To investigate the course of 3 bone turnover markers in relation to bonemineral density, in adolescents with gender dysphoria during GnRH analogue and gender-affirming hormones. 2001 to 2011	Adolescents with gender dysphoria, n=70. Median age (range) 15.1 years (11.7 to 18.6) for transmales and 13.5 years (11.5 to 18.3) for transfemales at start of GnRH analogues. Participants were included if they had a diagnosis of gender dysphoria according to DSM-IV-TR criteria who were treated with GnRH analogues and then gender-affirming hormones. No concomitant treatments were reported. The study categorised participants into a young and old pubertal group, based on their bone age. The young transmales had a bone age of <14 years and the old transmales had a bone age of ≥14 years. The young transfemales group had a bone age of <15 years and the old transfemales group ≥15 years.	GnRH analogues (triptorelin pamoate 3.75 mg every 4 weeks subcutaneously).	**Critical outcomes** No critical outcomes reported **Important outcomes** ***Bone density: lumbar*** **Lumbar spine bone mineral apparent density (BMAD)** Change from starting GnRH analogue to starting gender-affirming hormones in transfemales (bone age of <15 years; median [range]), GnRH analogue: 0.21 (0.17 to 0.25) g/cm3, gender-affirming hormones: 0.20 (0.18 to 0.24) g/cm3 (NS); z-score GnRH analogue: −0.20 (−1.82 to 1.18), gender-affirming hormones: −1.52 (−2.36 to 0.42) (p=0.001) Change from starting GnRH analogue to starting gender-affirming hormones in transfemales (bone age of ≥15; median [range]), GnRH analogue: 0.22 (0.18 to 0.25) g/cm3, gender-affirming hormones: 0.22 (0.19 to 0.24) g/cm3 (NS); z-score GnRH analogue: −1.18 (−1.78 to 1.09), gender-affirming hormones: −1.15 (−2.21 to 0.08) (p≤0.1) Change from starting GnRH analogue to starting gender-affirming hormones in transmales (bone age of <15 years; median [range]), GnRH analogue: 0.23 (0.20 to 0.29) g/cm3, gender-affirming	This study was appraised using the Newcastle-Ottawa quality assessment checklist for cohort studies. **Domain 1: Selection** 1. Somewhat representative of children and adolescents who have gender dysphoria 2. Not applicable 3. Via routine clinical records 4. No **Domain 2: Comparability** 1. No control group **Domain 3: Outcome** 1. Via routine clinical records 2. Yes 3. Follow-up rate variable across outcomes and no description of those lost **Overall quality is assessed as poor**. Other comments: Within person comparison. No concomitant treatments were reported. Source of funding: grant from Abbott diagnostics

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
			hormones: 0.23 (0.19 to 0.28) g/cm3 (NS); z-score GnRH analogue: −0.05 (−0.78 to 2.94), gender-affirming hormones: −0.84 (−2.20 to 0.87) (p=0.003) Change from starting GnRH analogue to starting gender-affirming hormones in transmales (bone age of ≥15; median [range]), GnRH analogue: 0.26 (0.21 to 0.29) g/cm3, gender-affirming hormones: 0.24 (0.20 to 0.28) g/cm3 (p≤0.01); z-score GnRH analogue: 0.27 (−1.60 to 1.80), gender-affirming hormones: −0.29 (−2.28 to 0.90) (p≤ 0.0001) ***Bone density; femoral*** **Femoral neck BMAD** Change from starting GnRH analogue to starting gender-affirming hormones in transfemales (bone age of <15 years; median [range]), GnRH analogue: 0.29 (0.20 to 0.33) g/cm3, gender-affirming hormones: 0.27 (0.20 to 0.33) g/cm3 (p≤0.1); z-score GnRH analogue: −0.71 (−3.35 to 0.37), gender-affirming hormones: −1.32 (−3.39 to 0.21) (p≤0.1) Change from starting GnRH analogue to starting gender-affirming hormones in transfemales (bone age of ≥15; median [range]), GnRH analogue: 0.30 (0.26 to 0.36) g/cm3, gender-affirming hormones: 0.30 (0.26 to 0.34) g/cm3 (NS); z-score GnRH analogue: −0.44 (−1.37 to 0.93), gender-affirming hormones: −0.36 (−1.50 to 0.46) (NS) Change from starting GnRH analogue to starting gender-affirming hormones in transmales (bone age of <15 years; median [range]),	

Study details	Population	Interventions	Study outcomes	Appraisal and Funding
			GnRH analogue: 0.31 (0.26 to 0.36) g/cm3, gender-affirming hormones: 0.30 (0.22 to 0.35) g/cm3 (NS); z-score GnRH analogue: −0.01 (−1.30 to 0.91), gender-affirming hormones: −0.37 (−2.28 to 0.47) (NS) Change from starting GnRH analogue to starting gender-affirming hormones in transmales (bone age of ≥15; median [range]), GnRH analogue: 0.33 (0.25 to 0.39) g/cm3, gender-affirming hormones: 0.30 (0.23 to 0.41) g/cm3 (p≤0.01); z-score GnRH analogue: 0.27 (−1.39 to 1.32), gender-affirming hormones: −0.27 (−1.91 to 1.29) (p=0.002)	

Appendix F Quality appraisal checklists

Newcastle-Ottawa tool for cohort studies

Question	
Domain: Selection	
1. Representativeness of the exposed cohort	Truly representative of the average [describe] in the community Somewhat representative of the average [describe] in the community Selected group of users e.g. nurses, volunteers No description of the derivation of the cohort
2. Selection of the non-exposed cohort	Drawn from the same community as the exposed cohort Drawn from a different source No description of the derivation of the non-exposed cohort
3. Ascertainment of exposure	Secure record (e.g. surgical records) Structured interview Written self-report No description
4. Demonstration that outcome of interest was not present at start of study	Yes / No
Domain: Comparability	
1. Comparability of cohorts on the basis of the design or analysis	Study controls for [select most important factor] Study controls for any additional factor [this criteria could be modified to indicate specific control for a second important factor]
Domain: Outcome	
1. Assessment of outcome	Independent blind assessment Record linkage Self-report No description
2. Was follow-up long enough for outcomes to occur	Yes [select and adequate follow up period for outcome of interest] No
3. Adequacy of follow up of cohorts	Complete follow up (all subjects accounted for) Subjects lost to follow up unlikely to introduce bias (small number lost to follow up [select an adequate %] follow up or description provided of those lost) Follow up rate [select an adequate %] and no description of those lost No statement

Appendix G Grade profiles

Table 2: Question 1. For children and adolescents with gender dysphoria, what is the clinical effectiveness of treatment with GnRH analogues compared with one or a combination of psychological support, social transitioning to the desired gender or no intervention? – gender dysphoria

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result		
Impact on gender dysphoria									
Mean±SD Utrecht Gender Dysphoria Scale[1] (version(s) not reported), time point at baseline (before GnRH analogues) versus follow-up (before gender-affirming hormones, higher scores indicate more gender dysphoria)									
1 cohort study de Vries et al 2011	Serious limitations[2]	No serious indirectness	Not applicable	Not calculable	N=41	None	Baseline: 53.20±7.91 GnRH analogue: 53.9±17.42 *P*=0.333	Critical	VERY LOW

Abbreviations: GnRH, gonadotrophin releasing hormone; *P*, P-value; SD, Standard deviation.

1 The UGDS is a validated screening tool for both adolescents and adults to assess gender dysphoria. It consists of 12 items, to be answered on a 1- to 5-point scale, resulting in a sum score between 12 and 60. The higher the UGDS score the greater the gender dysphoria.
2 Downgraded 1 level - the cohort study by de Vries et al. (2011) was assessed as at high risk of bias (poor quality overall; lack of blinding and no control group).

Table 3: Question 1. For children and adolescents with gender dysphoria, what is the clinical effectiveness of treatment with GnRH analogues compared with one or a combination of psychological support, social transitioning to the desired gender or no intervention? – mental health

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result		
Impact on mental health									

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result		
Mean±SD Beck Depression Inventory-II, time point at baseline (before GnRH analogues) versus follow-up (just before gender-affirming hormones). (Lower scores indicate benefit)									
1 cohort study de Vries et al 2011	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N=41	None	Baseline: 8.31±7.12 GnRH analogue: 4.95±6.72 *P*=0.004	Critical	VERY LOW
Mean±SD Trait Anger (TPI), time point at baseline (before GnRH analogues) versus follow-up (just before gender-affirming hormones, lower scores indicate benefit)									
1 cohort study de Vries et al 2011	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N=41	None	Baseline: 18.29±5.54 GnRH analogue: 17.88±5.24 *P*=0.503	Critical	VERY LOW
Mean±SD Trait Anxiety (STAI), time point at baseline (before GnRH analogues) versus follow-up (just before gender-affirming hormones, lower scores indicate benefit)									
1 cohort study de Vries et al 2011	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N=41	None	Baseline: 39.43±10.07 GnRH analogue: 37.95±9.38 *P*=0.276	Critical	VERY LOW

Abbreviations: GnRH, gonadotrophin releasing hormone; *P*, P-value; SD, Standard deviation.

1 Downgraded 1 level - the cohort study by de Vries et al. (2011) was assessed as at high risk of bias (poor quality overall; lack of blinding and no control group).

Table 4: Question 1. For children and adolescents with gender dysphoria, what is the clinical effectiveness of treatment with GnRH analogues compared with one or a combination of psychological support, social transitioning to the desired gender or no intervention? – body image

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result		
Impact on body image									
Mean±SD Body Image Scale (primary sexual characteristics), time point at baseline (before GnRH analogues) versus follow-up (just before gender-affirming hormones, lower scores indicate benefit)									
1 cohort study de Vries et al 2011	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N=57	None	Baseline: 4.10±0.56 GnRH analogue: 3.98±0.71 *P*=0.145	Important	VERY LOW
Mean±SD Body Image Scale (secondary sexual characteristics), time point at baseline (before GnRH analogues) versus follow-up (just before gender-affirming hormones, lower scores indicate benefit)									
1 cohort study de Vries et al 2011	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N=57	None	Baseline: 2.74±0.65 GnRH analogue: 2.82±0.68 *P*=0.569	Important	VERY LOW
Mean±SD Body Image Scale (neutral characteristics), time point at baseline (before GnRH analogues) versus follow-up (just before gender-affirming hormones, lower scores indicate benefit)									
1 cohort study de Vries et al 2011	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N=57	None	Baseline: 2.41±0.63 GnRH analogue: 2.47±0.56 *P*=0.620	Important	VERY LOW

Abbreviations: GnRH, gonadotrophin releasing hormone; *P*, P-value; SD, Standard deviation.

1 Downgraded 1 level - the cohort study by de Vries et al. (2011) was assessed as at high risk of bias (poor quality overall; lack of blinding and no control group).

Table 5: Question 1. For children and adolescents with gender dysphoria, what is the clinical effectiveness of treatment with GnRH analogues compared with one or a combination of psychological support, social transitioning to the desired gender or no intervention? – psychosocial impact

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result		
Psychosocial impact									
Mean [±SD] Children's Global Assessment Scale score, at baseline, higher scores indicate benefit)									
1 cohort study Costa et al 2015	Serious limitations[1]	No serious indirectness	No serious inconsistency	Not calculable	n=101 58.72 [±11.38]	n=100 56.63 [±13.14]	*P*=0.23	Important	VERY LOW
Mean [±SD] Children's Global Assessment Scale score, at 6 months[2] (higher scores indicate benefit).									
1 cohort study Costa et al 2015	Serious limitations[1]	No serious indirectness	No serious inconsistency	Not calculable	n=101 60.89 [±12.17]	n=100 60.29 [±12.81]	*P*=0.73	Important	VERY LOW
Mean [±SD] Children's Global Assessment Scale score, at 12 months[3] (higher scores indicate benefit).									
1 cohort study Costa et al 2015	Serious limitations[1]	No serious indirectness	No serious inconsistency	Not calculable	n=60 64.70 [±13.34]	n=61 62.97 [±14.10]	*P*=0.49	Important	VERY LOW
Mean [±SD] Children's Global Assessment Scale score, at 18 months[4] (higher scores indicate benefit).									
1 cohort study Costa et al 2015	Serious limitations[1]	No serious indirectness	No serious inconsistency	Not calculable	n=35 67.40 [±13.93]	n=36 62.53 [±13.54]	*P*=0.14	Important	VERY LOW
Mean [±SD] Children's Global Assessment Scale score, participants at 6 months compared to baseline (higher scores indicate benefit).									
1 cohort study Costa et al 2015	Serious limitations[1]	No serious indirectness	No serious inconsistency	Not calculable	N=101 N=101	None	Baseline: 58.72±11.38 6 months: 60.89±12.17 *P*=0.19	Important	VERY LOW
Mean [±SD] Children's Global Assessment Scale score, participants at 12 months compared to baseline (higher scores indicate benefit).									
1 cohort study Costa et al 2015	Serious limitations[1]	No serious indirectness	No serious inconsistency	Not calculable	N=101 N=60	None	Baseline: 58.72±11.38 12 months: 64.70±13.34 *P*=0.003	Important	VERY LOW

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result		
Mean [±SD] Children's Global Assessment Scale score, participants at 18 months compared to baseline (higher scores indicate benefit).									
1 cohort study Costa et al 2015	Serious limitations[1]	No serious indirectness	No serious inconsistency	Not calculable	N=101 N=35	None	Baseline: 58.72±11.38 18 months: 67.40±13.93 *P*<0.001	Important	VERY LOW
Mean [±SD] Children's Global Assessment Scale score, participants at 12 months compared to 6 months (higher scores indicate benefit).									
1 cohort study Costa et al 2015	Serious limitations[1]	No serious indirectness	No serious inconsistency	Not calculable	N=101 N=60	None	6 months: 60.89±12.17 12 months: 64.70±13.34 *P*=0.07	Important	VERY LOW
Mean [±SD] Children's Global Assessment Scale score, participants at 18 months compared to 6 months (higher scores indicate benefit).									
1 cohort study Costa et al 2015	Serious limitations[1]	No serious indirectness	No serious inconsistency	Not calculable	N=101 N=35	None	6 months: 60.89±12.17 18 months: 67.40±13.93 *P*<0.001	Important	VERY LOW
Mean [±SD] Children's Global Assessment Scale score, participants at 18 months compared to 12 months (higher scores indicate benefit).									
1 cohort study Costa et al 2015	Serious limitations[1]	No serious indirectness	No serious inconsistency	Not calculable	N=60 N=35	None	12 months: 64.70±13.34 18 months: 67.40±13.93 *P*=0.35	Important	VERY LOW
Mean [±SD] Children's Global Assessment Scale score, in all participants (including those not treated with GnRH analogues) at 6 months[2] compared to baseline (higher scores indicate benefit).									
1 cohort study Costa et al 2015	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N=201	None	Baseline: 57.73±12.27 6 months: 60.68±12.47 *P*<0.001	Important	VERY LOW
Mean [±SD] Children's Global Assessment Scale score, in all participants (including those not treated with GnRH analogues) at 12 months[3] compared to baseline (higher scores indicate benefit).									
1 cohort study Costa et al 2015	Serious limitations[1]	No serious indirectness	No serious inconsistency	Not calculable	N=201 N=121	None	Baseline: 57.73±12.27 12 months: 63.31±14.41 *P*<0.001	Important	VERY LOW

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result		
Mean±SD Children's Global Assessment Scale score, in all participants (including those not treated with GnRH analogues) at 18 months[4] compared to baseline (higher scores indicate benefit).									
1 cohort study Costa et al 2015	Serious limitations[1]	No serious indirectness	No serious inconsistency	Not calculable	N=201 N=71	None	Baseline: 57.73±12.27 18 months: 64.93±13.85 *P*<0.001	Important	VERY LOW
Mean±SD Children's Global Assessment Scale score, in all participants (including those not treated with GnRH analogues) at 12 months compared to 6 months (higher scores indicate benefit).									
1 cohort study Costa et al 2015	Serious limitations[1]	No serious indirectness	No serious inconsistency	Not calculable	N=201 N=121	None	6 months: 60.68±12.47 12 months: 63.31±14.41 *P*<0.08	Important	VERY LOW
Mean±SD Children's Global Assessment Scale score, in all participants (including those not treated with GnRH analogues) at 18 months compared to 6 months (higher scores indicate benefit).									
1 cohort study Costa et al 2015	Serious limitations[1]	No serious indirectness	No serious inconsistency	Not calculable	N=201 N=71	None	6 months: 60.68±12.47 18 months: 64.93±13.85 *P*<0.02	Important	VERY LOW
Mean±SD Children's Global Assessment Scale score, in all participants (including those not treated with GnRH analogues) at 18 months compared to 12 months (higher scores indicate benefit).									
1 cohort study Costa et al 2015	Serious limitations[1]	No serious indirectness	No serious inconsistency	Not calculable	N=121 N=71	None	12 months: 63.31±14.41 18 months: 64.93±13.85 *P*<0.45	Important	VERY LOW
Mean±SD Children's Global Assessment Scale score, time point at baseline (before GnRH analogues) versus follow-up (just before gender-affirming hormones, higher scores indicate benefit).									
1 cohort study de Vries et al 2011	Serious limitations[5]	No serious indirectness	Not applicable	Not calculable	N=41	None	Baseline: 70.24±10.12 GnRH analogue: 73.90±9.63 *P*=0.005	Important	VERY LOW

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result		
Mean±SD Child Behaviour Checklist (total T) score, time point at baseline (before GnRH analogues) versus follow-up (just before gender-affirming hormones, lower scores indicate benefit).									
1 cohort study de Vries et al 2011	Serious limitations[5]	No serious indirectness	Not applicable	Not calculable	N=54	None	Baseline: 60.70±12.76 GnRH analogue: 54.46±11.23 *P*<0.001	Important	VERY LOW
Mean±SD Child Behaviour Checklist (internalising T) score, time point at baseline (before GnRH analogues) versus follow-up (just before gender-affirming hormones, lower scores indicate benefit).									
1 cohort study de Vries et al 2011	Serious limitations[5]	No serious indirectness	Not applicable	Not calculable	N=54	None	Baseline: 61.00±12.21 GnRH analogue: 52.1±9.81 *P*<0.001	Important	VERY LOW
Mean±SD Child Behaviour Checklist (externalising T) score, time point at baseline (before GnRH analogues) versus follow-up (just before gender-affirming hormones, lower scores indicate benefit).									
1 cohort study de Vries et al 2011	Serious limitations[5]	No serious indirectness	Not applicable	Not calculable	N=54	None	Baseline: 58.04±12.99 GnRH analogue: 53.81±11.86 *P*=0.001	Important	VERY LOW
Proportion of adolescents scoring in the clinical range Child Behaviour Checklist total problem scale, time point at baseline (before GnRH analogues) versus follow-up (just before gender-affirming hormones, lower scores indicate benefit).									
1 cohort study de Vries et al 2011	Serious limitations[5]	No serious indirectness	Not applicable	Not calculable	N=54	None	Baseline: 44.4% GnRH analogue: 22,2% *P*=0.001	Important	VERY LOW
Mean±SD Youth Self-Report (total T) score, time point at baseline (before GnRH analogues) versus follow-up (just before gender-affirming hormone, lower scores indicate benefit).									
1 cohort study de Vries et al 2011	Serious limitations[5]	No serious indirectness	Not applicable	Not calculable	N=54	None	Baseline: 55.46±11.56 GnRH analogue: 50.00±10.56 *P*<0.001	Important	VERY LOW

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result		
Mean±SD Youth Self-Report (internalising T) score, time point at baseline (before GnRH analogues) versus follow-up (just before gender-affirming hormones, lower scores indicate benefit).									
1 cohort study de Vries et al 2011	Serious limitations[5]	No serious indirectness	Not applicable	Not calculable	N=54	None	Baseline: 56.04±12.49 GnRH analogue: 49.78±11.63 *P*<0.001	Important	VERY LOW
Mean±SD Youth Self-Report (externalising T) score, time point at baseline (before GnRH analogues) versus follow-up (just before gender-affirming hormones, lower scores indicate benefit).									
1 cohort study de Vries et al 2011	Serious limitations[5]	No serious indirectness	Not applicable	Not calculable	N=54	None	Baseline: 53.30±11.87 GnRH analogue: 49.98±9.35 *P*=0.009	Important	VERY LOW
Proportion of adolescents scoring in the clinical range Youth Self-Report (internalising T) score, time point at baseline (before GnRH analogues) versus follow-up (just before gender-affirming hormones, lower scores indicate benefit).									
1 cohort study de Vries et al 2011	Serious limitations[5]	No serious indirectness	Not applicable	Not calculable	N=54	None	Baseline: 29.6% GnRH analogue: 11.1% *P*=0.017	Important	VERY LOW
Mean±SD Child Behaviour Checklist score, transfemales (lower scores indicate benefit									
1 cross-sectional study Staphorsius et al 2015	Serious limitations[6]	No serious indirectness	Not applicable	Not calculable	N=8	N=10	GnRH analogue: 57.4 [±9.8] No GnRH analogue: 58.2 [±9.3]	Important	VERY LOW
Mean±SD Child Behaviour Checklist score, transmales (lower scores indicate benefit)									
1 cross-sectional study Staphorsius et al 2015	Serious limitations[6]	No serious indirectness	Not applicable	Not calculable	N=12	N=10	GnRH analogues: 57.5 [±9.4] No GnRH analogue: 63.9 [±10.5]	Important	VERY LOW

Abbreviations: GnRH, gonadotrophin releasing hormone; *P*, P-value; SD, Standard deviation.

1 Downgraded 1 level - the cohort study by Costa et al. (2015) was assessed as at high risk of bias (poor quality overall; lack of blinding and no control group).

2 6 months from baseline (after 6 months of psychological support – both groups).
3 12 months from baseline (delayed eligible gender dysphoria [GD] adolescents, after 12 months of psychological support; immediately eligible GD adolescents, after 12 months of psychological support + 6 months of puberty suppression).
4 18 months from baseline (delayed eligible gender dysphoria [GD] adolescents, after 12 months of psychological support; immediately eligible GD adolescents, after 12 months of psychological support + 6 months of puberty suppression).
5 Downgraded 1 level - the cohort study by de Vries et al. (2011) was assessed as at high risk of bias (poor quality overall; lack of blinding and no control group).
6 Downgraded 1 level - the cohort study by Staphorsius et al. (2015) was assessed as at high risk of bias (poor quality overall; lack of blinding and no randomisation).

Table 6: Question 1. For children and adolescents with gender dysphoria, what is the clinical effectiveness of treatment with GnRH analogues compared with one or a combination of psychological support, social transitioning to the desired gender or no intervention? – engagement with healthcare services

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients% (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result		
Engagement with healthcare services									
Number (proportion) failing to engage with health care services (did not attend clinic), at (up to) 9 years follow-up									
1 cohort study Brik et al 2018	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	9/214 (4.2%)	None	9 adolescents out of 214 failed to attend clinic and were excluded from the study (4.2%)	Important	VERY LOW
Loss to follow-up									
1 cohort study Costa et al 2015	Serious limitations[2]	No serious indirectness	Not applicable	Not calculable	201	None	The sample size at baseline and 6 months was 201, which dropped by 39.8% to 121 after 12 months and by 64.7% to 71 at 18 months follow-up. No explanation of the reasons for loss to follow-up are reported.	Important	VERY LOW

Abbreviations: GnRH, gonadotrophin releasing hormone.

1 Downgraded 1 level - the cohort study by Brik et al. (2018) was assessed as at high risk of bias (poor quality overall; lack of blinding and no control group).
2 Downgraded 1 level - the cohort study by Costa et al. (2015) was assessed as at high risk of bias (poor quality overall; lack of blinding and no control group).

Table 7: Question 1. For children and adolescents with gender dysphoria, what is the clinical effectiveness of treatment with GnRH analogues compared with one or a combination of psychological support, social transitioning to the desired gender or no intervention? – stopping treatment

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients% (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result		
Stopping treatment									
Number (proportion) stopping GnRH analogues, at (up to) 9 years follow-up									
1 cohort study Brik et al 2018	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	9/143 (6.2%)	None	9/143 adolescents stopped GnRH analogues (6.2%)[2]	Important	VERY LOW
Number (proportion) stopping from GnRH analogues, at (up to) 13 years follow-up									
1 cohort study Khatchadourian et al 2014	Serious limitations[3]	No serious indirectness	Not applicable	Not calculable	11/27 (42%)	None	11/26 stopped GnRH analogues (42%)[4]	Important	VERY LOW
Number (proportion) stopping GnRH analogues but who wished to continue endocrine treatment, at (up to) 9 years follow-up									
1 cohort study Brik et al 2018	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	4/143 (2.8%)	None	4/143 adolescents stopped GnRH analogues but wished to continue treatment (2.8%)	Important	VERY LOW
Number (proportion) stopping GnRH analogues who no longer wished gender-affirming treatment, at (up to) 9 years follow-up									
1 cohort study Brik et al 2018	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	5/143 (3.5%)	None	5/143 adolescents stopped GnRH analogues and no longer wished to continue gender-affirming treatment (3.5%)	Important	VERY LOW

Abbreviations: GnRH, gonadotrophin releasing hormone.

1 Downgraded 1 level - the cohort study by Brik et al. (2018) was assessed as at high risk of bias (poor quality overall; lack of blinding and no control group).

2 Median duration of 0.8 years (range 0.1 to 3.0). Five adolescents stopped treatment because they no longer wished to receive gender-affirming treatment for various reasons. In 4 adolescents (all transmales), although they wanted to continue treatments for gender dysphoria, GnRH analogues were stopped mainly because of adverse effects (such as mood and emotional lability).

3 Downgraded 1 level - the cohort study by Khatchadourian et al. (2014) was assessed as at high risk of bias (poor quality overall; lack of blinding, no control group and high number of participants lost to follow-up).

4 Because of transitioning to gender-affirming hormones or gender-affirming surgery, adverse effects (such as mood and emotional lability) or no longer wishing to pursue transition.

Table 8. Question 2. For children and adolescents with gender dysphoria, what is the short-term and long-term safety of GnRH analogues compared with one or a combination of psychological support, social transitioning to the desired gender or no intervention? – bone density

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients% (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result		
Bone density: change in lumbar BMAD									
Change in lumbar spine BMAD from baseline to 1 year in transfemales									
1 observational study Joseph et al. (2019)	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N=31	None	Mean (SD), g/cm^3 Baseline: 0.235 (0.030) 1 year: 0.233 (0.029) p=0.459 z-score Baseline: 0.859 (0.154) 1 year: −0.228 (1.027) p=0.000	IMPORTANT	VERY LOW
Change in lumbar spine BMAD from baseline to 1 year in transmales									
1 observational study Joseph et al. (2019)	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N=39	None	Mean (SD), g/cm^3 Baseline: 0.196 (0.035) 1 year: 0.201 (0.033) p=0.074 z-score Baseline: −0.186 (1.230) 1 year: −0.541 (1.396) p=0.006	IMPORTANT	VERY LOW

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients% (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result		
Change in lumbar spine BMAD from baseline to 2 years in transfemales									
1 observational study Joseph et al. (2019)	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N=10	None	Mean (SD), g/cm^3 Baseline: 0.240 (0.027) 2 years: 0.240 (0.030) p=0.865 z-score Baseline: 0.486 (0.809) 2 years: −0.279 (0.930) p=0.000	IMPORTANT	VERY LOW
Change in lumbar spine BMAD from baseline to 2 years in transmales									
1 observational study Joseph et al. (2019)	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N=21	None	Mean (SD), g/cm^3 Baseline: 0.195 (0.058) 2 years: 0.198 (0.055) p=0.433 z-score Baseline: −0.361 (1.439) 2 years: −0.913 (1.318) p=0.001	IMPORTANT	VERY LOW
Change in lumbar BMAD from starting GnRH analogue (mean age 14.9±1.9) to starting gender-affirming hormones (mean age 16.6±1.4) in transfemales									
1 observational study Klink et al. 2015	Serious limitations[2]	No serious indirectness	Not applicable	Not calculable	N=11 N=12	None	Mean (SD), g/cm^3 GnRH analogue: 0.22 (0.03) Gender-affirming hormones: 0.22 (0.02) NS z-score GnRH analogue: −0.44 (1.10) Gender-affirming hormones: −0.90 (0.80) p-value: NS	IMPORTANT	VERY LOW
Change in lumbar BMAD from starting GnRH analogue (mean age 15.0±2.0) to starting gender-affirming hormones (mean age 16.4±2.3) in transmales									

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients% (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result		
1 observational study Klink et al. 2015	Serious limitations[2]	No serious indirectness	Not applicable	Not calculable	N=18	None	Mean (SD), g/cm^3 GnRH analogue: 0.25 (0.03) Gender-affirming hormones: 0.24 (0.02) NS z-score GnRH analogue: 0.28 (0.90) Gender-affirming hormones: −0.50 (0.81) p-value: 0.004	IMPORTANT	VERY LOW
Change in lumbar BMAD from starting GnRH analogue to starting gender-affirming hormones in transfemales (bone age of <15 years)									
1 observational study Vlot et al. 2017	Serious limitations[3]	No serious indirectness	Not applicable	Not calculable	N=15	None	Median (range), g/cm^3 GnRH analogue: 0.21 (0.17 to 0.25) Gender-affirming hormones: 0.20 (0.18 to 0.24) NS z-score GnRH analogue: −0.20 (−1.82 to 1.18) Gender-affirming hormones: −1.52 (−2.36 to 0.42) p-value: <0.01	IMPORTANT	VERY LOW
Change in lumbar BMAD from starting GnRH analogue to starting gender-affirming hormones in transfemales (bone age of ≥15)									
1 observational study Vlot et al. 2017	Serious limitations[3]	No serious indirectness	Not applicable	Not calculable	N=5	None	Median (range), g/cm^3 GnRH analogue: 0.22 (0.18 to 0.25) Gender-affirming hormones: 0.22 (0.19 to 0.24) NS z-score GnRH analogue: −1.18 (−1.78 to 1.09)	IMPORTANT	VERY LOW

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients% (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result		
							Gender-affirming hormones: −1.15 (−2.21 to 0.08) p-value: p≤0.1		
Change in lumbar BMAD from starting GnRH analogue to starting gender-affirming hormones in transmales (bone age of <14 years)									
1 observational study Vlot et al. 2017	Serious limitations[3]	No serious indirectness	Not applicable	Not calculable	N=11	None	Median (range), g/cm^3 GnRH analogue: 0.23 (0.20 to 0.29) Gender-affirming hormones: 0.23 (0.19 to 0.28) NS z-score GnRH analogue: −0.05 (−0.78 to 2.94) Gender-affirming hormones: −0.84 (−2.20 to 0.87) p-value: ≤0.01	IMPORTANT	VERY LOW
Change in lumbar BMAD from starting GnRH analogue to starting gender-affirming hormones in transmales (bone age of ≥14)									
1 observational study Vlot et al. 2017	Serious limitations[3]	No serious indirectness	Not applicable	Not calculable	N=23	None	Median (range), g/cm3 GnRH analogue: 0.26 (0.21 to 0.29) Gender-affirming hormones: 0.24 (0.20 to 0.28) p≤0.01 z-score GnRH analogue: 0.27 (−1.60 to 1.80) Gender-affirming hormones: −0.29 (−2.28 to 0.90) p-value: p ≤ 0.01)	IMPORTANT	VERY LOW
Bone density: change in lumbar BMD									
Change in lumbar spine BMD from baseline to 1 year in transfemales									

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients% (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result		
1 observational study Joseph et al. (2019)	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N=31	None	Mean (SD), kg/m2 Baseline: 0.860 (0.154) 1 year: 0.859 (0.129) p=0.962 z-score Baseline: −0.016 (1.106) 1 year: −0.461 (1.121) p=0.003	IMPORTANT	VERY LOW
Change in lumbar spine BMD from baseline to 1 year in transmales									
1 observational study Joseph et al. (2019)	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N=39	None	Mean (SD), kg/m2 Baseline: 0.694 (0.149) 1 year: 0.718 (0.124) p=0.006 z-score Baseline: −0.395 (1.428) 1 year: −1.276 (1.410) p=0.000	IMPORTANT	VERY LOW
Change in lumbar spine BMD from baseline to 2 years in transfemales									
1 observational study Joseph et al. (2019)	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N=10	None	Mean (SD), kg/m2 Baseline: 0.867 (0.141) 2 years: 0.878 (0.130) p=0.395 z-score Baseline: 0.130 (0.972) 2 years: −0.890 (1.075) p=0.000	IMPORTANT	VERY LOW
Change in lumbar spine BMD from baseline to 2 years in transmales									
1 observational study	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N=21	None	Mean (SD), kg/m2 Baseline: 0.695 (0.220) 2 years: 0.731 (0.209) p=0.058	IMPORTANT	VERY LOW

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients% (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result		
Joseph et al. (2019)							z-score Baseline: −0.715 (1.406) 2 years: −2.000 (1.384) p=0.000		
Change in lumbar BMD from starting GnRH analogue (mean age 14.9±1.9) to starting gender-affirming hormones (mean age 16.6±1.4) in transfemales									
1 observational study Klink et al. 2015	Serious limitations[2]	No serious indirectness	Not applicable	Not calculable	N=12 N=11	None	Mean (SD), g/m2 GnRH analogue: 0.84 (0.13) Gender-affirming hormones: 0.84 (0.11) NS z-score GnRH analogue: −0.77 (0.89) Gender-affirming hormones: −1.01 (0.98) NS	IMPORTANT	VERY LOW
Change in lumbar BMD from starting GnRH analogue (mean age 15.0±2.0) to starting gender-affirming hormones (mean age 16.4±2.3) in transmales									
1 observational study Klink et al. 2015	Serious limitations[2]	No serious indirectness	Not applicable	Not calculable	N=18	None	Mean (SD), g/m2 GnRH analogue: 0.95 (0.12) Gender-affirming hormones: 0.91 (0.10) p-value: 0.006 z-score GnRH analogue: 0.17 (1.18) Gender-affirming hormones: −0.72 (0.99) p-value: <0.001	IMPORTANT	VERY LOW
Bone density: change in femoral neck (hip) BMD									
Change in femoral neck BMD from baseline to 1 year in transfemales									
1 observational study	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N=31	None	Mean (SD), kg/m2 Baseline: 0.894 (0.118) 1 year: 0.905 (0.104) p=0.571	IMPORTANT	VERY LOW

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients% (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result		
Joseph et al. (2019)							z-score Baseline: 0.157 (0.905) 1 year: −0.340 (0.816) p=0.002		
Change from baseline to 1 year in femoral neck BMD in transmales									
1 observational study Joseph et al. (2019)	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N=39	None	Mean (SD), kg/m2 Baseline: 0.772 (0.137) 1 year: 0.785 (0.120) p=0.797 z-score Baseline: −0.863 (1.215) 1 year: −1.440 (1.075) p=0.000	IMPORTANT	VERY LOW
Change from baseline to 2 years in femoral neck BMD in transfemales									
1 observational study Joseph et al. (2019)	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N=10	None	Mean (SD), kg/m2 Baseline: 0.920 (0.116) 2 years: 0.910 (0.125) p=0.402 z-score Baseline: 0.450 (0.781) 2 years: −0.600 (1.059) p=0.002	IMPORTANT	VERY LOW
Change from baseline to 2 years in femoral neck BMD in transmales									
1 observational study Joseph et al. (2019)	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N=21	None	Mean (SD), kg/m2 Baseline: 0.766 (0.215) 2 years: 0.773 (0.197) p=0.604 z-score Baseline: −1.075 (1.145) 2 years: −1.779 (0.816) p=0.001	IMPORTANT	VERY LOW

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients% (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result		
Bone density: change in femoral neck (hip) BMAD									
Change from starting GnRH analogue to starting gender-affirming hormones in femoral neck BMAD in transfemales (bone age of <15 years)									
1 observational study Vlot et al. 2017	Serious limitations[3]	No serious indirectness	Not applicable	Not calculable	N=16	None	Median (range), g/cm3 GnRH analogue: 0.29 (0.20 to 0.33) Gender-affirming hormones: 0.27 (0.20 to 0.33) p≤0.1 z-score GnRH analogue: −0.71 (−3.35 to 0.37) Gender-affirming hormones: −1.32 (−3.39 to 0.21) p≤0.1	IMPORTANT	VERY LOW
Change in femoral neck BMAD from starting GnRH analogue to starting gender-affirming hormones in transfemales (bone age of ≥15)									
1 observational study Vlot et al. 2017	Serious limitations[3]	No serious indirectness	Not applicable	Not calculable	N=6	None	Median (range), g/cm3 GnRH analogue: 0.30 (0.26 to 0.36) Gender-affirming hormones: 0.30 (0.26 to 0.34) NS z-score GnRH analogue: −0.44 (−1.37 to 0.93) Gender-affirming hormones: −0.36 (−1.50 to 0.46) NS	IMPORTANT	VERY LOW
Change in femoral neck BMAD from starting GnRH analogue to starting gender-affirming hormones in transmales (bone age of <14 years)									
1 observational study	Serious limitations[3]	No serious indirectness	Not applicable	Not calculable	N=10	None	Median (range), g/cm3 GnRH analogue: 0.31 (0.26 to 0.36) Gender-affirming hormones: 0.30 (0.22 to 0.35)	IMPORTANT	VERY LOW

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients% (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result		
Vlot et al. 2017							NS z-score GnRH analogue: −0.01 (−1.30 to 0.91) Gender-affirming hormones: −0.37 (−2.28 to 0.47) NS		
Change in femoral neck BMAD from starting GnRH analogue to starting gender-affirming hormones in transmales (bone age of ≥14)									
1 observational study Vlot et al. 2017	Serious limitations[3]	No serious indirectness	Not applicable	Not calculable	N=23	None	Median (range), g/cm3 GnRH analogue: 0.33 (0.25 to 0.39) Gender-affirming hormones: 0.30 (0.23 to 0.41) p-value: ≤0.01 z-score GnRH analogue: 0.27 (−1.39 to 1.32) Gender-affirming hormones: −0.27 (−1.91 to 1.29) p-value: ≤0.01	IMPORTANT	VERY LOW
Bone density: change in femoral area BMD									
Change in femoral BMD from starting GnRH analogue (mean age 14.9±1.9) to starting gender-affirming hormones (mean age 16.6±1.4) in transfemales									
1 observational study Klink et al. 2015	Serious limitations[2]	No serious indirectness	Not applicable	Not calculable	N=14 N=6	None	Mean (SD), g/m2 GnRH analogue: 0.88 (0.12) Gender-affirming hormones: 0.87 (0.08) NS z-score GnRH analogue: −0.66 (0.77) Gender-affirming hormones: −0.95 (0.63) NS	IMPORTANT	VERY LOW

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients% (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result		
Change in femoral BMD from starting GnRH analogue (mean age 15.0±2.0) to starting gender-affirming hormones (mean age 16.4±2.3) in transmales									
1 observational study Klink et al. 2015	Serious limitations[2]	No serious indirectness	Not applicable	Not calculable	N=18 N=13	None	Mean (SD), g/m2 GnRH analogue: 0.92 (0.10) Gender-affirming hormones: 0.88 (0.09) p-value: 0.005 z-score GnRH analogue: 0.36 (0.88) Gender-affirming hormones: −0.35 (0.79) p-value: 0.001	IMPORTANT	VERY LOW
Bone density: change in femoral area BMAD									
Change in femoral BMAD from starting GnRH analogue (mean age 14.9±1.9) to starting gender-affirming hormones (mean age 16.6±1.4) in transfemales									
1 observational study Klink et al. 2015	Serious limitations[2]	No serious indirectness	Not applicable	Not calculable	N=12 N=10	None	Mean (SD), g/cm3 GnRH analogue: 0.28 (0.04) Gender-affirming hormones: 0.26 (0.04) NS z-score GnRH analogue: −0.93 (1.22) Gender-affirming hormones: −1.57 (1.74) p-value: NS	IMPORTANT	VERY LOW
Change in femoral BMAD from starting GnRH analogue (mean age 15.0±2.0) to starting gender-affirming hormones (mean age 16.4±2.3) in transmales									
1 observational study Klink et al. 2015	Serious limitations[2]	No serious indirectness	Not applicable	Not calculable	N=18 N=18	None	Mean (SD), g/cm3 GnRH analogue: 0.32 (0.04) Gender-affirming hormones: 0.31 (0.04) NS z-score	IMPORTANT	VERY LOW

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients% (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result		
							GnRH analogue: 0.01 (0.70) Gender-affirming hormones: −0.28 (0.74) NS		

Abbreviations: BMAD, bone mineral apparent density; BMD, bone mineral density; GnRH, gonadotrophin releasing hormone; NS, not significant; SD, standard deviation.

1 Downgraded 1 level - the cohort study by Joseph et al. (2019) was assessed as at high risk of bias (poor quality overall; lack of blinding and no control group).
2 Downgraded 1 level - the cohort study by Klink et al. (2015) was assessed as at high risk of bias (poor quality overall; lack of blinding, no randomisation, no control group and high number of participants lost to follow-up).
3 Downgraded 1 level - the cohort study by Vlot et al. (2017) was assessed as at high risk of bias (poor quality overall; lack of blinding and no control).

Table 9 Question 2: For children and adolescents with gender dysphoria, what is the short-term and long-term safety of GnRH analogues compared with one or a combination of psychological support, social transitioning to the desired gender or no intervention? – cognitive development or functioning

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients% (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result		
Cognitive development or functioning (1 cross-sectional study)									
IQ (4 subscales: arithmetic, vocabulary, picture arrangement, and block design) at a single time point between GnRH analogue treated and untreated transfemales									
1 Cross-sectional study Staphorsius et al. 2015	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N=8 Mean (SD) 94.0 (10.3)	N=10 Mean (SD) 109.4 (21.2)	NR	IMPORTANT	VERY LOW
IQ (4 subscales: arithmetic, vocabulary, picture arrangement, and block design) at a single time point between GnRH analogue treated and untreated transmales									

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients% (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result		
1 Cross-sectional study Staphorsius et al. 2015	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N=12 Mean (SD) 95.8 (15.6)	N=10 Mean (SD) 98.5 (15.9)	NR	IMPORTANT	VERY LOW
Reaction time at a single time point between GnRH analogue treated and untreated transfemales									
1 Cross-sectional study Staphorsius et al. 2015	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N=8 Mean (SD) 10.9 (4.1)	N=10 Mean (SD) 9.9 (3.1)	NR	IMPORTANT	VERY LOW
Reaction time at a single time point between GnRH analogue treated and untreated transmales									
1 Cross-sectional study Staphorsius et al. 2015	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N=12 Mean (SD) 9.9 (3.1)	N=10 Mean (SD) 10.0 (2.0)	NR	IMPORTANT	VERY LOW
Accuracy at a single time point between GnRH analogue treated and untreated transfemales									
1 cohort study Staphorsius et al. 2015	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N=8 Mean (SD) 73.9 (9.1)	N=10 Mean (SD) 83.4 (9.5)	NR	IMPORTANT	VERY LOW
Accuracy at a single time point between GnRH analogue treated and untreated transmales									
1 cohort study Staphorsius et al. 2015	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N=12 Mean (SD) 85.7 (10.5)	N=10 Mean (SD) 88.8 (9.7)	NR	IMPORTANT	VERY LOW

Abbreviations: GnRH, gonadotrophin releasing hormone; NR, not reported; *P*, P-value; SD, Standard deviation.

1 Downgraded 1 level - the cohort study by Staphorsius et al. (2015) was assessed as at high risk of bias (poor quality overall; lack of blinding and no randomisation).

Table 10: Question 2: In children and adolescents with gender dysphoria, what is the short-term and long-term safety of GnRH analogues compared with one or a combination of psychological support, social transitioning to the desired gender or no intervention? – other safety outcomes

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of events/No of patients% (n/N%)		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	Intervention	Comparator	Result		
Other safety outcomes: change in serum creatinine									
Change in serum creatinine (micromol/l) between baseline and 1 year in transfemales									
1 observational study Schagen et al. 2016	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N=28	None	Mean (SD) Baseline: 70 (12) 1 year: 66 (13) p-value: 0.20	IMPORTANT	VERY LOW
Change in serum creatinine (µmol/l) between baseline and 1 year in transmales									
1 observational study Schagen et al. 2016	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	N=29	None	Mean (SD) Baseline: 73 (8) 1 year: 68 (13) p-value: 0.01	IMPORTANT	VERY LOW
Other safety outcomes: liver enzymes									
Presence of elevated liver enzymes (AST, ALT, and glutamyl transferase) between baseline and during treatment									
1 observational study Schagen et al. 2016	Serious limitations[1]	No serious indirectness	Not applicable	Not calculable	39	None	Glutamyl transferase was not elevated at baseline or during treatment in any subject. Mild elevations of AST and ALT above the reference range were present at baseline but were not more prevalent during treatment than at baseline.	IMPORTANT	VERY LOW

CERTIFICATE OF SERVICE

I certify that I e-filed this appendix on ECF, which will email everyone requiring notice.

Dated: October 13, 2023 /s/ Mohammad O. Jazil