Medicines & Healthcare Products Regulatory Agency
10 South Colonnade
Canary Wharf
London E14 4PU

Research Ethics Committee for PATHWAYS
and Health Research Authority
2 Redman Place
Stratford
London E20 1 JQ

By email to: info@mhra.gov.uk and approvals@hra.nhs.uk

cc.

1. **Secretary of State for Health and Social Care**
   Attn: Government Legal Department
   By email to: newproceedings@governmentlegal.gov.uk

2. **NHS England**
   By email

3. **King's College London**
   Attn: Ann-Marie Murtagh
   By email to: qm.khpcto@kcl.ac.uk

4. **South London and Maudsley NHS Foundation Trust**
   By email to: slam-ioppn.research@kcl.ac.uk

5 December 2025

To whom it may concern,

Re: Judicial review challenging the approval of the PATHWAYS Trial

This is a formal letter before claim in accordance with the Pre-Action Protocol for Judicial Review. Your response is required by 4pm on 19 December 2025.

A Proposed claimant and their legal representatives

1. Our clients are the Bayswater Support Group ('Bayswater'), Mr James Esses and Ms Keira Bell.

2. Bayswater is a company limited by guarantee which represents approximately 800 parents and guardians of children and young adults who identify as trans or non-binary. It was established in 2019 because of a concern that the public discourse about gender-distressed young people was often occupied by people who were not directly impacted by the issue and to give such parents a voice directly. It has members in all regions of England and in Wales, Scotland, Northern Ireland and the Republic of Ireland. Its members are overwhelmingly parents whose children are adolescents or young adults but also includes parents of younger children. They are at different stages of gender transition and have different experiences of NHS services. Bayswater's members have a direct interest in the results of the PATHWAYS Trial. It is also possible that the children of some members may become involved in the Trial once recruitment starts.

3. Mr Esses is a practising psychotherapist whose clients include children suffering from gender dysphoria. He is the founder of the therapeutic organisations Thoughtful Therapists and Just Therapy. He campaigns and advocates for ethical treatment for gender dysphoria.

4. Ms Bell was the lead claimant in judicial review proceedings brought against the Tavistock and Portman NHS Trust. She was provided with treatment for gender dysphoria by the Tavistock Centre, having been referred aged 15 to its (now closed) Gender Identity Development Service ("**GIDS**") due to gender dysphoria. Upon her insistence on her desire to transition to the male gender, Ms Bell received puberty blockers from the age of 16 to 18. At age 17, she received cross-sex hormones in the form of testosterone. She ostensibly provided 'consent' to each of these treatments.

5. When Ms Bell was 20, she had a double mastectomy and had undergone significant physiological changes. However, as she matured, she recognised that her gender dysphoria was a "*symptom of [her] overall misery*" and not its cause. She has now sought to detransition but continues to suffer from long-term effects of these treatments. Ms Bell describes the profound consequences of these events as including "*possible infertility, loss of my breasts and inability to breastfeed, reproductive atrophy, a permanently changed voice, and facial hair*."

6. Bayswater, Mr Esses and Ms Bell have an interest in the Puberty suppression And Transitional Healthcare With Adaptive Youth Services (PATHWAYS) clinical trial ("**the Trial**"), which proposes to administer and study the effects of Gonadotrophin-

Releasing Hormone Analogues ("**GnRHa**"), commonly known as 'puberty blockers', on vulnerable children.

7. Our reference for this matter is PC/BEB. The solicitors with conduct of this matter are James Gardner and Paul Conrathe of Conrathe Gardner LLP, 167-169 Great Portland St, London W1W 5PF.

8. Our client accepts service by email subject to Mr Gardner and Mr Conrathe being in receipt of, or copied into, all relevant correspondence.

9. Please would each of the proposed Defendants and Interested Parties (or their respective legal representative) confirm by return whether they are prepared to accept service of legal proceedings by email, and if so, to whom service by email should be directed. If you are prepared to accept service by email, please confirm if there are any requirements to which we should adhere, either generally or specifically, under paragraph 4.1 of Practice Direction 6A of the Civil Procedure Rules.

B Proposed defendants

10. The proposed Defendants are (1) the Medicines & Health Products Regulatory Agency ("**MHRA**") as the licensing authority for the Trial and (2) the Health Research Authority ("**HRA**"), which is responsible for the establishment and regulation of Research Ethics Committees ("**RECs**") under ss. 109 to 117 of the Care Act 2014. The HRA is required to publish a policy which specifies the requirements with which RECs must comply, and to monitor RECs' compliance with that policy (s. 112(3) Care Act 2014). The current policy in place is the Governance Arrangements for Research Ethics Committees ("**GAfREC**").

11. The HRA may also exercise discretionary powers in relation to RECs as it considers appropriate, including coordinating their work and providing them with assistance (s. 112(4) Care Act 2014). Under s.110(2) of the Care Act 2014, the main objective of the HRA in exercising its functions is:

    (a) To protect participants and potential participants in health or social care research and the general public by encouraging research that is safe and ethical, and

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(b) To promote the interests of those participants and potential participants and the general public by facilitating the conduct of research that is safe and ethical (including by promoting transparency in research)

12. Clarification is sought from the HRA as to whether the REC responsible for assessing the ethical issues arising from the Trial ("**the PATHWAYS REC**"), is an independent legal entity and relevant decision-maker distinct from the HRA itself. If that is the HRA's position, then the PATHWAYS REC is a separate proposed Defendant. It is contended that the PATHWAYS REC is amenable to judicial review given, among others, its performance of the public function of assessing publicly funded clinical trials in the public interest, its legislative underpinning, its operation as part of a system of public regulation and under the supervision of the HRA as a public authority, and its public funding. Please confirm whether or not you agree.

C Interested Parties

13. The Secretary of State for Health and Social Care is an Interested Party. He has overall responsibility for the conduct of clinical trials in the UK. The MHRA falls under the authority of the Secretary of State as it is an executive agency of the Department of Health and Social Care. The Secretary of State also has powers to direct the HRA in relation to the performance of its functions (para 16, Sch 7, Care Act 2014). Furthermore, as set out below, the Secretary of State has previously considered it appropriate to ban the sale and supply of puberty blockers to children and young persons via private prescriptions, and their supply under the NHS, on the grounds of patient safety, and subject to identified exceptions (one of which is use in the course of an authorised clinical trial).

14. The Trial is being funded by NHS England under the National Research Collaboration Programme. NHS England is therefore also an Interested Party. The co-sponsors of the Trial, King's College London and the South London and Maudsley NHS Foundation Trust, are also Interested Parties.

D Details of the matter under challenge

Gender incongruence and its diagnosis

15. Gender incongruence of childhood is defined in the International Statistical Classification of Diseases and Related Health Problems (ICD-11) as "*a marked incongruence between one's experienced/expressed gender and the assigned sex"* of at least two years in duration, which is associated with a strong desire to be a different gender than the assigned sex, and 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.[1]

16. The current state of scientific knowledge in relation to gender incongruence indicates that it is not linked to physical pathology (i.e. it is not a disease or illness requiring physical medical intervention in the usual way). Until relatively recently it has been understood to be a mental disorder (and still is within the DSM-5). However, the ICD-11 no longer characterises it in this way. This makes it a *sui generis* condition – neither a physical nor a mental health matter, but some hitherto unknown third category. This raises the fundamental question of why it should require any kind of medical intervention or treatment at all. As a recent review by the US Department of Health and Human Services ("**the HHS Review**") explains:

> ...the diagnosis of gender dysphoria[2] is based entirely on subjective self-reports and behavioural observations, without any objective physical, imaging, or laboratory markers. The diagnosis centres on attitudes, feelings, and behaviours that are known to fluctuate during adolescence.[3]

17. Prior to the introduction of puberty blockers, clinical experience of patients who had been gender incongruent since childhood suggested that it was resolved during puberty or early adulthood.

18. Children and young persons suffering from gender dysphoria are highly vulnerable and demonstrate higher than expected rates of Autism Spectrum Disorder,

[1] International Classification of Diseases Eleventh Revision (ICD-11) (World Health Organization, 2022).
[2] Gender dysphoria is the term used in the Diagnostic and statistical manual of mental disorders (DSM-5), American Psychiatric Pub., 2022. It broadly refers to gender incongruence associated with clinically significant distress.
[3] U.S. Department of Health and Human Services (HHS), *Treatment for Pediatric Gender Dysphoria: Review of Evidence and Best Practices*. Washington, DC: HHS, November 2025.

Attention Deficit Hyperactivity Disorder, anxiety, depression, eating disorders, suicidality, self-harm, and Adverse Childhood Experiences (such as physical, sexual, and emotional abuse or neglect).[4]

Treatment for gender incongruence

19. There is no international consensus on the best practice for care and treatment of children and young persons with gender dysphoria or incongruence.

20. Early gender services in this area focused on therapeutic work and psychosocial approaches. However, the approach to treatment changed following the 'Dutch protocol', which emerged from a single case study in 1998 involving a female to male transition via puberty blockers at age 13. There was a subsequent expansion of the Dutch protocol to a larger group of patients, but it is difficult to draw conclusions from the results of this study due to concerns regarding bias and the confounding factor that all patients were also provided with psychological treatment whilst on the puberty blockers.[5]

21. Since then, however, there has been an increasing trend towards a 'gender-affirming model' which presumes that a "*child of any age may be cognisant of their authentic identity and will benefit from a social transition at any stage of development*".[6] Gender affirmative care emphasises the use of puberty blockers, cross-sex hormones, and surgery to facilitate gender transition and manage gender dysphoria.

22. In the UK, the move towards gender affirmative care began with an early intervention study between 2011 and 2014, preliminary findings from which "*did not demonstrate improvement in psychological wellbeing, and in fact some birth-registered females had a worsening of 'internalising problems (depression, anxiety) based on parental report*". The results showed a significant increase in adolescents scoring the statement "*I deliberately try to hurt or kill myself*" as "*sometimes true*"

[4] Cass Review Final Report, §5.68.
[5] Cass Review Final Report, §§2.7 to 2.12.
[6] Cass Review Final Report, §2.14, referring to Ehrensaft, D. (2017). Gender nonconforming youth: Current perspectives. *Adolescent Health, Medicine and Therapeutics,* Volume 8, 57-67.

following a year of treatment on puberty blockers.[7] However, the results of this study were not published until December 2020.

23. In the interim, from 2014, puberty blockers became available in the UK in routine clinical practice despite the lack of evidence base for this approach. Concerningly, without any underpinning rationale, puberty blockers were made available to those who would not have met the strict inclusion criteria of the Dutch protocol or the UK early intervention study.[8] Reflecting on the global move towards gender affirmative care, the HHS Review concluded:

> *In many areas of medicine, treatments are first established as safe and effective in adults before being extended to paediatric populations. In this case, however, the opposite occurred: clinician-researchers developed the paediatric medical transition protocol in response to disappointing psychosocial outcomes in adults who underwent medical transition.*

24. Following increased scrutiny of the risks of hormonal and surgical intervention in vulnerable children, the HHS Review now identifies a "*global reversal*" in approach which it attributes to "*a significant shift in the patient population; uncertainty surrounding the natural history and prognosis of gender dysphoria; increasing recognition of the risks associated with medical interventions; a more accurate understanding of the suicide risk; the collapse of the original treatment rationale; and a weak underlying evidence base*".[9] The Review notes that health authorities in an increasing number of countries now recommend psychosocial approaches rather than hormonal or surgical interventions as the primary treatment, and have introduced restrictions on the latter.[10]

The Cass Review and its findings

25. The increasing national and international concerns over the safety of the administration of puberty blockers on vulnerable children culminated in the UK with Ms Bell's litigation against the Tavistock and Portman NHS Trust in October 2019.

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[7] Cass Review Final Report, §§2.19 to 2.20, referring to the Tavistock and Portman NHS Foundation Trust (2015) Board papers – June 2015 and Carmichael P. 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)).
[8] Cass Review Final Report, §2.24.
[9] HHS Review, §4.3, p.67.
[10] HHS Review, p.13.

26. Against this background, the Independent Review of Gender Identity Services for Children and Young People chaired by Dr Hilary Cass ("**the Cass Review**") was commissioned by NHS England to make recommendations regarding the provision of treatment for children and young people experiencing gender incongruence and gender dysphoria. The Cass Review published an Interim Report in February 2022 and a Final Report on 10 April 2024.

27. Among the conclusions of the Cass Review were the following:

    (1) The initial movement towards treatment with puberty blockers lacked a sound evidence base. The adoption of such treatment with uncertain benefits without further scrutiny was a significant departure from established practice and has had significant consequences on patient expectations and demand for treatment.[11]

    (2) The focus on the use of puberty blockers for managing gender-related distress has overshadowed the possibility that other evidence-based treatments may be more effective.[12]

    (3) The systematic and independent evidence review commissioned by the Cass Review and undertaken by the University of York found multiple studies demonstrating that puberty blockers exert their intended effect in suppressing puberty, and that bone density is compromised during puberty suppression. No changes in gender dysphoria or body satisfaction were demonstrated. There was insufficient/inconsistent evidence about the effects of puberty suppression on psychological or psychosocial wellbeing, cognitive development, cardio-metabolic risk or fertility.[13]

    (4) Although a diagnosis of gender dysphoria has been seen as necessary for initiating medical treatment, it is not reliably predictive of whether that young person will have longstanding gender incongruence in the future, or whether medical intervention will be the best option for them.[14] Thus, assessing whether a hormone pathway is indicated is challenging. The poor evidence base makes

[11] Cass Review Final Report, §§22 to 23.
[12] Cass Review Final Report, §69.
[13] Cass Review Final Report, 81 to 83.
[14] Cass Review Final Report, 58.

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it difficult to provide adequate information on which a young person and their family can make an informed choice.[15]

28. In July 2023, Dr Cass wrote to NHS England to advise that treatment using puberty blockers should be restricted to a research protocol due to potential risks to neurocognitive development, psychosexual development, and longer-term bone health.

The ban on puberty blockers

29. On 9 May 2024, following the publication of the Cass Review's Final Report, the Secretary of State made a temporary emergency order (SI 2024/727) which came into force on 3 June 2024. The Explanatory Memorandum to the emergency order stated that its aim was to "*reduce and remove risks to patient safety*" by (among other measures) prohibiting the sale and supply of puberty blockers to children and young persons under 18, subject to certain exceptions.

30. At the same time, the Secretary of State made regulations (SI 2024/728) restricting NHS Primary Care under 18 prescriptions of puberty blockers to where treatment is part of a National Institute for Health and Care Research ("**NIHR**") clinical trial, or the person had started a course of treatment on puberty blockers before 26 June 2024.

31. In November 2024, the Secretary of State requested advice from the Commission on Human Medicines ("**CHM**") regarding the proposal to introduce a permanent restriction on the administration of puberty blockers. The CHM concluded, among others, that the prescribing and care pathway for puberty blockers for gender incongruence at the material time constituted an "*unacceptable safety risk*" for children. It noted:

> **The reasons for the dramatic increase in the use of GnRH agonists to suppress puberty over the past 10 to 15 years remains unexplained.** CHM found no evidence that previous populations in this age range identified as transgender in the volume currently doing so or that similar volumes expressed regret at not receiving GnRH agonists for the suppression of puberty. Of those receiving GnRH agonists for pubertal suppression, the majority do not regret their use when asked 6 to 10 years later (reference 2). Some suggest this data

[15] Cass Review Final Report, 98 to 99.

> supports the use in this population. Others consider this a self-fulfilling prophecy (reference 3). One in 18 do regret the decision and may have lifelong impact from GnRH agonist use. **There are valid concerns to be addressed that social constructs are driving behaviours for some transgender youth where children and young people and parents or carers feel compelled to seek pubertal suppression** [emphasis added].[16]

32. On 11 December 2024, the Secretary of State announced his intention to make the temporary ban on puberty blockers permanent.

The PATHWAYS Trial

33. The PATHWAYS study was commissioned by NHS England in partnership with the NIHR. It is funded by the National Research Collaboration Programme, an NHS England and NIHR partnership, in the sum of £10,694,902.24. It is sponsored by King's College London and the South London and Maudsley NHS Trust.

34. On 21 August 2025, the HRA received an application for the approval of the PATHWAYS Trial. The Trial is the clinical trial component of the wider PATHWAYS study. It is described on the NIHR funding awards platform as follows:[17]

> *PATHWAYS Trial focusses on the effects of GnRHa on young people's physical, social, and emotional wellbeing. It involves young people who want to delay puberty and whose parents and Gender Service agree with this treatment option. Everyone taking part will be followed for two years during the trial, with regular checks on their physical, social, and emotional wellbeing.*

35. Between 11 April 2025 and 14 November 2025, our clients, Mr Esses and Ms Bell, engaged in correspondence with the MHRA and the HRA to obtain information related to the Trial, including confirmation as to whether the MHRA had received, assessed or approved the Trial. The MHRA refused to confirm or deny the existence of this information on the basis that the request related to "*commercially sensitive*

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[16] Commission on Human Medicines report on proposed permanent order to restrict the sale and supply of gonadotrophin-releasing hormone agonists in children and young people under 18 years of age for the purpose for puberty suppression in gender incongruence and/or gender dysphoria, 24 January 2025: https://assets.publishing.service.gov.uk/media/678e6994ea48a571517acf98/chm-advice-to-sos-on-gnrh-agonists-for_pubertal-suppression.pdf ("**CHM Report**")

[17] https://fundingawards.nihr.ac.uk/award/NIHR167530 (accessed 20 November 2025).

information" under s.43(3) of the Freedom of Information Act 2000. Similarly, the HRA refused to disclose documents in relation to the Trial application on the basis, among others, that the information sought was exempt under s.22A of the Freedom of Information Act 2000 as information in the course of programme of research which is continuing with a view to publication of the results.

36. On 6 November 2025, the PATHWAY REC gave a favourable opinion in respect of the Trial. However, the fact of this opinion being issued was not disclosed to the public until 21 November 2025 when the MHRA and HRA announced that the PATHWAYS Trial had been approved ("**the Approval**"). The four-word 'summary' of the PATHWAY REC's opinion published on the HRA website states that it is a '*Further Information Favourable Opinion*'.[18] No other information in relation to that opinion has been published or otherwise disclosed.

E The applicable law

Regulatory framework

37. Clinical trials in the UK are primarily regulated by the Medicines for Human Use (Clinical Trials) Regulations 2004 ("**the 2004 Regulations**").

38. GnRHa is a 'investigational medicinal product' within the definition of Regulation 2 of the 2004 Regulations, as it is not authorised for use to suppress puberty in children with gender incongruence. Such unlicensed usage is conventionally described as 'off-label' use of a product.

39. Under Regulations 12(1) and (2) of the 2004 Regulations, a clinical trial for investigational medicinal products may not be started or conducted unless:

    (1) The relevant REC[19] has given a favourable opinion in relation to the clinical trial; and

    (2) The clinical trial has been authorised by the licensing authority.

[18] https://www.hra.nhs.uk/planning-and-improving-research/application-summaries/research-summaries/pathways-trial/ (accessed 25 November 2025).
[19] Or appeal panel appointed under Sch 4 of the 2004 Regulations.

40. For the purposes of this matter, the PATHWAYS REC is the relevant REC to which the Trial application has been made, and the MHRA is the relevant licensing authority.

41. As to licensing authorisation, by Regulation 18(2) of the 2004 Regulations, the licensing authority may, within a period of 30 days from receipt of a valid request for trial authorisation, give a written notice to the sponsor: (i) setting out a refusal of the request with reasons; (ii) accepting the request; or (iii) accepting the request subject to conditions specified. The procedure by which applications for authorisation are made is set out in Sch 5 of the 2004 Regulations. By Regulation 31(1)(b), the licensing authority may suspend or terminate a trial if it has information raising doubts about the safety or scientific validity of the trial.

42. As to REC opinions, Regulation 15 of the 2004 Regulations provides that the REC may seek further information to give an opinion (Regulation 15(2)) and give a favourable opinion subject to specified conditions (Regulation 15(3A)).

43. Regulation 15(5) of the 2004 Regulations states that the REC, in preparing its opinion, must consider the matters specified therein, including:

    (1) Whether the evaluation of the anticipated benefits and risks as required under paragraph 10 of Part 2 of Sch 1 is satisfactory and whether the conclusions are justified; and

    (2) If the subjects are to include minors, whether the research is justified having regard to the conditions and principles specified in Part 4 of Sch 1.

44. Part 2 Sch 1 of the 2004 Regulations ("**the GCP Principles**") apply to all clinical trials (under paragraph 1(1), Pt 1, Sch 1, 2004 Regulations) and are based on the Good Clinical Practice Directive (2001/20/EC). Principle 6 of the GCP Principles further states that clinical trials shall be conducted in accordance with the principles of the Declaration of Helsinki.

Ethical guidelines for clinical trials

45. A clinical trial must be conducted ethically.

46. We do not rehearse in full the ethical guidelines applying to clinical trials, of which the Defendants and Interested Parties should be aware, and upon which our clients

intend to rely. Notwithstanding the above, the following key principles are identified as forming the core bases against which the Trial should be examined.

The safety and wellbeing of participants ("the Harm Principle")

47. Regulation 28(1)(a) of the 2004 Regulations provides that no person shall conduct a clinical trial otherwise than in accordance with the conditions and principles of Good Clinical Practice. Further, Principle 1 of the GCP Principles states:

> The rights, safety and wellbeing of the trial subjects shall prevail over the interests of science and society.

48. This is supported by the GCP guidance as produced by the International Conference on Harmonisation, which provides that institutional review boards and ethics committees regulating clinical trials "*should safeguard the rights, safety, and well-being of all trial subjects. Special attention should be paid to trials that may include vulnerable subjects*".[20]

49. Pt 4, Sch 1, of the 2004 Regulations apply in relation to clinical trials involving children (paragraph 1(3), Pt 1, Sch 1, 2004 Regulations). Principle 14, Pt 4, Sch 1 requires that:

> *The clinical trial has been designed to minimise pain, discomfort, fear and any other foreseeable risk in relation to the disease and the minor's stage of development.*

50. The responsibility to avoid harm to participants rests not only on the licensing authority and the relevant REC, but on the prescribing clinicians in relation to each individual patient. Principles 4 and 9 of the Declaration of Helsinki[21] state as follows:

> (4) It is the duty of the physician to promote and safeguard the health, wellbeing and rights of patients, including those who are involved in medical research. The

[20] The current version of the ICH GCP is available at: https://www.ema.europa.eu/en/ich-e6-good-clinical-practice-scientific-guideline#ich-e6r3-principles-and-annex-1-current-version-effective-from-23-july-2025-8264. The HRA accepts that the principles in the ICH GCP should be applied proportionately in CTIMPs: https://www.hra.nhs.uk/planning-and-improving-research/policies-standards-legislation/good-clinical-practice/ (accessed 25 November 2025).

[21] World Medical Association Declaration of Helsinki – Ethical Principles for Medical Research involving Human Participants, 19 October 2024, https://www.wma.net/policies-post/wma-declaration-of-helsinki/.

physician's knowledge and conscience are dedicated to the fulfilment of this duty.

(9) …The responsibility for the protection of research participants must always rest with physicians or other researchers and never with the research participants, even though they have given consent.

51. This is supplemented by the General Medical Council ("**GMC**") guidance on clinical care, which states that clinicians must "*propose, provide, or prescribe drugs or treatment (including repeat prescriptions) only when [they] have adequate knowledge of the patient's health and are satisfied that the drugs or treatment will meet their needs*"[22]. GMC guidance in relation to prescribing off-label medication states:[23]

> *If proposing, prescribing or providing an unlicensed medicine, you must be satisfied that there is sufficient evidence or experience of using the medicine to demonstrate its safety and efficacy.*

The necessity and justification for a trial ("the Justification Principle")

52. Principles 10 and 12 of the GCP Principles emphasise the need for a risk-benefit analysis in relation to clinical trials, and for such trials to be justified:

(10) Before the trial is initiated, foreseeable risks and inconveniences have been weighed against the anticipated benefit for the individual trial subject and other present and future patients. A trial should be initiated and continued only if the anticipated benefits justify the risks.

(12) A trial shall be initiated only if an ethics committee and the licensing authority comes to the conclusion that the anticipated therapeutic and public health benefits justify the risks and may be continued only if compliance with this requirement is permanently monitored.

53. In relation to children, Principle 10, Pt 4, Sch 1, 2004 Regulations requires that:

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[22] General Medical Council, *Good medical practice,* 30 January 2024, §7d https://www.gmc-uk.org/professional-standards/the-professional-standards/good-medical-practice

[23] General Medical Council, *Good practice in proposing, prescribing, providing and managing medicines and devices*, 18 February 2021, §105a https://www.gmc-uk.org/professional-standards/the-professional-standards/good-practice-in-prescribing-and-managing-medicines-and-devices

Some direct benefit for the group of patients involved in the clinical trial is to be obtained from that trial.

54. Principle 11 further requires that in relation to children approval must been the condition that:

The clinical trial is necessary to validate data obtained:

(a) In other clinical trials involving persons able to give informed consent, or

(b) By other research methods

55. The Declaration of Helsinki states that the purposes of medical research can never take precedence over the rights and interest of individual research participants.[24] It further states that:[25]

Medical research involving human participants may only be conducted if the ***importance of the objective outweighs the risks and burdens*** *to the research participants.*

All medical research involving human participants must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with the foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.

Medical research involving human participants must have a scientifically sound and rigorous design and execution that are ***likely to produce reliable, valid, and valuable knowledge and avoid research waste.*** *[emphases added].*

56. In assessing the justification for a clinical trial, the principle of equipoise is therefore relevant. The Cass Review observed:[26]

An important principle in treatment trials is equipoise. This means that the researchers genuinely do not know which treatment is better – the existing

[24] World Medical Association Declaration of Helsinki – Ethical Principles for Medical Research involving Human Participants, 19 October 2024, Principle 7 https://www.wma.net/policies-post/wma-declaration-of-helsinki/.
[25] *Ibid*., Principles 16 to 21.
[26] Cass Review Final Report, Explanatory Box 1, at p.49.

treatment or the new treatment. If they have very strong reasons to believe the new treatment is better, or indeed, worse, they cannot ethically carry out a trial. Occasionally a trial may be stopped early if it is obvious that the new treatment is causing harm or is strongly beneficial.

The requirement of informed consent ("the Consent Principle")

57. The Declaration of Helsinki recognises that "*free and informed consent is an essential component of respect for individual autonomy*".[27] It further states that:

> *Those persons incapable of giving free and informed consent are in situations of particular vulnerability and are entitled to the corresponding safeguards. In addition to receiving the protections for the particularly vulnerable, those incapable of giving consent must only be included if the research is likely to either personally benefit them or if it entails only minimal risk and minimal burden.*[28]

58. Paragraph 3, Pt 1, Sch 1 of the 2004 Regulations states that a person gives informed consent to take part, or that a subject is to take part, in a clinical trial only if his decision "*is given freely after that person is informed of the nature, significant, implications and risks of the trial*" and is evidenced in accordance with that paragraph. Where the trial subject is a minor (under the age of 16, per Regulation 2), informed consent may be provided by a person with parental responsibility or a legal representative (paragraph 1, Pt 4, Sch 1).

59. The GCP guidance as produced by the International Conference on Harmonisation contains detailed requirements on the informed consent process.[29]

60. At common law, capacity to consent is informed by the test set out in *Gillick v West Norfolk and Wisbech Area Health Authority* [1986] AC 112 ("***Gillick***"), which

[27] World Medical Association Declaration of Helsinki – Ethical Principles for Medical Research involving Human Participants, 19 October 2024, Principles 25 to 32, https://www.wma.net/policies-post/wma-declaration-of-helsinki/.
[28] *Ibid.*, §28.
[29] International Conference on Harmonisation, ICH E6 (R3) *Guideline for good clinical practice*, 23 January 2025, §2, p.8, https://www.ema.europa.eu/en/ich-e6-good-clinical-practice-scientific-guideline#ich-e6r3-principles-and-annex-1-current-version-effective-from-23-july-2025-8264.

involved a challenge regarding contraceptive advice and treatment. The House of Lords held (at 184B) that:

> *When applying these conclusions to contraceptive advice and treatment it has to be borne in mind that there is much that has to be understood by a girl under the age of 16 if she is to have legal capacity to consent to such treatment. It is not enough that she should understand the nature of the advice which is being given: she must also have a sufficient maturity to understand what is involved.*

61. The Court of Appeal in *Bell v Tavistock and Portman NHS Foundation Trust* [2021] EWCA Civ 1363 emphasised that assessing *Gillick* competence lay within the remit of the responsible clinicians ([87]), but recognised that children suffering from gender dysphoria are "*deeply distressed and highly vulnerable*" ([85]). The Court stated ([92]):

> *We should not finish this judgment without recognising the difficulties and complexities associated with the question of whether children are competent to consent to the prescription of puberty blockers and cross-sex hormones. They raise all the deep issues identified in Gillick, and more. Clinicians will inevitably 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 by the advantages and disadvantages of the proposed course of treatment and in the light of evolving research and understanding of the implications and long-term consequences of such treatment. Great care is needed to ensure that the necessary consents are properly obtained. As Gillick itself made clear, clinicians will be alive to the possibility of regulatory or civil action where, in individual cases, the issue can be tested.*

F The claim

The Trial Protocol

62. The Trial Protocol was published on 21 November 2025.[30] The Trial is anticipated to involve approximately 226 children aged below 15 years and 11 months. The Trial is claimed to take place as a form of randomised controlled trial ("**RCT**") for the short-

[30] https://fundingawards.nihr.ac.uk/award/NIHR167530 (accessed 25 November 2025).

term duration of two years. Long-term follow-up with participants following the first two years is optional and limited to the period of funding (a further 3.5 years).

63. Children will be allocated at random to one of two groups: The first group will receive GnRHa immediately via injection every six months; the second group will receive GnRHa after a delay of one year via the same method. The Trial aims to compare observations at midpoint (one year post-randomisation) and endpoint (two years).

64. Informed consent to the Trial is obtained by interviews and clinical meetings with children and their parents, caregivers, or legal guardians, including discussion of fertility preservation options and specialist referral. The Protocol states that informed consent procedures will adhere to GCP guidelines.[31] There are no specific guidelines in the Protocol regarding consent processes for neurodiverse children.

65. The Trial does not include a placebo group on the basis that it is not possible to 'blind' participants to the effects of GnHRa, since normal pubertal processes such as menstruation will cease upon administration.[32] The Trial recognises that "*knowledge of the intervention is part of the effect*" in that "*part of the potential benefit (to be studied) of GnRHa, is patients' knowledge that their puberty is being suppressed*"[33], which suggests that any placebo effect of GnHRa will be interpreted as part of the 'benefit' of the administration of puberty blockers.

[31] Trial Protocol, v.2.2 (20 November 2025), §3.5, p.38 to 41.
[32] Trial Protocol, v.2.2 (20 November 2025), §2.1.1 p. 28.
[33] Trial Protocol, v.2.2 (20 November 2025), §2.1.1, p.28.

66. The primary outcome[34] measure of the Trial is the 'KIDSCREEN-10' questionnaire, which asks children to rate their health in general, and to answer the following ten questions:[35]

Thinking about the last week...						
1.	Have you felt fit and well?	not at all	slightly	moderately	very	extremely
2.	Have you felt full of energy?	never	seldom	quite often	very often	always
3.	Have you felt sad?	never	seldom	quite often	very often	always
4.	Have you felt lonely?	never	seldom	quite often	very often	always
5.	Have you had enough time for yourself?	never	seldom	quite often	very often	always
6.	Have you been able to do the things that you want to do in your free time?	never	seldom	quite often	very often	always
7.	Have your parent(s) treated you fairly?	never	seldom	quite often	very often	always
8.	Have you had fun with your friends?	never	seldom	quite often	very often	always
9.	Have you got on well at school?	not at all	slightly	moderately	very	extremely
10.	Have you been able to pay attention?	never	seldom	quite often	very often	always

67. The Trial includes three hip and spine bone mineral density scans, optional bone X-rays at 12-months and 24-months[36], and cognitive assessments at 3-months, 12-months, and 24-months. The Trial Protocol recognises that it is "*uncertain*" whether the one-year delay timeframe is sufficient to show differences in mental health, psychosocial, and cognitive outcomes.[37]

68. The Trial does not attempt to examine the effects of puberty blockers independent of any other treatment; tailored psychosocial care is provided alongside the administration of puberty blockers during the Trial.

[34] Trial Protocol, v.2.2 (20 November 2025), p. 2.
[35] https://www.kidscreen.org/english/questionnaires/language-versions-view-and-download/ (accessed 25 November 2025).
[36] Trial Protocol, v2.2 (20 November 2025), 4.14.7
[37] Trial Protocol, v.2.2 (20 November 2025), p.29.

The existing scientific and medical evidence

69. As above, we do not here set out in full the existing scientific and medical evidence available in relation to the administration of puberty blockers on children which our clients intend to rely upon. Much of the review of this evidence has already been undertaken by the Cass Review and related work by National Institute for Health and Care Excellence ("**NICE**""), the CHM, the Gender Dysphoria Multi-Professional Review Group ("**MRPG**"), the University of York, and the HHS Review. The following selected evidence is set out as an outline of the medical and scientific evidence available.

Evidence on harm ("the Harm Evidence")

70. The primary harm caused by puberty blockers is its impact on sexual and reproductive health. The prevention of the normal development of primary and secondary sexual characteristics, which is itself the purpose of prescribing GnRHa, interrupts an essential process for physically healthy children.[38] The CHM report notes that biologically male children "*who subsequently decide not to transition will likely have an underdeveloped penis throughout adulthood*", and that even where transition is desired, "*an underdeveloped penis can make it difficult to surgically create a vagina in adulthood*".[39] It is expected that treatment with puberty blockers will also interfere with the development of female genitalia, leading to problems in achieving satisfactory vaginal intercourse. Normal breast development in biologically female children, which even if subsequently enhanced by breast surgery, will irreversibly impair the ability to breastfeed.

71. The administration of GnRHa will also prevent the development of reproductive function and fertility in children. The evidence in relation to fertility preservation indicates that gamete retrieval is unlikely at Tanner stage 2 as neither sperm nor ova have matured. Similarly, the CHM reported observed that "*for transgender men, prepubertal cryopreservation of ovarian tissue is considered experimental, with oocyte preservation possible once perimenarchal*"[40], and that azoospermia and

[38] The explanation of these harms is drawn from the letter of Professor Curtis, Honorary Professor at the UCL Genetics Institute, which was signed by nine other academics and clinicians and sent to the HRA on 19 March 2025 for consideration by the PATHWAYS REC.
[39] CHM Report, §36.
[40] CHM Report, §32

abnormal sperm motility had been reported.[41] This means it is unlikely that the children's fertility can be effectively preserved, even if it is desired.

72. The existing evidence also indicates significant potential risks of harm to children on puberty blockers, including but not limited to neuropsychological development and bone health. These are distinguished from the expected harms to sexual and reproductive health above, which will almost inevitably occur.

73. In relation to cognitive development, the CHM report observed:

> *GnRH agonists provided as medicines can cross from the blood to the brain, and thus long-term GnRH agonist treatment may influence brain function and have cognitive and behavioural effects. In animal models studied in a developmental period relevant to puberty, GnRH agonists reduced spatial memory, increased anxiety and depressive behaviours in mice, and had an impact on nerve activity in an area of the brain called the hippocampus which is involved in stress, depression and cognition. GnRH agonists decreased reproductive organ weight with potential effects on reproduction. It is not known whether these animal observations may have corresponding clinical relevance in children and young people.*[42]
>
> *During representation, CHM was provided with valid hypotheses that cognition may be irreversibly impacted by the use of GnRH agonists in the adolescent age range (references 6 and 7). However, further evidence is required to explore this important human development and should be included in the future research agenda.*[43]

74. The letter sent by Dr Cass to NHS England on 19 July 2022 stated:

> *A further concern is that adolescent sex hormone surges may trigger the opening of a critical period for experience-dependent rewiring of neural circuits underlying executive function (i.e. maturation of the part of the brain concerned with planning, decision-making and judgment). If this is the case, brain maturation may be temporarily or permanently disrupted by puberty blockers, which could have significant impact on the ability to make complex*

[41] CHM Report, §19, referring to Yellow Card safety reporting data.
[42] CHM Report, §23. See also Appendix 1 of the report.
[43] CHM Report, §29.

risk-laden decisions, as well as possible longer-term neuropsychological consequences.

75. A 2024 literature review by Professor Baxendale concluded that "*there is no evidence that cognitive effects are fully reversible following discontinuation of treatment. No human studies have systematically explored the impact of these treatments on neuropsychological function with an adequate baseline and follow-up. There is some evidence of a detrimental impact of pubertal suppression on IQ in children*". These concerns have particular weight in relation to neurodiverse children, where the differences in brain development between autistic or other neurodiverse children and a neurotypical child have yet to be fully understood or explored.

76. In relation to bone health, the CHM report concluded that "*it is widely accepted that there are detrimental impacts on bone mineralisation*".[44] Similarly, the systematic review University of York ("**the York Review**") concluded that "*there is moderate-quality evidence, albeit mainly from pre-post studies, that bone density and height may be compromised during treatment*". [45] The review of evidence by NICE in October 2020, whilst noting the low quality of studies available, conclude that GnRHa may reduce the expected increase in bone density which is expected during puberty.[46] The HHS Review concluded:

> *When puberty blockers are followed by cross-sex hormones, as has occurred in studies over 90% of the time, bone mineralisation will increase, but a critical developmental window for bone density accrual during adolescence may have been missed or foreshortened, as bone density accrual slows down during the 20s and then begins to decline. These patients may never reach the peak bone density they otherwise would have achieved. Research on medium and long-term outcomes is limited.*[47]

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[44] CHM Report, §26, referring to Ludvigsson (2023), Thompson (2023), Tayloer (2024, and Miroshnychenko (2024).
[45] University of York, *The epidemiology, care pathways, outcomes, and experiences of children and adolescents experiencing gender dysphoria/incongruence: a series of linked systematic reviews and an international survey*, p.6.
[46] NICE, *Evidence review: Gonadotrophin releasing hormone analogues for children and adolescents with gender dysphoria*, October 2020, ("**NICE Review**"), p.13.
[47] HHS Review, p.120.

77. Other evidence in relation to harms include cancer,[48] the development of idiopathic intracranial hypertension,[49]lack of sexual function,[50] sterile abscesses, leg pains, headaches, and weight gain,[51] besides the obvious harm that normal development of puberty would have been impeded in children whose gender incongruence may have resolved naturally upon puberty or adulthood, but who are influenced to progress along the hormonal and surgical transition pathway due to the administration of puberty blockers. As the Cass Review noted:

> *For the majority of young people, a medical pathway may not be the best way to achieve [the aim of helping young people to thrive and achieve their life goals].*[52]
>
> *Moreover, given the vast majority of young people started on puberty blockers proceed from puberty blockers to masculinising/feminising hormones, there is no evidence that puberty blocker buy time to think, and some concern that they may change the trajectory of psychosexual and gender identity development.*[53]

Lack of evidence of justification ("the Justification Evidence")

78. The existing evidence indicates that the administration of puberty blockers is of limited benefit to children.

(1) The York Review did not identify any good quality evidence of the benefit of puberty blockers. No changes in gender dysphoria or body satisfaction were demonstrated.[54]

(2) The NICE Review concluded that puberty blockers do not affect gender dysphoria, anger, anxiety, or body image. They may reduce depression and

[48] CHM Report, p.28 referring to Chandhoke (2018), Crowley (2022), and Panagiotakopoulos and others (2020).
[49] CHM Report, §19, referring to Yellow Card safety reporting data.
[50] https://pubmed.ncbi.nlm.nih.gov/36120756/
[51] NICE Review, p.32, referring to Khatchadourian et al (2014).
[52] Cass Review Final Report, §66.
[53] Cass Review Final Report, §83.
[54] Cass Review Final Report, §81.

improve psychosocial impact, but the quality of evidence overall was of very low certainty.[55]

(3) As to the risk of suicide, the Cass Review observed that the suicide rate in gender-referred youth was higher than in the general population, but this difference levelled out when specialist mental health treatment was taken into account, although firm conclusions could not be drawn given the small numbers reviewed.[56] The Review further stated, "*it has been suggested that hormone treatment reduces the elevated risk of death by suicide in this population, but the evidence found did not support this conclusion*".[57]

79. Moreover, the design of the Trial itself is unlikely to yield significant value in bridging the knowledge gaps in relation to gender incongruence and its treatment, for reasons including that:

(1) The short-term length of the Trial will not sufficiently address the primary gap in knowledge base regarding long-term effects of puberty blockers. The main outcomes of interest, for example, in relation to bone density, will require assessment of children into adulthood, rather than a comparison between 15- and 17-year-olds. The limitations of the Trial results in this respect are acknowledged by the Trial protocol as set out in paragraph 0 above, but the offered rationale for proceeding nonetheless is that "*long-term effects can only be evaluated following research examining short- or medium-term effects*".[58]

(2) As set out in paragraphs 65 and 68 above, the Trial outcomes will be affected by, among others: (i) bias engendered by the lack of a blind control group such that any placebo effect will be attributed to the administration of the treatment; (ii) the confounding factor of psychosocial intervention being provided alongside the hormone treatment, as well as the impact of other factors such as social transition,[59] particularly where the primary outcome expected relates to self-reports by children on emotional wellbeing; and (iii) the likelihood that the

[55] NICE Review, pp. 4 to 5, and 13.
[56] Cass Review Final Report, §5.66.
[57] Cass Review Final Report, §86.
[58] Trial Protocol, v2.2. (20 November 2025), at p.27.
[59] See for example, the observation of the Cass Review Final Report at §12.31 that "*it is unclear whether [social transition] alters the trajectory of gender development, and what short- and longer-term impact this may have on mental health*".

administration of treatment itself may change the trajectory of gender identity development in children.

(3) The Trial aims to "*determine the short/medium-term benefits and risks of GnRHa…across quality of life, mental health, gender identity/dysphoria, body satisfaction, cognition, brain development and physical effects including bone mineral density*" but defines its primary outcome in relation to the limited and basic 10-question KIDSCREEN10 questionnaire which is exclusively self-reported by children.

(4) The Trial does not effectively allow valuable comparative assessment to be made between participants who are administered with puberty blockers and participants who are not, as both randomised groups will receive puberty blockers and are differentiated only by timing. The PATHWAYS Horizon Intensive group is not randomised and does not provide an adequate control comparison.

80. Alternatives exist which will assist in developing a knowledge base in relation to gender incongruence and its treatment. These include, but are not limited to:

(1) The Cass Review had proposed a data linkage study which would assess the management and outcomes for children and young persons who had accessed the GIDS previously. The study could not be progressed in time for the Final Report due to lack of cooperation by NHS gender clinics. Dr Cass, in her letter dated 20 March 2024, made several recommendations to NHS England to pursue this option.[60]

(2) There appears to be a study by the Tavistock and Portman NHS Foundation Trust involving longitudinal investigation of outcomes and predictors of outcome for children and young people referred to UK gender identity services. It has been funded in the sum of £1,799,292.15.[61]

(3) Further research into psychotherapy and other psychosocial interventions have been recommended by the Cass Review and the HHS Review. The Cass Review observed, "*A problem that has become increasingly apparent as the Review has progressed is that research on psychosocial interventions and longer-term outcomes for those who do no access endocrine pathways is as weak as*

[60] Cass Review Final Report, Appendices 12 and 13.
[61] https://fundingawards.nihr.ac.uk/award/17/51/19

research on endocrine treatment. This leaves a major gap in our knowledge about how best to support and help the growing population of young people with gender-related distress in the context of complex presentations."[62] Similarly, the HHS Review observed that psychotherapy is a non-invasive alternative to hormone and surgical intervention, which has not been shown to have adverse effects.[63]

(4) Animal studies on puberty blockers are ongoing, which the HHS Review suggests "*could help clarify how hormonal interventions affect fertility, brain development, bone development (including future risk of fracture) and cardiovascular outcomes. Such studies also could help clarify to what extent and under what conditions fertility can be recovered after suppression by hormonal interventions*."[64]

81. Our clients' position as to the lack of ethical (and hence legal) justification for the Trial is neatly encapsulated by the conclusion of the HHS Review as follows (emphasis added):

> *It is not ethical to subject adolescents to hormonal and surgical interventions used in paediatric medical transition, even in a research trial,* ***until and unless the state of the evidence suggests a favourable risk/benefit profile for the studied intervention, and the researchers have well-grounded confidence that the foreseeable "risks and burdens have been adequately assessed and can be satisfactorily managed."*** *As explained in this Review, the state of the science does not support a favourable risk/benefit profile, nor does it give researchers a basis for confidence that the risks of paediatric medical transition can be satisfactorily managed.*[65]

Challenges to informed consent ("the Consent Evidence")

82. In view of the complex implications of the administration of puberty blockers on a child's long-term physical, emotional, and social wellbeing, there are significant

[62] Cass Review Final Report, §88.
[63] HHS Review, p.16.
[64] HHS Review, p.244 to 245.
[65] HHS Review, p.245.

challenges in ensuring that the vulnerable children participating in the Trial can provide informed consent or assent.

83. These challenges are well-documented. In relation to fertility, for example, the CHM report observed:

> *Given the complexities, probable finality, and experimental nature of these considerations, Gillick competence would be more challenging to achieve than in many other therapeutic areas in paediatric practice. Provision of adequate consent in relation to fertility has been an identified issue raised by the GMC with private practitioners providing gender services.*[66]

84. Similarly, the Cass Review states:[67]

> *Although as described in Chapter 4 in the Bell v Tavistock judgment, the Court of Appeal rejected the High Court's guidance on whether particular age groups would be likely to be able to make such decisions, these decisions would be uniquely difficult for children to be able to make for themselves, for all the reasons set out above.*
>
> *Even at Tanner stages 2-3, young people have had minimal experience of their own biological puberty, and such experience as they have had may have been distressing for a wide range of reasons.*
>
> *Once on puberty blockers, they will enter a period when peers are developing physically and sexually whilst they will not be, and they may be experiencing the side effects of the blocker. There are no good studies on the psychological, psychosexual and developmental impact of this period of divergence from peers.*

85. The Trial Protocol states "*For children, informed assent will include demonstrating understanding, retention, and the ability to weigh up the potential benefits and risks of participation, and to communicate their decision freely and without coercion. Clinicians must document the young person's and parent(s)' understanding of the trial, including direct quotes where possible, and ensure that both individual and joint discussions have taken place.*" Detailed information is not provided as to how consent discussions and processes are to be managed by the Trial, such as what

[66] CHM Report, §33.
[67] Cass Review Final Report, §§16.25 to 16.31.

risks and benefits children and their parents will be informed of and in what terms, particularly where any adequate explanation of risks must involve complex medical information.

86. Moreover, there is evidence that most individuals have decided whether to take part in a trial before attending the interview or consultation process at which they are provided with further information about the trial. Thus, the information provided such consultations is not in fact used to weigh the benefits and disadvantages of participation.[68] This is especially likely to occur in relation to the Trial, where, as the Cass Review and the CHM agree,[69] the expectations of children and their parents have been significantly shaped by poorly evidenced narratives regarding the benefits of puberty blockers. As the HHS Review notes, hormonal and surgical interventions have been described as "*medically necessary*" and even "*lifesaving*" despite the poor evidence base for such treatment.[70]

87. Further, particular consideration must be given to neurodiverse children, given their likelihood of incidence within any Trial cohort. Children experiencing neurodevelopmental disabilities such as autism spectrum disorder struggle with social functioning and acceptance, giving rise to specific challenges including ease of influence or manipulation, hyper-focusing on chosen issues, low levels of self-awareness or self-reflection, and impaired ability to assess risks and dangers. As stated above, there is no indication in the Trial Protocol of a recognition of these challenges, nor of whether and how consent processes will be adapted to respond.

The grounds of challenge

88. We note that this Trial is unlike any other clinical trial of which we or our clients are aware, in at least four respects:

    a. As set out above, gender incongruence as understood in the Trial Protocol, based on the ICD-11 definition, is a *sui generis* condition – neither a physical disease or illness, nor a mental health disorder. The Trial therefore proposes to provide a pharmacological intervention which prevents a

[68] Jackson, *Law and the Regulation of Medicines* (2012), referring to JA Fisher, *Medical Research for Hire: The Political Economy of Pharmaceutical Clinical Trials* (2009) 192.
[69] See paragraphs 27(1) and 31 above.
[70] HHS Review, p.9.

physiologically normal process in order to treat a presentation which involves neither physical nor mental ill-health. This is not medicine as it is usually understood.[71]

b. The intervention being studied in the Trial is one which has otherwise been permanently banned due to concerns about unacceptable risks to patient safety. The Trial is only possible because it falls within an exception in the relevant legislation.

c. The proposed benefit for the clinical group in the Trial is neither clearly identified nor understood; indeed, a core purpose of the Trial is to work out what benefits there are, if any, to this intervention.

d. The Trial has been approved before the conclusion of other much less risky research, most obviously (i) animal trials; and (ii) the data-linkage study recommended in the Cass Report.

89. It was incumbent on the REC and MHRA to recognise these highly unusual aspects of this Trial and explain how and why in the light of them the Trial is capable of being approved within the usual framework of the 2004 Regulations. Nothing in the publicly available documentation addresses or confronts these aspects substantively.

90. Our clients intend to challenge the Approval of the Trial as being unlawful on familiar public law principles on the following grounds, which are based on the Harm, Justification, and Consent Principles ("**the Ethical Principles**") and the Harm, Justification, and Consent Evidence ("**the Evidence**") set out above. These grounds are subject to amendment following the disclosure required by the Defendants' duty of candour and/or requested below at (I).

(1) Illegality

91. The Trial is unlawful because it fails to comply with the GCP Principles set out within the 2004 Regulations. In order to be approved, the REC must consider (regulation 15(5)(b)) whether the evaluation of the anticipated benefits and risks

[71] With the exception of cosmetic or aesthetic medicine, which is prohibited for under-18s where there are any significant risks – see for example the Botulinum Toxin and Cosmetic Fillers (Children) Act 2021.

as required under Part 2 of Sch 1 (the GCP Principles) is satisfactory and whether the conclusions are justified.

92. The only reference to ethics in the Trial Protocol is at section 12 (page 82) which simply states the Trial "*will be conducted in compliance with the principles of the Declaration of Helsinki (1996), the principles of GCP and all of the applicable regulatory requirements (specify current legislation)*." There is no further detail or explanation provided. The fact that an obvious placeholder '(specify current legislation)' is still in the final version and was not picked up on review or updated before publication is a worrying indication that very little attention has been paid to this element of the Trial or this part of the documentation.

93. As set out in the Harm Evidence, the Trial fails to safeguard the rights, safety, and wellbeing of its subjects, who constitute highly vulnerable children, by subjecting them to treatment which:

(1) will irreversibly impact their sexual and reproductive health, including by damaging fertility and interrupting the development of essential reproductive organs;

(2) risks permanent deterioration in cognitive development and bone mineralisation as well as possible cancer, idiopathic intracranial hypertension, and haemorrhage;

(3) has known <u>common</u> side effects listed within the Trial Protocol which include anxiety, depression, unexpected PV bleeding, hot flushes, weight gain, dizziness, reduced libido, ovarian and fallopian tube disorders, and diabetes mellitus. Significantly, the majority of the side effects listed in the Protocol were reported by adults, which underlines the novel nature of such treatment for children.

94. Moreover, the harms of the Trial are such that prescribing such treatment is likely to conflict with a physician's duties under the GMC Guidelines and the Declaration of Helsinki, as clinicians cannot be assured of that "*there is sufficient evidence or experience of using the medicine to demonstrate its safety and efficacy*".

95. On the harms basis alone, the Trial cannot meet the requirements of the GCP Principles and should be considered unlawful.

96. However, even where a justification assessment is undertaken, the Trial is unlawful given the limited known benefits of treatment with puberty blockers, where there is a notable lack of evidence regarding any beneficial impact on gender dysphoria, body image, and suicide risk. Indeed, the single-sentence reference in the Trial Protocol to side effects for children states, "*in under 18s, common side effects that have been reported are depression and altered mood*"[72], which indicates that treatment may in fact worsen a child's psychological symptoms. Further, as to wider community or scientific benefit (which in any event, cannot override the rights and interests of the patient), the flawed design of the Trial means that it does not answer the key question of whether GnRHa treatment is beneficial in the long-term, if at all.

97. It follows from the above that the Trial cannot rationally be considered to be in the best interests of the vulnerable child subject or the relevant group of children. In such circumstances, the weight given to parental consent, even if informed, should be duly tempered,[73] particularly as "*parents and patients may be vulnerable to unsubstantiated promises of hope*"[74] especially in situations where, as here, parents may have faced substantial distress in attempting to manage gender incongruence against a backdrop of limited support and significant isolation. Moreover, as the Trial Protocol notes and the Cass Review explored in detail, the "*toxicity of the debate is exceptional*" around these issues (Cass Final Report p13) and in relation to use of GnRHa for gender incongruence has "*elicited differing and often strongly held and polarised views*" (Trial Protocol paragraph 1.2.2). In these circumstances, it is unfair to parent and child for treatment which is risky and almost certainly harmful, to be offered as a means of potential benefit in the Trial. Furthermore clinicians do not know whether the treatment will benefit a particular child. (Cass 16.11). It is simply not possible to comply with the requirement that the treatment will 'either personally benefit them or if it entails only minimal risk and minimal burden'. (para 56 supra). The Consent Evidence simply reinforces the reality that Consent Principles cannot meaningfully be adhered to in the Trial.

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[72] Trial Protocol, v2.2 (20 November 2025), §8.2.
[73] See for example, the series of cases involving Charlie Gard ([2017] EWHC 972; ECtHR Case No. 39793/17; [2017] EWCA Civ 410; and [2017] EWHC 1909).
[74] Brazier et al, *Medicines, Patients and the Law* (2023, 7th edn.), §18.09 referring to Cave and Nottingham, *Who Knows Best (Interests)? The Case of Charlie Gard* (2018) 26 Med Law Rev 500, 503.

98. Moreover, as set out above, for clinical trials which relate to children there are several additional necessary conditions in the 2004 Regulations which must be fulfilled before approval can be given. Two of these are particularly relevant. First (Principle 10) is that some direct benefit for the group of patients involved in the clinical trial is to be obtained. In this Trial no direct benefit has been identified in advance. Indeed, the primary objective is to identify the short/medium-term benefits (as well as risks) and the secondary objective is to understand which potential outcomes are the priority goals for GnRHa treatment. The Trial Protocol notes at paragraph 1.2.2 that "*several possible benefits of GnRHa were hypothesised for CYP experiencing gender incongruence*", namely reducing feelings of distress, making any subsequent physical transition to the opposite gender more straightforward, and providing 'time to think'. However, as the Protocol acknowledges (see para 1.5.1), and as summarised above in the Evidence, there is a very limited evidence base for these benefits. Rather (see p22 of the Protocol) decisions about care have recently been made "*in the context of very limited evidence and against a background of strong personal preferences.*" In these circumstances, it seems clear that there is no compliance with Principle 10.

99. It seems equally clear that the second relevant principle, Principle 11, has not been fulfilled. This requires that a trial is <u>necessary</u> to validate data obtained in other clinical trials or by other research methods. However, the Trial Protocol recognises that there have been no previous rigorous evaluations of non-endocrine intervention for CYP with gender incongruence (paragraph 1.2.2, p22) nor previous randomised controlled trials (paragraph 1.5.1, p25), nor retrospective studies (paragraph 1.5.2). There is therefore no extant data, whether obtained in other clinical trials or by other research methods, which this Trial is necessary to validate.

100. For all the above reasons, the Trial violates the Ethical Principles and is unlawful.

<u>(2) Irrationality</u>

101. For similar reasons, the Approval is *Wednesbury* irrational. No reasonable licensing authority or REC could have considered that the Trial should be approved upon proper application of the Ethical Principles to the Evidence.

102. At the outset, it is noted that the Court will adopt a heightened review in the context of decision-making where vulnerable children are involved.[75]

103. It is also noted that for the four reasons set out above this Trial is unlike any other clinical trial, and therefore requires cogent explanation for how it could be approved under the standard legal framework. Yet none of those four issues have been acknowledged, let alone has any explanation been given for how they are resolved in a manner compatible with the Ethical Principles.

104. As stated above, Regulation 15(5) of the 2004 Regulations requires the PATHWAYS REC to give particular consideration to whether risk-benefit assessment of the Trial is satisfactory and its conclusions are justified, and whether the research is justified having regard to the consent conditions in Part 4, Sch 1. Due to refusals of disclosure by the MHRA and the HRA in the FOIA process or otherwise, our clients have not had sight of the material considered by the Defendants in their assessment of the Trial. However, on the basis of the publicly available documents and for the reasons already stated, the Trial cannot satisfy a risk-benefit assessment on any analysis, and cannot be justified in light of the limited results it is likely to produce.

105. To the extent that a risk-benefit assessment is demonstrated in the Trial Protocol, the Protocol recognises that "*the currently available evidence (described above) is inconsistent in whether GnRHa has positive short-term benefits*"[76] and appears therefore to accept that there is no meaningful evidence of material benefit to trial subjects from the treatment. However, despite the long list of risks arising from GnRHa treatment (which in any event, our clients contend is flawed as being incomplete), the Protocol suggests that there is 'clinical equipoise' in respect of GnRHa treatment.[77] There is no explanation of how the 'benefits' of the Trial are thought to balance or outweigh the risks. *Prima facie*, acceptance by the Defendants of this risk-benefit assessment as satisfactory is irrational.

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[75] See, for example, R (Hillingdon London Borough Council) v Lord Chancellor [2008] EWHC 2683 (Admin) per Dyson LJ at §50 ("*at the heart of this case is the risk posed to vulnerable children")* and §67 *("I agree that, because the interests of vulnerable children are potentially at stake, the court should consider the issue of irrationality with anxious scrutiny*").
[76] Trial Protocol, v2.2 (20 November 2025), p.27.
[77] *Ibid*.

106. Further, as set out in the Justification Evidence above, it is equally irrational to consider that the Trial is justified.

(1) §2.4.1 of the Protocol states that its primary objective is "*To determine the short/medium term benefits and risks of GnRHa for puberty suppression in CYP with gender incongruence. This will take a comprehensive approach to domains of possible benefit and risk, including quality of life, mental health, gender identity/dysphoria and body satisfaction, impact on cognition and brain development and physical effects including bone density.* The Trial purports to observe medium-term effects in subjects and defines this as being the trial endpoint (i.e. two years).[78] It is not understood how two years in an average lifespan of c.70 years could be considered 'medium-term'. In fact, the Trial's objective observations are limited to short-term assessments; and its subjective observations are largely based on self-reporting of subjective emotional health by children.

(2) §2.4.2 of the Protocol sets out five further secondary objectives. Objective (1) is to understand the priority goals for CYP receiving GnRHa. This can be achieved by an observational study. Objective (2) is to describe the characteristics of those seeking GnRHa; again, achievable by an observational study. Objective (3) is to describe decisions which CYP make at the end of GnRHA in terms of gender care, such as moving to cross-sex hormones or pausing endocrine interventions. There is already evidence in this sphere from the GIDS that a large majority proceed to cross-sex hormones.[79] Objective (4) is to link trajectories of brain development to cognitive measures, which does not require GnRHa treatment. Objective (5) is simply to engage CYYP and their parents in study methods to promote longer-term follow up.

(3) §2.4.3 of the Protocol set out the 'exploratory' objectives of the Trial, which relate to risk-benefit profiles for GnRHa treatment, based on age, Tanner stage, birth-registered sex, neurodiversity, and length of treatment. The evidence on these outcomes will be limited given the narrow category of subjects and the short duration of the Trial.

[78] Trial Protocol, v2.2 (20 November 2025), p.31.
[79] See, for example, the Cass Review Final Report at §2.20, §§13.11 to 13.12.

107. None of the identified objectives is capable of justifying subjecting vulnerable children to the actual harms and risk of harms (established by evidence that does not appear to be disputed, and has not been substantively addressed) in the Trial. It is irrational to conclude otherwise.

(3) Failure to have regard to relevant considerations/breach of the *Tameside* duty of reasonable inquiry

108. In determining whether the Trial should be approved, the Defendants were expressly required in the 2004 Regulations to have regard to the Evidence (in respect of harms, justification, and consent), which is highly relevant to the Approval, particularly as regards the ethical principles on clinical trials and the risks of harm to child subjects.

109. Insofar as the Defendants were unaware of the Evidence, they are in breach of the duty in *Secretary of State for Education and Science v Tameside MBC* [1977] AC 1014 ("***Tameside***") to take into account all relevant considerations and to take reasonable steps to obtain relevant information to performs its functions.

110. This is particularly so in circumstances where our clients are aware that several interested parties, such as the Clinical Advisory Network on Sex and Gender ("**CAN-SG**") and Professor David Curtis of UCL, wrote to the HRA setting out various concerns along the lines of the Evidence set out above, and to the best of our knowledge none of this was passed to the REC.

111. Moreover, on behalf of our clients we have engaged in extensive correspondence between February and October 2025 with the HRA, MHRA and sponsors of the Trial making requests for information about the regulatory and approval processes and asking for opportunities to provide input. These requests were all refused. This refusal to engage was inconsistent with the statutory obligation on the HRA to promote transparency in clinical research under s.110(2)(b) of the Care Act 2014. It is all the more unjustifiable in circumstances where the subject of this Trial is one of the most controversial and debated in current healthcare, and therefore where transparency and engagement with those who have concerns is all the more essential. This constitutes a clear breach of the *Tameside* duty to take reasonable steps to obtain relevant information to perform a statutory function. The HRA and MHRA were directly offered an opportunity to engage with the Evidence (and issues

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to which it gives rise) and failed to do so, including apparently deliberately deciding to withhold that from the full REC.

112. The two most obvious examples of areas in which there has been a failure to give adequate consideration to relevant factors or take reasonable steps to obtain relevant information are (a) the failure to undertake the data-linkage study recommended by Dr Cass (Recommendation 5), which would shed significant light on long-term harms, an essential matter about which to have better information before it is possible to decide whether the Trial should be approved; and (b) the failure to analyse existing animal study data and consider further animal studies first, particularly in relation to effects on bone density, cognition and fertility.

113. The reason for the delay in undertaking the data-linkage study appears (see paragraph 92 of the final Cass Report) to have been lack of cooperation from the NHS adult gender clinics. This is not an adequate reason to proceed with the Trial first. Approving the Trial when there is a much less risky alternative that would provide important information that would inform the approval process is a clear failure to comply with the *Tameside* duty.

114. Various concerns raised about GnRHa side-effects from animal studies were highlighted in the CHM advice and yet there is nothing in the publicly available information about the Trial approval process to suggest that this was taken into account or further research using animals considered. The Helsinki Declaration (principle 21) expressly requires that research should be informed by animal experimentation where appropriate.

115. Further or in the alternative, where in fact the Evidence was within the Defendants' knowledge, they failed to give adequate consideration to it, despite it being highly relevant, for the reasons already stated above.

(4) Breach of the duty to give reasons

116. The Defendants are in breach of the common law duty to give reasons for their decision, which applies in this situation. As set out in *Oakley v. South Cambridgeshire District Council* [2017] EWCA Civ 71 reasons should be give unless there is a proper justification for not doing so, and where a decision is aberrant or there is a legitimate expectation that reasons will be given, a duty to give reasons

will arise. In relation to clinical trials, there is a legitimate expectation that reasons will be given due to the legislation underpinning the Approval which clearly places an emphasis on transparency – for example, Regulation 15(9) of the 2004 Regulations requires the REC to publish a summary of its opinion; Regulation 27B of the 2004 Regulations allows the licensing authority to publish information regarding an approved clinical trial, including the REC's opinion and the request for trial authorisation; and s.110(2) of the Care Act 2014 (as above) recognises the HRA's duty to promote transparency. This is logical, given that there is public interest in scrutiny of the approval (or refusals) of clinical trials, particularly where public funds are invested. The Defendants are performing a public, quasi-judicial function in assessing whether trials should be approved, and in the absence of reasons provided, these decisions cannot be scrutinised or challenged, thus being contrary to the principle of fairness.[80] Moreover, the significance of the Approval is such as to weigh heavily in favour of a duty to give reasons, as it impacts upon the physical integrity of a large number of vulnerable individuals.[81]

117. The Approval is also aberrant in that, for all the reasons set out above, it appears to be unlawful and irrational and to have failed to take into account relevant considerations. In order, therefore, to have any prospect of being lawful there need to be cogent reasons provided.

118. To date, despite the multiple requests for information from our clients to the MHRA and the HRA, there has been no disclosure as to what information the Defendants considered in issuing the Approval, nor any explanation at all as to their reasons for doing so. All that is known about the Approval is that the PATHWAYS REC issued a 'Further Information Favourable Opinion'. This is clearly insufficient and does not begin to meet any of the requirements set out in the classic summary in *South Bucks District Council v. Porter* [2004] 1 WLR 1953 at [36]: it is not intelligible nor adequate, it does not enable the reader to understand why the matter was decided as it was and what conclusions were reached on the principal important controversial issues.

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[80] See, for example, *R (Savva) v Kensington and Chelsea Royal LBC* [2010] EWCA Civ 1209, where the imposition of a duty was explained solely by reference to the fact that absence of explanation would make it impossible for the decision to be challenged (as described in Auburn et al, *Judicial Review* (2013), §10.19).
[81] See, for example, *R (Wooder) v Feggetter* [2002] EWCA Civ 554, involving the compulsory medical treatment of a non-consenting adult.

(5) Human Rights considerations

119. **Finally**, our clients further note that the Approval of the Trial is also likely to be unlawful for breach of s.6 of the Human Rights Act 1998 in that the Trial constitutes an unjustified and disproportionate interference with the Article 8 rights of the vulnerable child participants under the European Convention of Human Rights, including read with Article 14 given (as set out above) the disproportionately high numbers of children in this cohort with neurodevelopmental disabilities such as Autism Spectrum Disorder.

120. It is accepted that there are gaps in knowledge and evidence regarding certain effects of puberty blockers on children. Nevertheless, mere knowledge gaps and patient demand[82] cannot justify administering experimental treatment on children that appears liable to cause significant harm and be contrary to their best interests. The existing evidence already indicates that the benefits of such treatment are limited, that irreversible impact on sexual and reproductive health will occur, and that the other potential harms arising from such treatment may be severe.

121. On that basis, the necessary justification for a Trial which administers unlicensed medication of uncertain impact on vulnerable children has not been shown, particularly where the Trial itself cannot yield information on long-term effects and where alternatives can be pursued including those which may increase certainty as to the scientific and evidential basis for such treatment.

G Action the Defendants are expected to take

122. To avoid litigation, our clients ask that the MHRA terminate its authorisation of the Trial and/or the PATHWAYS REC vary its opinion to issue an unfavourable opinion in respect of the Trial on the basis of the reasons given above. In any event, pending the resolution of these proceedings, they ask that the MHRA suspend the Trial under Regulation 31(1)(b) of the 2004 Regulations.

123. Our clients also request an indication of the likely timetable for recruitment of participants into the Trial and commencement of any treatment or interventions.

[82] Which has recognisably been shaped by societal expectations and pressures, as set out in paragraphs 20 and 24(1) above.

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Depending on how imminent these steps are, our clients may wish to seek interim relief and an expedited hearing and so we seek clarity urgently on this point.

H Alternative dispute resolution

124. While our clients are open to engaging in meaningful discussion to resolve this matter without recourse to litigation, the urgency and significance of the issues raised may make judicial determination necessary. Please let us know if you wish to arrange such discussion.

I Details of information sought

125. Our clients repeat their request for disclosure of all documents relating to the decision-making process and final approval of the PATHWAYS clinical trial by the MHRA and the PATHWAYS REC, including but not limited to:

(1) The application for MHRA authorisation of the Trial;

(2) The PATHWAYS REC's opinion

(3) Any documents and/or information referred to in the above material;

(4) All documents, correspondence and other information submitted to the PATHWAYS REC;

(5) All documents, correspondence and other information received by the HRA and/or by the chair of the PATHWAYS REC but not shared, in whole or in part, with the members of the PATHWAYS REC; and

(6) Any other material considered by the Defendants in relation to the Approval of the PATHWAYS Trial.

126. Our clients reserve the right to amend the grounds of their claim following disclosure of this material.

J Address for reply and service

127. We will accept service of documentation on behalf of our client.

K Proposed reply date

128. Please provide a response within 14 days of this letter as required under the Pre-Action Protocol for Judicial Review.

129. If we do not receive a response within that time, or if your response fails adequately to address the matters raised, our client reserves the right to issue judicial review proceedings, including an application for interim relief, without further notice.

Yours faithfully

Conrathe Gardner LLP

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