HOUSE OF COMMONS

Women and Equalities Committee

Oral evidence: Evidence base on the safety and effectiveness of puberty blockers, HC 503

Wednesday 22 January 2025

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Watch the meeting

Members present: Sarah Owen (Chair); Alex Brewer; David Burton-Sampson; Rosie Duffield; Kirith Entwistle; Catherine Fookes; Christine Jardine; Samantha Niblett; Rachel Taylor.

Questions 1 - 58

Witnesses

I: Professor Gary Butler MD FRCPCH, Professor in Child and Adolescent Health (Honorary), UCL Great Ormond Street Institute of Child Health; Professor Simona Giordano PhD, Professor in Bioethics, Centre for Social Ethics and Policy, University of Manchester; and Professor Ashley Grossman MD FRCP FMedSci, Emeritus Professor of Endocrinology, Green Templeton College, University of Oxford.

Examination of witnesses

Witnesses: Professor Gary Butler, Professor Simona Giordano and Professor Ashley Grossman.

Chair: Good afternoon, and welcome to the Women and Equalities Committee. Today, we will be looking at the evidence base on the safety and effectiveness of puberty blockers. I want to welcome our panel; thank you very much for attending today's session, and we look forward to hearing about your experience and expertise on this matter. We will be hearing from Professor Gary Butler, professor in child and adolescent health at UCL Great Ormond Street Institute of Child Health, Professor Simona Giordano, professor in bioethics, Centre for Social Ethics and Policy at University of Manchester, and Professor Ashley Grossman, emeritus professor of Endocrinology at University of Oxford. Welcome all, thank you very much. I will hand over to David for the first set of questions.

Q1 **David Burton-Sampson:** Professor Butler, my first question is possibly for you. From a medical perspective, and not taking into account the current ban on puberty blockers, can you explain the process for prescribing puberty blockers to a child in relation to gender dysphoria and any oversight that happens as part of that process?

Professor Butler: Thank you very much. I can explain the previous NHS processes, which are different at present. When there was the existence of the Gender Identity Development Service, often called GIDS—a clinical service under the Portman and Tavistock NHS Foundation Trust funded directly by the NHS Specialist Services Commission—it was the point of reference for all young people under the age of 18 in England and Wales who perhaps had some question around their gender.

The GIDS was a specialist service set up to review the young people there and to explore what actually went on within their background, their history, their family, and their social environment. That was usually quite an extensive review. According to the service specifications, there were four to six sessions over a minimum of six months, but often many years, particularly for the presenting young people.

A small proportion of young people who had persistent gender dysphoria, which is a clinical diagnosis according to standardised processes of being a major discomfort with their gender being different from their biological gender, could then be referred to one of two endocrine clinics either in UCLH London or Leeds Children's Hospital. Each place had a team of people who could assess the young people there as well. When the diagnosis of gender dysphoria had been made and a recommendation, for instance, for puberty blockers from the GIDS, they would then be seen at one of the two centres, one of which I worked at in London.

Again, suitability for puberty blockers was assessed. That took a minimum of two appointments and reviews with assessment of competence or capacity, physical wellbeing, full understanding and full background given

as to the implication of any intervention, including future fertility, sexual function, long-term wellbeing and so on. If somebody wanted to go ahead and everything was appropriate, all with full support in person by the GIDS members of staff in parallel, then the recommendation would be sent to the GP to prescribe. There was what is called a shared agreement, a sort of contract with the GP, to provide the treatment. That was very similar to what happens in the use of puberty blockers in the other forms of treatment, for instance, precocious puberty; in that respect it was identical.

Q2 **David Burton-Sampson:** During the actual treatment, what oversight would happen?

Professor Butler: The young people underwent a follow-up programme with the endocrine team at three to six months to check on how things were getting on, but that was also in parallel with the ongoing psychosocial support by the members of the GIDS, who would often see the young person more.

Q3 **David Burton-Sampson:** Thank you. What happens to both children and adults if they stop taking the medication?

Professor Butler: We know very well from studies in the field on using the treatment for precocious puberty—which I have conducted in my previous history—that the hormonal process from the signals or hormones from the brain, the hypothalamus, to the pituitary gland and then to the testicles or ovaries starts again. How quickly it restarts depends how far somebody has got into their pubertal process, but in the main, relatively quickly. We know that it is very unusual from follow-up studies with children who have received it for precocious puberty that there are no ill health effects in the long term nor are there any negative effects on fertility recovery.

Q4 **David Burton-Sampson:** Can you confirm that the evidence so far shows that stopping taking puberty blockers is always reversible, pretty much always reversible, or sometimes reversible?

Professor Butler: There is never an always in medical practice but, in the main, it is recognised as a reversible treatment. Certainly, again from my clinical studies and those we followed up who have had treatment for precocious puberty, I cannot recall a case where puberty did not restart.

Q5 **David Burton-Sampson:** What would be the process for withdrawing puberty blockers, and do you ever see any side effects to withdrawing them?

Professor Butler: The process is really just stopping treatment because puberty blockers work in a slightly different way from other medical treatments and hormones in that they effectively flood the message production through the whole reproductive process; they basically overwhelm it from working. Puberty blockers are very much analogous to natural hormones with only a subtle chemical difference between the two. Essentially, when you take the overwhelming treatment drug away, it

allows the natural processing signals to restart. So, there are no side effects as such; it is just a resumption of normal puberty.

Q6 **David Burton-Sampson:** Thank you, Professor Butler, that is really helpful. Did either of the other witnesses want to add anything to those questions I have just asked?

Professor Grossman: I agree with everything Professor Butler has said. By the way, I am an adult endocrinologist, not a paediatrician, so I deal only with adult patients. Obviously, I am aware and have been for 40 years of the introduction of GnRH and GnRH analogues and how it was first discovered that, surprisingly, by using these peptides, you would not only stimulate but eventually block the whole axis. As I understand the situation, you use a puberty blocker to an adult age and then having stopped them you immediately transfer the great majority of these children, now adults, into the cross-sex hormones. As I understand it, you do not go back into puberty, you simply go into adult life hormones. Gary, is that right?

Professor Butler: Yes, certainly in those who are trans male. For those who are trans female and born as male, they continue with the puberty blockers or GnRH analogues as their medical treatment goes on until their treatment is adjusted or until they have the surgical procedure to remove the gonads or testicles when they would not need it any more. In the recognised practice in the adult gender identity clinics in this country, the standard approach is to start puberty blockers or GnRH analogues in parallel with oestrogen in a trans female person.

Professor Giordano: One minor point is that you refer to this patient population as children, and legally they would be minors, but biologically they would be adolescents.

Professor Butler: Yes, that is absolutely right.

Professor Giordano: So, my understanding is that GnRH would not be prescribed or used in very young children for this specific indication.

David Burton-Sampson: Thank you all very much.

Q7 **Chair:** Professor Butler, I just wanted to come back to one of the points that you made. You said that you do not recall any cases where hormones did not go back to normal after using puberty blockers. How many cases have you worked on throughout your career?

Professor Butler: Certainly, treating early and precocious puberty it would run into the hundreds; I could not put numbers on it. With trans young people through both clinics in the country, it runs into the hundreds as well.

Chair: Thank you very much.

Q8 **Kirith Entwistle:** What other medical reasons are there for being

prescribed GnRH analogues both for children and adults?

Professor Grossman: As I said, I was involved right at the beginning when GnRH was introduced and, rather to our surprise, after stimulation, even GnRH itself, better still with the analogues, you switch off the axis. We did some early work using rat cells showing exactly the same thing. You give these things over a period of time, hours to days, and the whole situation turns off. We had a lot of discussion at the time as to how this might be therapeutically or clinically useful. Initially, we wondered about things like breast cancer, turning off the ovaries. But eventually, the major uses—one of my colleagues was starting this—moved into carcinoma of the prostate and you can then turn off testosterone. That is now in common use as a standard treatment for some types of prostate cancer. It has also been very useful for turning off menstruation and oestrogen in women with really unpleasant endometriosis. Various other uses were suggested, but they are much less common. So, to switch off the reproductive axis in adult women, it is mainly endometriosis, and in adult men it is mainly prostate cancer.

Q9 **Kirith Entwistle:** Are there other uses?

Professor Grossman: There are indeed other uses.

Q10 **Kirith Entwistle:** How does the process for prescribing GnRH analogues to under-18s for health concerns other than gender dysphoria differ?

Professor Butler: Certainly in children and adolescents, it is regarded as just a standard treatment. It is licensed, it is approved with a lot of clinical studies, so it is then just a recommendation from the treating paediatrician to the GP. As I mentioned before to your colleague, there is a contract—a shared care agreement—which is done through the national society, an agreed approach with the GPs, so that they know what to do. It provides information on the responsibilities of both parties. For use in adults and in children with true precocious puberty, it is clear. However, the majority of the use by paediatric endocrinologists in the non-transgender field is around managing the timing of puberty and puberty changes. It is certainly licensed, but it is, I suppose, within the in-between areas of off-label use.

For instance, children who are perhaps going through early but not precocious puberty in whom there is some form of emotional disturbance and disruptiveness in the family and those who are on other parallel treatments, including growth hormone to manage their growth, are often given puberty blockers to manage the pace of puberty. This is now common usage in two groups of children: for those who have brain tumours, radiotherapy and surgery, and those who are born particularly small and their growth does not catch up, it is recommended that they are given puberty blockers in the teenage years to help with managing their growth and the outcome of the treatments. Again, that is just a contract with the GP; they are not dealt with differently from any other medication.

Q11 **Kirith Entwistle:** Are there any other things that a doctor might take into consideration when making these decisions, and are there any differences

compared to prescribing puberty blockers for gender dysphoria?

Professor Butler: Yes, absolutely. As mentioned to your colleague, the full assessment from the psychosocial assessment beforehand, particularly around the diagnosis of gender dysphoria. The principal difference between the two types of treatment approaches is that the paediatric endocrinologist is not making the decision to treat with gender dysphoria—that is the psychosocial team, whereas we are in the regular practices.

Q12 **Kirith Entwistle:** Did you have anything else to add?

Professor Grossman: Just to add that in the treatment of precocious puberty, people want to refer to it now as premature sexual maturation. They do not like the word "precocious". Anyway, that is semantic. There are physical changes, often in young girls—often what we call idiopathic, with no obvious cause—which can be quite distressing in a five or six-year-old going into puberty with emotional changes and, most importantly, with the changes in their bones, because they can undergo fast growth, fuse their bones and then end up very short. There, you actually have a whole matrix of physical and biochemical changes, and you are changing, as it were, an abnormal puberty, hopefully, into a normal puberty. As Professor Butler says, there is a huge amount of evidence, originally from Harvard, showing this is highly successful and that the outcomes from these usually young women are also very positive in terms of fertility and their subsequent life. It is a slightly different situation when you are changing a normal puberty into an "abnormal" puberty.

Q13 **Samantha Niblett:** Thank you very much for coming in today; I am really grateful. If I may, I am just going to move on to some of the concerns and mitigations to do with puberty blockers. I will ask this question and then you can suggest who is probably best to answer, and maybe you all might want to answer. What does the evidence say so far about the short and long-term physiological risks for children and adults who are prescribed gonadotropin-releasing hormone analogues for gender dysphoria?

Professor Butler: This is a very broad question, and one needs to look into the aspects of long-term wellbeing of the individual concerned, their gender identity and how any intervention might contribute to them living their lives according to their identification. More specifically, you were talking about physiological. I know there are anxieties around bone health in particular. Would you like me to expound on either of those particular areas?

Samantha Niblett: Yes, please. We are really keen to dig under the physiological to the potential physical risks.

Professor Butler: There are a lot of anxieties around the effect on, for instance, bone health because the background to that is that with the process of growth, the bones get bigger and they acquire more calcium, which gives the strength of the bones, akin to using concrete in a skyscraper which would be quite flexible if you did not have a steel structure. The amount of calcium in the bones accelerates during

adolescence and into early adult life, so much so that your bones are strongest by their mid-20s. So, that acquisition period in the early years is quite fundamental. If you are taking steps to slow down puberty, the bone mineral content, which is the amount of calcium in the bones, is carefully monitored and it is routine part and parcel of the assessments there.

When you instigate puberty blockers in a trans young person, there is a delay of the calcium going into the bones. It does not actually reduce, it just stands still and does not increase quite as quickly. However, what we know from follow-up studies which have been published from Amsterdam—and what we in the UK are about to publish soon—is that that bone calcium content recovers once sex hormones are started. It would be the same, and we know, certainly from those who have treatment for precocious puberty, that the calcium in the bones also recovers. What is unclear at the present time from the research so far is that it is a slower acceleration back to normal in the trans girls, trans women. But what the Dutch researchers have found—we are beginning to identify the same in the UK cohort—is that perhaps the trans women start off with lower calcium in the bones before they start puberty blockers or any intervention. We do not know why that is—it is nothing to do with any medical treatment—but this is some of the research under way to try to throw some light on that.

Q14 **Samantha Niblett:** As research is still being done, does that mean we do not know how to mitigate the risk of the treatment you can give alongside that addresses the calcium in the bones?

Professor Butler: Yes, of course. Things that are important and which we always assess are appropriate nutrition, vitamin D, and exercise. When sex hormone treatment is started, if that is appropriate for the person, then that is monitored as well. It is all part of the routine monitoring process in the children and young people's services.

Professor Grossman: You mentioned the use of GnRH analogues in the adult patient. When they are used in that situation, it has nothing to do with puberty. I would use a GnRH analogue in a transgender female in order to switch off her testosterone and then treat her as appropriate with oestrogens or other agents. That is purely as it would be in a man with carcinoma of the prostate to simply turn off the reproductive axis. The GnRH analogue in the adult patient post puberty is not involved in any way in pubertal delay; it is a different type of use.

Q15 **Samantha Niblett:** Would that have the same impact on the strength of bones?

Professor Grossman: Yes, because bone is dependent on testosterone. If you switch off testosterone you are at risk of osteoporosis and bone thinning. Then, in a trans female, you replace that with oestrogens and other forms of bone protection, which you would normally do as a woman, as a normal female. So, you are using it in that situation as a way of switching from male to female, and therefore, there should not be any irreversible long-term effects on bone in that situation in the adult.

Professor Butler: If I may just add a point to that, in the whole process of normal or typical puberty, there is a very wide range of timing of the events. You can get some young people starting puberty, going through the process at age eight or nine. For some, it might not be until 14, 15, 16, and so on. The timing of the acquisition of increased bone density and, indeed, physical growth is going to be varied at that stage. So, someone going through puberty later will have an apparently lower bone density, bone mineral content, as will be their growth. At the present time we have no way of being able to control for that. I was part of the Royal College of Paediatrics and Child Health working group to establish new growth charts for children in this country and we have included new growth lines for children going through early and late puberty because their relationship to the normal range is quite different. So, someone who is going through puberty at the age of 15, 16 might appear to have shrunk compared with their peers. It is the same with measuring bone density when you are using puberty blockers. It appears it shrinks by standard methods but, actually, the bones do not crumble or reduce in their bone content.

Professor Giordano: Is the Committee considering other types of risks and benefits that are currently being discussed besides bone?

Chair: Yes.

Professor Giordano: There are two other main areas of concern with regard to puberty blockers. One is tissue availability and sexual satisfaction. This particularly concerns trans women. The second is the potential effect on the brain. So, with regard to tissue availability, one concern is that if you stop pubertal development at early stages of puberty, what is known as Tanner Stage 2, the penile development, is not sufficient for the creation of a successful new vagina. The other concern is that if the person has not experienced orgasm before the vaginoplasty, they might have damage in the nerves or not have the psychological awareness, and that might result in poor sexual satisfaction later in life.

Research carried out in the last two years has compared the sexual satisfaction outcomes in trans women who have had vaginoplasty without having received puberty suppression or having received puberty suppression in later stages of adolescence, and trans women who have had their puberty suppressed early in life and then received vaginoplasty. The results are not different. There are statistically significant similarities in satisfaction rates which I think, across the board, were around 77%. Of course, we do not have gender satisfaction studies, so we cannot say this is a good rate of satisfaction or a bad rate of satisfaction. It is also difficult to tell what this satisfaction gets down to, whether it is having been followed up psychosocially and having had a lot of therapy and being able to discuss your sexual life openly. So, it is difficult to pinpoint, but it is interesting that there was no statistically significant difference between the two groups.

The other concern is around the brain development. Animal studies suggest that sex hormones affect brain changes. One question is whether this would be true for humans as well. Of course, we cannot do the same studies on humans that we would be able to do on animals. Studies have looked at what can be looked at: cognitive functioning, executive functioning and IQ scores. Again, the scientists who have looked into this matter have found no difference in executive functioning, cognitive functioning and IQ scores of trans young people treated with puberty blockers compared to the cisgender cohorts. Gary, do you have anything to add?

Professor Butler: No, that is very helpful to know, thank you.

Q16 **Samantha Niblett:** Thank you. Sarah, I do not know what you think, but that feels like it has answered another of my questions. My last question is: how would a physician balance the risks that you have mentioned and decide if and when the benefits of prescribing puberty blockers outweigh the risks of not prescribing them?

Professor Butler: Do you want to take that from the ethical perspective and then I can?

Professor Giordano: These are balancing exercises that are ubiquitous in medicine: clinicians have to make those determinations every day. One very important thing I noticed from an ethical perspective that was quite interesting for me was that when I started working in this area a lot of clinicians were very concerned about the side effects of the treatment, and I read this in the Cass Review as well. We need to be very careful about the side effects, the known and potential side effects, of the treatment that we provide, and that is missing out the consideration of what happens to the young person if they do not receive the medication which, incidentally, is also a big part of the legal reasoning about the treatment of children that appears even in legal judgments like Gillick.

So, judges said clinicians need to consider what would happen to young people if they did not receive medical treatment. I suppose that clinicians, particularly psychiatrists and psychologists who are involved in the early stages of the assessment, would have to make that assessment. Can this person live satisfactorily without medical intervention, or is the dysphoria so significant that it will cause mood disorders similar to mood disorders that would be caused to young people who suffer from precocious puberty, anxiety and depression? Would they be able to attend school? Would they be able to integrate with other people? Would they become suicidal? The vast majority of young people who are gender incongruent can function reasonably well without hormonal intervention. Statistics are quite consistent across countries. Only about 20% to 25% of young people who are seen by the specialist services will actually be referred for endocrinology.

Professor Butler: That is right, yes.

Professor Giordano: That is the kind of determination that psychologists and mental health professionals will make in the assessment and when the risks of not treating seem to outweigh, then they would consider medical treatment. It seems to me that that is the right way.

Professor Grossman: As a non-paediatrician, I am not sure if it complements or in any way disagrees with your view, but my major concern is that, as we know, there has been a huge increase in referrals. Whereas previously they were mainly youngish males, it now tends to be adolescent females. My concern is that our assessments, not the endocrine assessments but the psychosocial, the counselling and psychiatric assessments, are not totally and completely validated. We know that adolescence is a very difficult time. We know that during adolescence, the teenage years, the brain—according to works of Professor Blakemore—is highly pliable and it is developing. There may be many reasons: these young women may have problems at school and problems with their parents who may wonder whether they are gay or not. There is a lot of social media influence, and my concern is that we know that the great majority of young women who are placed on pubertal blockers automatically transition into the transgender state.

The risk is that we are placing a number of young women on this treatment who do not actually need it, and it may have long-term effects; we do not know, no one knows. As you rightly point out, the risk on the other side is that we are taking young women who are truly transgender and undergoing a great deal of dysphoria and distress and denying them the possible advantage of delaying puberty until a later age. However, as you quite reasonably point out, we do not have full information. We do not know how much not delaying puberty in these true transgender young women is ultimately going to be damaging to them. So, it is a very difficult decision. From a fairly personal point of view, these are highly potent drugs being given to children, as I would still describe them, with rather uncertain consequences. However, there may well be a small group, and I suspect it is small, who would indeed benefit, but we cannot identify them at present on the current estimates and psychometric and other assessments. Gary, would you like to say anything about the assessment techniques?

Professor Butler: It is difficult to work out which assessments are best. Observational studies which have been published have come under criticism for being low-quality evidence because that is how the evidence hierarchy is formulated: that observational clinical studies are low quality by definition and that is what has been published. It is fair to say that a lot of the psychological experts are unable to agree completely on which are the best measures to try to assess what is happening to a treatment. There have been studies which have shown some outcomes but not necessarily clear results, and that is where the challenge happens. I know there is currently a reanalysis of a lot of those studies taking place within the German and central European countries, which are reviewing a lot of that evidence at the present time to see what that means, and they are due to publish their report pretty much any time soon.

Q17 **Samantha Niblett:** Did you say that if a young woman who feels she was born into the wrong body was prescribed these blockers so she could present as male but then stopped that treatment, that there would be no physiological issue for them, or not?

Professor Butler: It is not a question of presenting as male; it is just a question of the puberty processes. Whatever the natural physiological changes brought about by testosterone and oestrogen through puberty, that would temporarily be halted.

Q18 **Samantha Niblett:** Then, say it was a mistake later once they stopped, they would be okay physiologically?

Professor Grossman: I do not think we actually have that information, do we? So, there would be a young female, say, the age of 14 having a puberty blocker for three years then stopping and deciding to remain as a female, would she then go through a normal pubertal process?

Professor Butler: Yes, there are some people who have been through that situation and chosen to stop treatments and the physiological processes, both for those born male and those born female, have resumed.

Q19 **Chair:** Thank you, Samantha. Before I bring Rosie in, could I just ask the panel: if there are the same concerns and measures for mitigation for when GnRH is being used for reasons other than gender dysphoria, say for example the issues of endometriosis or prostate cancer, are there the same concerns for the patient using those as there are for gender dysphoria?

Professor Grossman: No, I do not think so. In this situation, you know that you have biological, biochemical and other measures of an abnormality and you know that you are simply switching off the reproductive axis, and you understand why you are doing it, and what the purpose of that happens to be with those measures. Huge trials have taken place, for example, in prostate cancer and, to some extent, endometriosis, showing if it is valuable or not. This is a rather different situation because you are interfering on subjective dysphoric grounds on what would otherwise be a natural process. So, my personal feeling is these are quite distinct situations.

Q20 **Chair:** So, puberty blockers are safe for, for example, endometriosis and prostate cancer but not safe for gender dysphoria?

Professor Grossman: Yes.

Q21 **Chair:** Does the rest of the panel agree?

Professor Butler: Could I comment from a physiological perspective? When I mentioned that puberty blockers are used in adolescents for other reasons, we would use the same measures as with a young person with gender dysphoria. We would look at their height, clinical stage of puberty, hormone levels, and at the changes in the bone growth with X-rays. So, those things would be monitored in the same way.

Q22 **Chair:** Would they be monitored in the same way that any other medication would have an impact on bone density? There are other medications that have impacts on bone density; you can take measures to mitigate those. Could you just outline them again for the Committee, please?

Professor Butler: Certainly. It is probably different from adult practice, but in children and young people the first thing is to ensure they are eating well and appropriately with adequate nutritional balance, particularly calcium in the diet. We always ensure that young people on those treatments will have vitamin D supplementation, which is not an exceptional thing for recommendation for adolescent health, and that they partake in physical exercise where possible because that is also noted to promote bone health.

Q23 **Chair:** Thank you. Professor Butler, have you noted throughout your work that those steps to mitigate the concerns have been successful?

Professor Butler: By and large, yes, that is right. We do not tend to see a loss of the amount of bone, as I explained to your colleague earlier. We do not tend to see, overall, a loss of the total amount of calcium in the bone during the GnRH treatment and perhaps that shortfall compared with the norms will catch up if the young person undertakes a sex hormone treatment.

Q24 **Chair:** Thank you. Professor Giordano, did you have anything to add to that?

Professor Giordano: Perhaps just a small point to add on this. In the literature, there is no reported case of complaint around loss of mineral density from the cohort of children treated since the mid-1990s. There is no report in the literature, no litigation, no complaint through clinical authorities from patients. Another perhaps very small point in terms of the increased rates of referrals is that a recent study in Germany reports that there has been, in the same years, comparable increases in rates of adults referred to the services, so it would be interesting to see if that is the same. The increases in referrals seem to concern adults as well as young people.

Chair: Thank you very much. Rosie?

Q25 **Rosie Duffield:** Thank you, Chair. Dr Butler, just following on from the Chair's question about whether the steps to mitigate those concerns about bones have been successful, can you explain how you know that? Do you personally follow up with your GIDS patients throughout the process or years later or when they are adults? I would just like to point out to the panel that Keira Bell is sitting behind you, and you mentioned earlier that all the processes have been resumed when treatment stopped. I think she and her court case would probably take issue with that, as would other GIDS transitioners. Could you just explain how you know those calcium bone levels have resumed or been okay?

Professor Butler: My original comment was with children having precocious puberty treatments, not necessarily in the gender field. Can I clarify that? I know there are some situations where we do not know the full outcome in terms of every person who has received puberty blockers from the trans field. We do not know all the details yet, so that is fair. Can I just clarify that, please?

In terms of knowing about bone health as a marker of, I suppose, biological effect, yes, we follow all the children and young people prospectively, so obtaining data and monitoring on a regular basis. We can see what happens as they go through the various steps and stages of treatment. We work in very similar practice to other major centres around Europe in that regard, and the information is already in the public domain and published, certainly from a clinic in Amsterdam, and our current research, which we are doing in parallel with them, actually mirrors those findings.

Q26 **Rosie Duffield:** Was there a study in Sweden that showed that bones were breaking quite often?

Professor Butler: I do not know about bones breaking. Breaking is very unusual to happen in adolescence because, as Professor Giordano said, that is not something that we would see because the bone, even if there is a change in bone density, rarely gets below the range or into the range you would expect fractures to occur.

Q27 **Rosie Duffield:** Dr Butler, what outcome is prescribing puberty blockers supposed to achieve other than precocious puberty? I know we have touched on this, but I just want to drill down a bit more.

Professor Butler: They have been advocated as part of the process of managing the dysphoria in an adolescent young person. As part of the recommendations, not only international but from the service specifications we follow from NHS England, they asked that and we have contracted with the various trusts to provide the service to actually begin to support the young people through their transgender journey, and this is one way of helping them in that regard.

Q28 **Rosie Duffield:** Do you know of any good quality evidence that Dr Hilary Cass did not look at that shows that puberty blockers achieved that purpose?

Professor Butler: If I can perhaps refer back to some previous comments, it is about the type of measures that are used and how you are going to assess the evidence. The problem is—I worked with Baroness Dr Cass on the evidence accrual process through NICE—that it is very clear that, according to the standard hierarchy of evidence, there is nothing, or a very minimal amount, that would fall within that high level of categorisation, most of it being observational, in other words just simple reports of what is happening at baseline or changes. Whether they are using physical or mental health measures is again regarded as not sufficient in that categorisation.

Q29 **Rosie Duffield:** Can I just ask you about your time at the GIDS? Why did you continue to prescribe puberty blockers when the preliminary results from the early intervention study in 2015, 2016 which, of course, you were heavily involved with, did not demonstrate clear benefit?

Professor Butler: At that stage, the contract was within NHS England, which provided the framework for the service specifications. The contract was then with the GIDS at the Tavistock, and the endocrine clinics provided support from that. So, that was within the bodies and within the NHS England service specifications and its commissioning.

Q30 **Rosie Duffield:** Why were the results not published until 2020?

Professor Butler: I was not directly involved in that study myself, but the issue around a lot of studies—having been involved with what is called longitudinal long-term studies in children—is that it takes a while to accrue the information and collect the evidence of or informational effect or changes over time. According to the leaders of the study at that stage, that is the report that was given to the Health Research Authority. Currently, as you are probably aware, there is a National Institute for Health and Care Research funded study looking at the longitudinal outcome of gender identity in children, called the LOGIC study, and that has been ongoing for a number of years. Clearly, although there is some preliminary information coming out, I hope that will provide answers to some of the questions that the Committee has, but that will take some years before the information is analysable.

Q31 **Rosie Duffield:** Thank you. Professor Grossman, you mentioned before that you were concerned about the number of young women who have been prescribed puberty blockers. Given that the Tavistock GIDS found that a high percentage of its patients had an emergent same-sex orientation—that is, they were likely to grow up gay or lesbian; I have written down that it was 68% of girls and 42% of boys—are you concerned that puberty blockers are being used to change children from being gay or lesbian to being able to pass as straight or as members of the opposite sex?

Do you echo the concerns of some former GIDS clinicians that they were, in their words, "transing away the gay"?

Professor Grossman: I understand your question. Yes, personally, I am concerned, but I speak as an adult endocrinologist, not as a paediatrician. I have a number of daughters. Adolescence and childhood is a difficult, highly confusing time for a lot of children. We know anorexia nervosa is a common problem now in young women who are uncertain as to their future and their sexuality. My concern is not the endocrinology per se, because as technicians we are very competent at doing that; it is the assessment of these young people who are put on a trajectory that takes them automatically into a transgender state.

Some 10 years ago I was asked by a newspaper how I felt about the concept of puberty blockers. At the time, I thought the concept was

reasonable. The original idea was that they would put everything on hold and give you time to consider, time to reflect maybe for six months, and you could then see which way you should go forward.

My concern about the work from the Tavistock and the Portman clinic was that patients were put on a conveyor belt and automatically transferred into a transgender state at the end, with what was certainly inadequate follow-up, but probably inadequate assessment in the first place of these young women who were clearly in a difficult situation. There may be many other problems going on. We know about problems with possible neurodivergence and autism and that these were not properly explored.

My concern for the future is that there may indeed be a cohort, which I would imagine is probably small, of young women who wish to be transgender and for whom pubertal blockers may be of assistance, but we are not adequately assessing the probably much larger numbers of young women who, with adequate counselling and psychological support, would eventually decide that they want to stay cisgender.

Q32 **Chair:** Before you move on, could I just offer that same question to Professor Butler and to Professor Giordano please?

Professor Butler: Absolutely. As far as the numbers who were being referred to the GIDS, as everybody knows, those went up exponentially from about 2010, 2015, onwards, but there is no clear explanation for that because it was happening across Europe and across the developed world.

It is fair to say, and everybody realises, that because the GIDS was set up as a highly specialist service, as was the endocrine support, it was overwhelmed by the number of referrals. As Professor Giordano explained, as the numbers increased in GIDS so did the proportion who were referred to endocrinology. It was, again, a much tinier minority of those referred to GIDS, particularly those who were birth-registered females actually ever got in the way of endocrinology, so we were not seeing them. Furthermore, just to make it clear, because they had already gone through their biological puberty there really was no place for puberty blockers. We had to use other ways, other hormonal methods of managing distress over menstruation.

Q33 **Rosie Duffield:** Professor, did you want to come in?

Professor Giordano: I would make two points. First, on the conveyor belt concern. I cannot comment on how the services were stretched and how the assessment was carried out because I was not part of that. However, the international consensus and the recognised practice is to consider puberty blockers as a complement of a number of other psychosocial measures only in those cases where the young person suffers from what was called until recently strong and persistent gender dysphoria that would not be alleviated by other means. In this cohort, in the persistence studies that have been conducted since at least 2016, it appeared that those individuals who after the onset of pubertal development would experience

and continue to experience strong and persistent gender dysphoria would nearly always later become applicants for medical treatment for transition regardless of whether or not they had been given puberty blockers. So to my mind, the correlation between puberty blockers, prescription, and later transition is not causation. It is most likely a need that explains the correlation there.

My second point concerns the benefit and your claim, Ms Duffield, that the study of that cohort published from the clinical trial concerning Tavistock did not show benefits. To say that puberty blockers do not have benefits in terms of suspending puberty is like denying that the earth is spherical. For someone who is distressed by pubertal development, suspending pubertal development is clearly a benefit. The question is whether that benefit outweighs the risks and whether that benefit is justified. When the measures of benefits are taken, sometimes they are taken in a questionable way. For example, the York study compared people before and after taking puberty blockers and found that their mental health did not improve or get worse. They concluded that therefore there was no need to give puberty blockers, and that conclusion fed into the Cass Review.

But from a clinical perspective, you can predict that a dysphoric adolescent will get worse and worse mentally, so stability can be a good clinical outcome. Therefore, you need to ask the correct question to have the correct answers and to understand the benefit in the correct way.

The same applies when people assume puberty blockers are not beneficial because they do not have any statistically significant impact on gender dysphoria. That is not what puberty blockers are intended for. They are not a treatment for gender dysphoria. If you measure the effect or benefits of puberty blockers on the reduction of gender dysphoria, you are clearly not going to find a benefit there. So, questions need to be pertinent to have pertinent answers.

Chair: Thank you very much. David.

Rosie Duffield: I have one final question.

Chair: You have had seven, which is nearly twice the amount of every other member, so unless it is urgent, no.

Q34 **Rosie Duffield:** It is just based on something Dr Butler said about the Tavistock clinic being overwhelmed. Was it your experience that it was overwhelmed with more autistic patients? Dr Grossman mentioned autism as being one of the comorbidities.

Professor Butler: It was overwhelmed with the number of referrals and NHS England was aware of that, but to my knowledge no actions were brought, nor were they able to deal with the expansion of the service at that stage.

Chair: Thank you. David.

Q35 **David Burton-Sampson:** Just a very brief question, and perhaps all three of you can very briefly answer it as well. I want to follow up on something Sarah asked you around the risks of taking this medication. You mentioned it in relation to treatment for cancer and so on, but obviously the big concern with the ban is the impact and the risk to children and particularly adolescents of taking this medication, issues with bone density, issues with the effect on the brain and on tissue availability for future potential surgery that might need to happen.

Is that risk the same for children who are going through precocious puberty as it is for people who have gender dysphoria, and should we therefore have the same concerns about people taking this medication for precocious puberty as we should be having for people who are taking it for gender dysphoria?

Professor Grossman: I think you can see my general attitude, but in terms of my reading of the data, and I know some major authors on precocious puberty, there have been no long-term problems. The long-term outlook in terms of bone density, in terms of development, in terms of subsequent fertility have been absolutely fine. It is a useful treatment, particularly for the very young child. Not so much for the seven, eight or nine-year-olds, but six years and below the outcomes have been extremely positive. It is a routine treatment for these young children.

Professor Butler: I completely agree with Professor Grossman in that regard because it is a routine treatment. Hence, from the paediatric endocrinology perspective, and I am not just speaking for myself, we do not see why outside the psychosocial side, in and around the gender side, there would necessarily be any other medical concerns to be considered around using puberty blockers in an adolescent who is otherwise healthy because we use them for children and adolescents with other medical problems for whom we have more concern.

One of the typical processes before offering any intervention is to assess for general health and look to ensure there are no other underlying medical problems and that the young person is healthy. That is part of the routine practice which has been in the service specification for many years.

David Burton-Sampson: Professor Giordano, do you have anything to add?

Professor Giordano: No, thank you.

Chair: We have four more members that have not spoken yet, so I want to move on to Alex.

Q36 **Alex Brewer:** Can you tell me what it means when a medication is prescribed off-label?

Professor Butler: I suppose we can both answer that from the paediatric and the adult medical perspective.

Professor Grossman: As I understand it as an adult endocrinologist, if a drug becomes licensed there are various ways that you get the drug. First the MHRA say, "Yes, it is going to be a safe drug. You can use this drug." The manufacturer then gets it licensed for a specific indication which means, "We are responsible for this drug. We think it is a good drug. You can take it." We know that it is available for that particular indication. If it is off-label, that means you as a physician know that the drug is a safe drug as it has gone through MHRA, but the drug company has not licensed it for this particular use, so you do it on your own cognisance. There are many drugs we use where the drug companies have not got around to deciding if they want to licence it as it might be too expensive or whatever, but we still use it because we know from published data that it is both a safe and effective drug in that situation.

Professor Butler: Absolutely, I fully agree, but as a paediatrician, almost everything that is recommended is off-label, including sometimes off-licence as well. Some treatments, for instance for premature babies who have open ducts in the heart, are used completely off-licence. Within endocrinology, very little has a licence for use in children, including growth hormones and puberty blockers. There are general guidelines, usually national, specialist or scientific society guidelines and international guidelines as well, and it is expected that we would refer to those in the use of treatments such as sex hormone treatments or even steroid treatments in children and young people. That approach is common not just in endocrinology but in cardiology and rheumatology too. It is only in the last 10 years or so that there has been a specific requirement for the MHRA to ensure that if a treatment is licensed for children the trials are carried out on children.

Professor Giordano: Not only is off-label prescription common in paediatrics but it is also necessary, and in fact it is endorsed by the Royal College of Paediatrics and Child Health.

Professor Butler: That is right.

Professor Giordano: Also, in quite a delicate area of psychiatry, child psychiatry, it is endorsed by the British Association for Psychopharmacology.

Q37 **Alex Brewer:** So, does that have any bearing on the safety or efficacy of medication, and how are the risks and benefits of this approach managed?

Professor Giordano: Maybe I can comment briefly. In this case, the pharmacological agent is quite well known. Triptorelin is a type of GnRHa which has been authorised and licensed in the UK for the treatment of central precocious puberty. The unlicensed use of this agent for adolescent endometriosis is also included in the British National Formulary, so it is a well-known drug in this particular case. Use for a different indication might be experimental at the very start, although in this particular case, the cohort was remarkably similar to the central precocious puberty cohort in that it still concerned adolescents and was intended for the purpose of

delaying pubertal development, but at that particular time, the application might be said to be experimental.

As knowledge builds up through clinical experience and through published studies, rather than on systematically collected clinical evidence, the treatment becomes less experimental and more standard and routine.

Professor Butler: I would agree entirely. When a treatment is prescribed or recommended off-label, the onus is on the prescriber to ensure monitoring of efficacy and outcomes. That is exactly what we do in our routine practice for any medication given to children and young people, but in this field especially we have very extensive information around monitoring the welfare of these young people.

Professor Grossman: It is a very interesting area. Any clinician prescribing a drug for a patient will work out the risk-benefit ratio, and that would depend on whether it is off-label or not. We will look at the likelihood of benefits, the possibility of side effects, and how the two correlate with each other.

Anecdotally, some time ago, I was asked to give a lecture on behalf of a drug company about a fairly rare disease, and I wanted to mention a drug which is in common use as a first-line treatment. They refused because it was their drug, and they had not recommended it to be on-label. On that basis, we reached a situation where I was not going to speak without mentioning this drug because I would have looked stupid, and they would not give me permission to talk about the drug, so the lecture was cancelled.

With every patient I see on a regular basis, and I still see patients, I have to think very carefully, even with very common antithyroid drugs, whether it is indicated, what the risks are, what the benefits are, and whether it is label or off-label, and that is an ongoing process that we take responsibility for.

Professor Giordano: I would like to add that the most likely reason why this particular GnRHa has not been licensed for this particular indication is that no pharmaceutical company has had a financial incentive to do so. If the pharmacological company is already the market leader in this area, there would be no increase in sales, but otherwise, a clinician could always go on and prescribe the agent in its generic form. It is likely that this medication would have been approved for this indication had someone applied. If we look at the studies that have resulted in the licencing of GnRHa for central precocious puberty, these were fairly short studies with a small number of patients, and they were open-label studies. That means that everyone knew who was taking the drug, so there was no control. So, it is likely that they would be licensed just with the amount of evidence that we have at the moment.

Q38 **Alex Brewer:** Just to clarify, is it fair to say that prescribing off-label is a normal part of the practice of a prescriber, especially in paediatrics?

Professor Butler: Yes.

Professor Grossman: Yes.

Q39 **Alex Brewer:** Thank you very much. Could you tell me how the safety of a medication is determined and monitored once it is in use?

Professor Butler: Are you talking generically, or specifically with GnRH analogues?

Alex Brewer: With any medication, when you are prescribing off-label, how do you go about that monitoring process that you talked about earlier?

Professor Butler: In the first instance, the reason for starting a treatment is to produce some clinical effect. One would monitor the patient to ensure that is happening. If there is any other appropriate monitoring to take place, whether through blood tests or checking physical or radiological changes, one would make sure that happens. Really, the onus is on the clinician.

In most cases there are standard recommended pathways but given that there are such a wide range of treatments around, we have a more extensive evaluation and monitoring process specifically with puberty blockers than we would for a child with precocious puberty.

Q40 **Alex Brewer:** Can you expand on that at all?

Professor Butler: We would often do more blood tests, more physical checks, more assessment of bone health and obviously in parallel with our psychometric colleagues, we would assess their mental health as well.

Professor Grossman: In any speciality, there are usually large numbers of guidelines, consensus agreements, and protocols in the published literature which you will try to follow. If you do not follow them, then you feel you need a reason why. For any given drug, you should only use it if you have either experience of its use or knowledge of its use and in that case, you are expected to know, "These are the possible side effects, whether common or uncommon, and these are the things I need to test for on a regular basis." But it is very much based on the consensus view of specialists in that area.

Q41 **Alex Brewer:** Thank you very much. Finally, can a drug become more or less safe once it has been put into use, and if so, how?

Professor Butler: There are a number of reports over the years of different treatments which have had to be withdrawn, not necessarily in our field. One for weight loss comes to mind, about 10, 15 years ago, that was withdrawn, but others get withdrawn from time to time.

Professor Grossman: Yes, definitely. I was thinking of the same drug, a very good drug, which was excellent for weight loss, which had a significant, not unexpected side effect, so the manufacturers withdrew it. But there are other drugs where we simply become aware that, "Gosh, this

causes cardiological changes or pulmonary fibrosis," and we were not aware of that before and now we have that information. There are yellow cards that you send out and you then start thinking, "Well, this has long-term side effects; maybe I will not use it so often." So yes, those side effects do develop over time. A lot of drug trials, although extensive, might just be for two or three years. Ten years down the line, it may be a whole different ballgame.

Q42 **Chair:** Are you drawing a parallel with the common use of Ozempic, as well as Wegovy, and their unknown future effects? Ozempic was originally a drug for diabetes and now it has the side effect of weight loss. Is that where you were going with that? We can say names.

Professor Grossman: I was not thinking of that particularly.

Professor Butler: I was not either, but it may well be the case in the future. Professor Grossman and I are thinking of just one similar example, but everything needs monitoring.

Chair: Thank you very much. Catherine?

Q43 **Catherine Fookes:** Thank you all for coming in today. We understand that the research trial is currently being established, and of course we do not want to prejudice that in any way, but we would like to understand how the research trial might be designed in this instance, and what clinical questions might be asked. I do not know who would like to start.

Professor Giordano: I have a number of perplexities on the use of the name clinical trial. Clinical treatment trials test new treatments, a new combination of drugs or new approaches to certain therapies, and they have a structured phase process. In the first instance, the new agent is given to a few healthy volunteers and then it gets given to a few patients affected with the condition. In phase three, the agent would be given to a fairly large number of patients affected by the condition, and then there would be a fourth phase with regulation and approval from, in our country, the MHRA, then marketing and a check on a large scale after the product is authorised.

Puberty blockers are already authorised by the regulatory authority, so they are only given off-label. The trial would concern their application to transgender and gender-diverse individuals. The claim is that, through a clinical trial, we would strengthen the evidence base, and it would become clearer whether a medical pathway is preferable as compared to a pathway that does not involve medications but only includes psychosocial intervention. My concern is that using the terminology of clinical trials misleads the public into—

Q44 **Catherine Fookes:** Excuse me, I said research trial, not clinical trial. Are you saying that is the wrong terminology?

Professor Giordano: A research programme in this area would include, as you correctly said, a determination of which outcome measures are

relevant. Now, as far as I understand in the Cass Review, there are three key elements of debate which would be part of this research: bone mineral density, brain development, and fertility. These three measures are quite difficult to study unless longitudinal research is carried out, so young people will have to be followed up into adulthood. The measures that we would take in the short period of time in which patients are in the paediatric services are standard measures which we should expect clinicians to take anyway without necessarily enrolling young people in clinical trials. The research would have to start with deciding which outcomes are relevant. Most clinicians would probably be interested in many other things apart from bone mineral density, brain development, and fertility. They might be interested in cognitive functioning, psychosexual or psychosocial wellbeing, ability to attend school, or school attainment. Many other outcomes might be relevant, and some outcomes might also be context-dependent. In situations where people might have difficulties attending school, for example, school attainment and attendance might be relevant outcomes to study; in others, it might be less interesting.

So, a research study is really welcome, but it should be designed in such a way that there is a conversation about which outcomes matter and why, and what is the most appropriate way to know more about those outcomes.

A clinical trial is generally used to provide evidence of a certain level, GRADE 1 or 2, which for many of the measures in this area will probably not be attainable. The concern is that if we talk about a research trial or clinical trial, we give the impression that certain hard evidence will be attainable when actually we will know more about health outcomes only by conducting long-term research, longitudinal studies and observational research.

Q45 **Catherine Fookes:** Would you like to comment, Professor Butler?

Professor Butler: Yes, I agree, it is a challenge. We welcome the Cass Review recommendation for funded research because that has been a challenge over many years. It is something that, with inherent prejudice against trying to get more information in this field, we have not been able to obtain. So, it is really good news that the NIHR is going to undertake the funding of that.

The other challenge, as we have mentioned before, and Professor Giordano mentioned, is: what are the right measures to assess when proving the success of an intervention? That is a challenge for the research committee at the present time, and I am doing my best to support them. Trying to design a trial which will produce definitive results, whether positive or negative, is a challenge given the fact that a lot of the measures of functioning and what we call psychometric measures or measures of quality of life are not very good.

The trouble is when you give an intervention you want to be able to look at it at the start of a treatment and once the treatment is completed, or a certain period of time later on. Some years ago, I was leading a national

study of the effect of helping children's growth with growth hormone. With expert psychologists, we thought we had designed the best study, and it appears that those children who were treated did just as well on the repeat of the questionnaire as those who did not receive any treatment, but in fact, they were just used to doing the tests and the assessments. There is a familiarity concept. So that is also one facet that perhaps makes the design even more challenging. I agree with Professor Giordano that the only way to really get an idea of whether an intervention is successful or not is the long-term outcome—how that is affecting people in their lives, whether cis or transgender, and whether it made a difference or not.

Q46 **Catherine Fookes:** Having said that, how can the study be designed to be safe and to come out with that outcome?

Professor Butler: I do not know what is being discussed at the present time, but I await hearing and will provide any support that I can.

Q47 **Catherine Fookes:** Professor Grossman, would you like to comment?

Professor Grossman: It is going to be an extremely difficult trial. From what Professor Giordano stated, the adolescents on pubertal blockers did not appear to improve in their mood or their dysphoria, but the concern, which I fully understand, is that those who did not receive pubertal blockers would actually deteriorate and become more distressed.

If you were to have a randomised trial of these young people and give half pubertal blockers and the other half not, and then look at them psychometrically, psychologically, whatever sort of assessment you wished, my concern for running that trial is that the 50% who were receiving the placebo or no treatment would remove themselves from the trial altogether and would look for alternative means of help. If they were sufficiently motivated to want to receive pubertal blockers, then they were told they were not going to be part of that trial, they may withdraw themselves and the trial would be vitiated. I am just picking up on an extra problem in designing these trials. Personally, I am not sure how it would run.

The retrospective LOGIC trial, which Professor Butler is involved in, will be really interesting because those are children who did not receive pubertal blockers because they were not able to access GIDS. Even though it is not exactly randomised, it will provide very useful information. For a prospective trial, I am a little sceptical as to how it can be arranged.

Q48 **Christine Jardine:** Before we start, I should mention, just so you are aware of where I am coming from, that, as the Liberal Democrats spokesperson for women and equalities, I have been working on a policy paper on this area for the best part of a year. One of the things we are looking at is the ethical issues involved in trials. Would you say there are any safety or ethical considerations in only allowing access to a drug through a research trial, particularly a drug that has previously been more readily available?

Professor Giordano: There are numerous ethical issues and ethical-legal issues in providing a medication only within the research trial. The most straightforward is that, in doing so, there is a risk that NHS England will violate fundamental principles contained in virtually all declarations and conventions on human rights as they apply to participation in research. For example, although the Helsinki Declaration is not enshrined in UK law, the UK Clinical Trial Regulation states clearly that it is inspired by the Helsinki Declaration, which states that it is the duty of the physician to take equal care of those who participate in clinical research and those who do not. The voluntary consent of a person of whatever age to participate in clinical research has to be protected by law. Providing medical treatment only on the condition that an individual signs up for a clinical trial risks eroding that fundamental ethical and legal principle.

The other problem concerns consent. In the Cass Review we read that consent would be sought for all the children enrolled in the clinical trial. This is partly proper. A minority of those who take puberty blockers will be 16 years old or over because most adolescents need puberty blockers earlier than that, but there will be a proportion of young people aged 16 or over who will need puberty blockers, and they have a statutory right to consent on their own, so consent should be sought from them and not for them. Under the UK clinical trial regulations, the consent of minors under the age of 16 will not be required. Parents will need to consent on their behalf. Now, this risks already skewing the sample. Part of the problem with the evidence that we currently have is that the results concern small cohorts and therefore have been deemed to be non-generalisable. But only providing treatment to young people who have supportive parents, therefore excluding children in care, for example, or children without supportive parents, even if that would be only a small minority of people, risks skewing the sample. That is one problem.

The other problem is that we get in a really convoluted situation where the recognised practice is to provide puberty blockers only to those people who can meaningfully engage in the therapeutic process. There are isolated best interest decisions made in this case; I know of one or two. Normally, a young person will have to be assessed for their capacity, for their competence, and for their ability to understand the risks and benefits of puberty blockers and balance those up in order to arrive at a choice. The ability to consent will be in all likelihood an eligibility criterion for obtaining puberty blockers and yet the consent to participation in research will not be required because it will be their parents who will have to consent on their behalf. So, there are a number of peculiarities that follow from the provision of medical treatment only within a research trial, which could be circumvented by providing treatment to all patients for whom the benefits ratio is similarly favourable and then engaging in research on a voluntary basis with long-term follow-ups.

Q49 **Christine Jardine:** Would either of the professors like to add anything to that?

Professor Grossman: I come from a libertarian type of background. An adult of 18 years and above takes total responsibility for their decisions and every discussion for every medication is discussed and taken forward on that basis. Fundamentally, I believe that below that age, particularly 16, we need to protect our children, and I do not understand how a child and more particularly their parents are able to consent to a medical procedure of which we are uncertain. I find it very difficult to understand and get my head around the possibility of consent by a child.

Professor Giordano: Thank you for making this point; I was not suggesting that children should consent on their own. I was just commenting on the convoluted situation in which recognised practice and clinical guidelines suggest two things which we would not normally expect. We would only consider eligible for treatment young people who prove competent to decide, but additionally parental consent would normally be required. Usually, it would either be one or the other, but in this case most new guidelines advise that extra level of safeguard.

Talking specifically from an exclusively ethical-legal perspective, it is a convoluted situation where competence will be, clinically speaking, an eligibility criterion, but then the adolescent will not be asked for their consent. Somebody else will have to consent on their behalf. It is quite peculiar. I have not come across a situation quite like this before.

Q50 **Christine Jardine:** Professor Butler, you looked as if you wanted to add something.

Professor Butler: I do not know whether you and members of the Committee are familiar with people who are transgender or living their lives differently from their birth gender, but as someone who has had clinical experience in this area, the distress and anxiety in the young person and their families is very, very clear in the majority. Many of them at that time are just not functioning despite psychological help or support. If one can provide that form of respite to prevent or reduce the physical changes and functions that are causing the dysphoria, then that can restore the function of the young person and the family in that regard.

It is that balance of doing harm versus not doing harm. Where is the harm? Where is the balance? We wrote a review commentary on this some years back about how when your back is against the wall it is very difficult not to be able to provide help where help is available. There is so much anxiety around access to treatment at the present time. My view is that specialist teams are the portal for access to the treatment. If this is highly restricted, it is only going to make worse the movement towards unregulated prescriptions. As is happening at present, a lot of young people will continue trying to access these treatments from abroad without appropriate assessment, pre-checks, or subsequent monitoring, so goodness knows what is happening. That is a worry. I have seen this many times up until now.

Q51 **Christine Jardine:** Would it be fair for me to characterise what you are

saying generally as: there would be ethical problems with having a drug that was available widely and then restricted because it would bring up these other pressures about accessibility and perhaps turning to other sources of getting the drug?

Professor Butler: Yes, that is the case. However, it needs to be like other drugs and hormone treatments, particularly in the field of paediatric endocrinology, which are recommended to be prescribed and administered only by people with specialist training in the area and of growth hormone in particular.

Q52 **Christine Jardine:** The other thing that stems from that is: what information do you believe should be given to young people to ensure they are making an informed decision, as has been mentioned, about taking part in the trial? What constitutes an informed decision? That is a difficult one, I know.

Professor Butler: It is difficult.

Professor Giordano: There is a clinical aspect to this: what kind of clinical needs and understanding a young person would need to have. Then there is an ethico-legal perspective. As Professor Butler was saying, a clinical trial that is the only way to obtain a medication that is felt as necessary by many trans people and their families, is already, by default, vitiating the informed consent process. From other research that has been conducted on eligibility criteria, we know that these strict rules most likely cause an alteration in the narratives because people are so desperate to obtain medication, they will say what is expected of them in order to obtain it.

There is a knock-on effect on the relationship of trust between clinicians and patients. All these things can become counterproductive in terms of what outcomes we are studying if we do not have reliable narratives because from the start, we have funnelled individuals into a research trial that might be perceived as coercive, because it is. The coercive nature of provision only within a research trial can have a knock-on effect on the reliability of the data that clinical services will be able to obtain.

Professor Grossman: I fully concur, and I fully understand all the problems and the distress of many of these children and their parents. I still feel uncomfortable with the use of a medication with uncertain long-term effects and uncertain short-term advantages because of public pressure and in girls who may or may not ultimately show any improvement. A trial is the only way to get the information to prove it one way or another. It will clearly be extremely difficult, and I take the point that saying, "You can only get this drug by being recruited into a trial," could cause its own problems.

Professor Giordano: Can I add one thing? There is one thing that is very clear. It is really a clear law in Europe and in the UK. It is that clinical research involving children has to be justified on very stringent grounds—more stringent than the grounds on which medical treatment gets

provided. You cannot either start or continue a treatment trial, a therapeutic trial—as this case would be—unless you are fairly certain that the benefits are highly likely to outweigh the risks and burdens. If you do not know that the benefit-risk ratio is likely to be positive, you cannot actually initiate the clinical trial at all.

The concerns that you have are concerns that would logically go towards a denial of the medication altogether. That is quite draconian, but the research can be done, so we can improve the evidence base. My concerns are about the feasibility of a clinical trial: what are we going to get through that? Are there more appropriate ways of doing research? My understanding is that we probably have more appropriate ways to do research in these areas, rather than a clinical trial. Secondly, is a coercive nature justified from an ethical perspective?

Q53 **Rachel Taylor:** You will be pleased to know this is the last set of questions, so thank you for persevering. Could there be any unintended consequences of the indefinite ban on prescribing puberty blockers for under-18s in relation to gender dysphoria?

Professor Butler: At the present time, the only young people who are currently eligible to receive puberty blockers are those who had been assessed and monitored by the previous Gender Identity Development Service. There are no new initiations at present. The new gender services are established but until the clinical trial is going there is no provision to do that. This is in accord with the NHS England guidelines and the legal statute. At the present time, there is a hiatus in the access to this sort of treatment by a lot of young people. It is one of the situations that I hope will be looked at in detail, as to the outcomes of mental health, wellbeing and long-term gender identity, which I hope in itself will inform the decision-making processes.

Q54 **Rachel Taylor:** Are you saying that there are people who have been assessed as being eligible to take the puberty blockers who will not now be receiving them?

Professor Butler: No, those young people have been permitted by NHS England, by a clause within the legal ban, to either continue or access treatment. Most of them have now started the treatment and can continue that, so that will not be withdrawn. It is the question of new starts, which are currently not able to happen.

Professor Grossman: I have a related point but maybe slightly different. If we ban puberty blockers, and at the age of 18 you are still entitled at that stage to undergo transgender endocrine reversal with the relevant hormones, I am still unclear in my own mind if an 18 or 19-year-old young person comes to me and says, "I am transgender. I wish to have the alternative hormone treatment," whether I am actually permitted to prescribe those drugs for that patient in the absence of a full psychological assessment and counselling. Now, you can say to those patients, "Well, I

will only do that when you have been fully assessed," but that may involve waiting for several years because of a lack of resources.

Equally, speaking to members of the transgender community who are adults, one of their major concerns is the amount of time and the number of doctors they have had to see before they could get their preferred hormone treatment, as adults. That would seem to me an extremely grey area, even for the adult. I am obviously less uncomfortable with not giving the treatment to these children; I agree that is highly arguable. But, once they are in an adult state, it is still a slightly grey area as to whether that patient can and should be given treatment. As I would understand it from the GMC, if a cisgender patient comes to me and says they are a male who lacks testosterone or a female who lacks oestrogen, it is part of my everyday job to treat them. But if a transgender patient said, "I wish to have the following hormones to optimise my state," it is legally and medically a rather grey area. I am very inclined to go ahead and do that, but I am not sure on what grounds I am enabled to do that if they have not had the counselling, which is not available. I am just raising a further problem in this whole rather difficult area.

It may be up to Parliament, or the law, or the GMC to actually give proper guidelines on this. At present, they are not there. If we do not have the resources—which we clearly do not—for these patients to be seen fairly early, then we are in a vague, in-between world.

Professor Butler: That is what is happening with children and young people getting medication from abroad, at the present time. There has been no assessment, they are just accessing medication. So many young people are self-medicating at present with treatment obtained over the internet.

Professor Giordano: That is a very serious concern. There are also some peculiarities in terms of the ban and the justification. Generally, a ban is issued when a medication is not regulated, for example. There have been cases of slimming pills or performance-enhancing drugs that are sold without going through that rigorous process, the MHRA finds out and recalls them, or, as we were saying before, there is new evidence about unintended side effects of medications. In this case, again, it is the role of the regulator to recall or ban a medication.

In this case, it is quite interesting because it is not the medication per se that is banned but the application. Endocrinologists can continue to prescribe that medication off-licence for adolescents with endometriosis, or precocious puberty on-licence, but not for gender dysphoria. That is quite a peculiar situation. Comparable situations are when a medication is found to have unintended side effects for only one particular category of patients—for example, a medication increases the risk of heart disease. In those cases, doctors will be told by the General Medical Council, "You should not prescribe this medication anymore to patients who are at high risk of cardiovascular diseases." It is usually not for the regulator to step

in and ban the application. The regulator will inform the clinicians, who will then not use that medication for that particular indication.

Moreover, the other peculiarity here is that when that happens, it is because new safety evidence appears that shows these side effects. In this case, there is no evidence of lack of safety. There are legitimate concerns, but concerns are not evidence. There are two different concepts here. As I was saying before, there is no complaint specifically concerning puberty blockers. There are small rates that concern irreversible changes procured by gender-affirming hormones or surgery, but no specific complaint, no litigation concerning puberty blockers specifically—legitimate concerns, not specific evidence.

The other thing that is unique is that it is generally the MHRA that is tasked with assessing the safety of medications and recalling or banning a medication when it is proven unsafe. In this case, the MHRA has not been involved. The Government have taken advice from a different commission, called the Commission on Human Medicines, which I had never heard of. It is a less-known commission. The membership of this commission is quite interesting as well because you would expect to have a paediatric endocrinologist there, but there was one paediatric endocrinologist specialised in respiratory medicine. There was no psychiatrist, no child and adolescent psychiatrist, and no child and adolescent psychologist. It is quite peculiar to me that it is not the drug but the application that has been banned not on grounds of safety, but on grounds of concerns, however legitimate and not by the MHRA but by another much less-known commission.

Q55 **Rachel Taylor:** Moving on to the next question, what evidence do you think needs to be available in 2027 when we are told the ban will be reviewed? How likely is it that that evidence will be available by that point in time? Professor Butler, perhaps you would like to answer that one first.

Professor Butler: If a trial is going to be established, and I hope they will be able to come to an agreement for an appropriate protocol, that will take a while to implement and recruit to. In this field, we are looking more at longer-term outcome measures rather than short-term changes; that is the key. I am hoping that by 2027 we will have more information on the long-term outcome in those young people who have already received intervention. That is something we are working towards at the present, including from our other parallel study, which is the NIHR-funded LOGIC study, which is following through young people who will not have received any intervention but will have been part of a research study and followed up prospectively. We will have more information then.

Q56 **Rachel Taylor:** Are you saying that there may not be information available from this clinical trial in 2027?

Professor Butler: It depends on the design and whether they can ascertain robust measures that they can demonstrate in a trial to change over time or not. That is the challenge of the design at the present time.

Professor Grossman: It is a very difficult point. I suspect a prospective clinical trial will not have that information available, looking at the way that clinical trials run and the time course. The retrospective trial, LOGIC, which Professor Butler has mentioned a number of times, may well have useful enough data that we can review the legislation at that time. I would very much hope so. Either way, all I am concerned about is the welfare of the children. If we have robust data that says, "Really this is a very good treatment, and we really should go ahead, and there are certain children who will really see advantage from that," I am very happy to alter my view. It is reasonably likely we will have that sort of information, so we can make an informed decision.

Professor Butler: As long as we continue to get research funding, which is the challenge at the present time.

Professor Giordano: I agree with what both my colleagues said. I agree entirely that it is very unlikely that whatever clinical trial starts—this year, with any luck—will give us any information that we do not have already. There are over 200 publications with statistically significant results, which have been excluded from the reviews that have fed into the Government decisions because they were mainly observational studies.

We need to not mislead the public into believing that in this area of care, we will be able to obtain so-called GRADE 1 or 2 evidence because that is only achieved through randomised controlled trials. Randomised controlled trials cannot be performed in this case both because blinding cannot be maintained and from an ethico-legal perspective because potentially beneficial treatment cannot ethically and lawfully be denied. As Professor Grossman was saying, the welfare of the child has to be the paramount consideration and has to come over and above the interests of science and society. So, you cannot withdraw treatment. Even if you technically could—which you cannot because within a month it would be clear to everyone who is in the control arm—legally and ethically you could not because the interests of the child have to be the paramount consideration there.

What kind of evidence could we have in two years? It will be very interesting to have the evidence from the retrospective studies, but we also need to accept that in this area of medicine, as in many other areas of medicine, we might not achieve that GRADE 1 evidence. It is perhaps necessary to change the goalposts and to accept that some areas of medicine have such vast repercussions in people's lives that what we want to measure is so nuanced it cannot fit into that scale of GRADE. It is also ethically problematic to withhold medical treatment that is experienced as beneficial and that nobody has complained about on grounds that there is not enough evidence yet, if what is meant by evidence is unattainable.

Q57 **Rachel Taylor:** I would like to go back to what you mentioned as side effects or potential harms that Dr Cass looked at around bone density and fertility. There are certainly hormones available and widely prescribed, including Depo-Provera injections, which have those similar potential

harms and are still licensed for use. Are you saying that there is a case for the drugs to still be available and used for this alongside a clinical trial? Are you saying that there should not be a ban but that there is a place for the drug to be used alongside clinical trials to gather more evidence?

Professor Giordano: My view is that a clinical trial might not be the right way of doing research and might mislead the public into believing that this study will give a level of evidence that is actually not appropriate to aim for in this area of care. In my opinion, puberty blockers should continue to be a matter to be discussed between patients, families and clinicians. It is not a matter for Parliament or the legislator. It is a clinical matter. I am not suggesting clinicians should give puberty blockers, but clinicians, patients and their families have to make that determination within the safety that guidelines would provide, usually within a multidisciplinary team after a certain number of assessments have been made, but at clinical discretion. Politics and law should perhaps tiptoe in this area and allow for clinical discretion.

Professor Butler: If there were a wonderful new oncological treatment which had a very high cure rate compared with existing treatments, then that would still need to be proven by a trial. You would hope, or expect, that most people offered that would opt for it. I am sure the children and young people taking part in the trial would opt to receive puberty blockers in that regard.

The question is not so much whether those going through the new services would be assessed properly or put forward for puberty blockers, but there is such a huge backlog, which in itself is distorting the whole flow and assessment process. The feeding into the trial is not necessarily going on. The young people who are at the head of the queue waiting to get through to the new services for assessment are actually so far down the process of puberty that within that period of time, if the question is being asked as to what happens when you interrupt early puberty, we will never get there, unfortunately. I am afraid it would take much longer to achieve any outcomes. I do not know what the current waiting list figure is, but it is many thousands. The new services are doing their level best to get through the waiting list, but it takes some time.

Q58 **Rachel Taylor:** Do you have anything to add?

Professor Grossman: No, I was just thinking through the point that Professor Giordano has brought up time and again, and the one that you mentioned: is Provera going to be a dangerous drug in terms of your bones? We do not know. Every day I will see a patient and I will explain the risks of the drug, which I personally might not want to take at this dose or this way. The adult and I will have a discussion, and I will explain the risks. They will understand them and say, "This is a risk which is small, but I'll undertake it because the benefits are great."

The real problem here is that we are dealing with very young people—children—and in a sense the state has become in loco parentis. We are

taking responsibility for looking after these very young people where we sometimes might feel that the parents, for one reason or another, might not have all the information or have their best interests at heart. As Professor Giordano points out, consenting in this situation is really problematic.

Chair: Thank you so much to our panel and to our Committee members for the questions today. We have done over two hours. I thank you very much for your time and expertise.

I would also like to say thank you to everybody. We have had differences of opinion, but we have been able to express them respectfully, with understanding and graciousness. That has happened in this Committee room, I hope that that continues to happen outside this Committee room as this discussion continues.

I am going to ask for the Public Gallery to be cleared while the witnesses and the Committee members stay seated, please. Thank you, and that brings proceedings to an end.