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Ethics and social acceptability of a proposed clinical trial using maternal gene therapy to treat severe early-onset fetal growth restriction

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KEYWORDS: ethics; fetal growth restriction; gene therapy; pregnancy; qualitative; translational medicine

ABSTRACT

Objective To evaluate the ethical and social acceptability of a proposed clinical trial using maternal uterine artery vascular endothelial growth factor (VEGF) gene therapy to treat severe early-onset fetal growth restriction (FGR) in pregnant women.

Methods We conducted a literature review on the ethics and legality of experimental treatments in pregnant women, in particular advanced therapeutics. Issues that were identified from the literature helped develop interview guides for semistructured, qualitative interviews, carried out in four European countries, with 34 key stakeholders (disability groups, professional bodies and patient support groups) and 24 women/couples who had experienced a pregnancy affected by severe early-onset FGR.

Results The literature review identified two main questions: 'is it ethical to give a pregnant woman a potentially risky treatment from which she does not benefit directly?' and 'is it ethical to treat a condition of the unborn child, who may then be born with a serious disability when, without treatment, they would have died?'. The review concluded that there were no ethical or legal objections to the intervention, or to a trial of this intervention. Overall, respondents viewed the proposed trial in positive terms. Women were generally interested in participating in clinical trials that conferred a potential benefit to their unborn child. The risk of disability of the premature child was a concern, but not considered a major stumbling block for maternal VEGF gene therapy.

Conclusions This study did not identify any fundamental or insurmountable objections to a trial of maternal gene therapy for severe early-onset FGR. Copyright © 2016 ISUOG. Published by John Wiley & Sons Ltd.

INTRODUCTION

Fetal growth restriction (FGR) is a serious obstetric condition, in which defects in placental development and function result in chronic fetal hypoxia and undernutrition, and thus failure of the fetus to reach its growth potential¹. There is currently no treatment for FGR; management involves regular monitoring of the mother and fetus, often culminating in the need for iatrogenic preterm delivery². When severe FGR is detected relatively early in pregnancy, e.g. before 28 weeks' gestation, this may lead to the stark choice between delivering a very small and premature baby or risking stillbirth by prolonging the pregnancy.

The EVERREST Project (doEs Vascular endothelial growth factor gene therapy safely impRove outcome in severe Early-onset fetal growth reSTriction?) is a multinational, multidisciplinary collaboration that aims to carry out a phase I/IIa trial examining the safety and efficacy of maternal gene therapy as a treatment for severe early-onset FGR³. Preclinical studies have shown that vascular endothelial growth factor (VEGF) gene therapy, delivered locally via an adenoviral vector into the maternal uterine arteries, increases uterine artery volume blood flow and vasodilates the uterine arteries in pregnant sheep over days⁴ and weeks⁵ through increased expression of endothelial nitric oxide synthase and perivascular adventitial angiogenesis^{5,6}. In animal models of FGR, it has also been shown to safely increase fetal growth velocity⁷.

The EVERREST clinical trial would involve administration, via interventional radiology, of VEGF gene therapy into the maternal uterine arteries in pregnancies affected by severe FGR between 22 and 26 weeks' gestation. The trial centers would be University College London Hospital in the UK, University Medical Centre Hamburg-Eppendorf in Germany, Hospital Clinic of Barcelona in Spain and Lund University in Sweden. As

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potentially the first clinical use of gene therapy during pregnancy, it raises important ethical questions.

By reviewing the relevant published and regulatory literature and undertaking qualitative semistructured interviews with key stakeholders and patients, this study aimed to establish whether there were any fundamental and insurmountable ethical or societal objections to a trial of maternal gene therapy for severe early-onset FGR.

METHODS

Literature review

A thematic review of the literature was conducted (by R.A.), addressing the ethics of research in pregnant women, the ethics of gene therapy in pregnancy, the ethical aspects and implications of the maternal–fetal relationship and ethical issues in neonatal care⁸. Searches for peer-reviewed articles on these topics were made in English, using MEDLINE and Google Scholar, Spanish, Catalan, Finnish, Swedish, German and French. Searches for relevant reports, regulations and other publications were made for European Union Institutions, the Council of Europe, the World Medical Association, the United Nations Educational, Scientific and Cultural Organization, the International Committee on Harmonisation and federal regulations of the USA, including guidance from the National Institutes of Health and the Food and Drug Administration. A full list of the literature reviewed is given in Appendix S1.

Stakeholder interviews

The issues identified by the literature review were used to develop an interview guide for semistructured qualitative interviews with key stakeholders. This included a one-page summary, to be read by the respondent, giving background information on severe early-onset FGR and outlining the proposed EVERREST clinical trial. A more technical summary was used for medical stakeholders and three additional questions relating to clinical trials in pregnancy were included for these participants. Interviews were designed to last approximately 30–40 min. Two pilot interviews were conducted in English before commencing the study.

Stakeholders from the four partner countries, as well as international stakeholders, were identified via internet searches and expert advice from members of the EVERREST Consortium. Initial purposive sampling included medical organizations, parental support groups and disability rights groups. In response to ongoing data analysis, theoretical sampling of midwifery organizations and additional disability groups was also undertaken. Responses from midwifery organizations were analyzed with those from parental support groups, reflecting the self-expressed role of these respondents as providing support and advocacy for pregnant women.

Interviews in the UK and Germany were performed by one bilingual, native language speaker (M.S.). Interviews

with Swedish stakeholders were conducted in English by the same interviewer, as all potential respondents had a good command of English. These interviews were mainly conducted via telephone or Skype, with some face-to-face interviews with UK participants. Interviews in Spain were conducted by a Spanish-speaking bilingual interviewer (M.Y.A.) who was briefed and debriefed in detail by the lead interviewer (M.S.). Interviews were recorded and transcribed, either verbatim for interviews in English or translated and transcribed into English for interviews in German and Spanish. Transcription and translation were carried out on an ongoing basis during the study, allowing the refinement of some of the questions and pursuit of specific avenues of enquiry in more depth. The interviews were content analyzed on an ongoing basis, from the beginning of the study (M.S.), to improve the collection of information in subsequent interviews. The data were coded manually, with sections of data labeled with a summative phrase and then analyzed thematically to identify patterns within the data⁹.

Patient interviews

The results of the stakeholder interviews, together with the findings of the literature review, were used to design the interview guide for semistructured qualitative interviews with patients. Fetal medicine specialists from London, Hamburg, Barcelona and Lund identified potential participants whom they had managed previously for severe early-onset FGR. Women and their partners were eligible to participate if they were between 18 and 65 years of age, spoke the native language of the country in which they were recruited and had a previous pregnancy affected by severe early-onset FGR that ended between 3 months and no more than 5 years before recruitment (an upper age limit was specified as part of the application for proportionate ethics review in the UK). Women were contacted and informed about the study by a healthcare professional from their original treatment center. In the UK, women were approached only after approval from their general practitioner. Written informed consent was given by all participants.

All patients were interviewed face-to-face by a native language speaker (by M.S. in UK and Germany, A.M.L. in Spain and P.L. in Sweden), either in the patient's home or at the original treatment center, according to the preference of the respondent. The UK interviewer attended the interviews in Spain and briefed and debriefed the Swedish interviewer via Skype. Interviews lasted 60–90 min, with digital recordings of all interviews stored as encrypted and password-protected files. Transcription, translation and analysis were performed in the same manner as for the stakeholder interviews.

The patient interview study was sponsored by University College London Comprehensive Clinical Trials Unit. Ethical approval was provided by the National Research Ethics Service Committee East of England in the UK, the Hospital Clinic of Barcelona's Clinical Research Ethics Committee in Spain, the Regional Ethical Review

Board in Lund in Sweden and the Ethics Committee of Hamburg Board of Physicians in Germany. Local research and development approval was obtained as required. All respondents had the option of receiving a summary report of the study findings.

RESULTS

Literature review

A fundamental issue identified by the literature review was the ethical status of offering a potentially risky medical treatment to a pregnant woman that confers no benefit to maternal health but may improve the health and survival prospects of her, as yet, unborn baby. It is central to medical ethics, and in most jurisdictions to medical law as well, that the primary patient in pregnancy is the woman herself, not the fetus. However, the ethical question remains as to whether the woman and the fetus constitute two patients with equal moral status, two patients with unequal moral status or one patient^{10–14}. Here ‘moral status’ refers to the moral value inherent in ‘personhood’. Although moral status is sometimes, especially in neonatology ethics, considered to be acquired gradually through gestation and birth, for practical purposes in reproductive ethics it is usually considered a categorical concept: one either has it or does not have it.

The simplest analysis considers that there is only one patient: the woman herself. Regardless of whether or not the fetus ‘matters’ from a moral standpoint, only the woman has the full moral status that goes with moral agency (the ability to make decisions, the capacity to value actions and states of affairs and the right to respect one’s autonomy). In light of respect for autonomy, we can say that, although we cannot oblige or compel a woman to undergo medical treatment for the sake of her fetus alone any more than we can oblige or compel a woman to undergo medical treatment for her own sake, we can also respect a woman’s choice to act (or refrain from acting) in the interests of her developing fetus. Thus, should she choose to risk her own health or undergo treatment that will benefit her fetus but not (necessarily) herself directly, this is a choice that should be respected and may be acted upon.

Many obstetricians, and some others, consider that, in care of the pregnant woman, they are looking after two patients: the woman and her unborn child. A weak version of this thesis is that there are two patients, but that if the interests of the two conflict, the interests of the woman take priority. A strong version of this thesis is that no such tie-break applies; both sets of interests are of equal strength and importance. In the two-patient model, it is clearer that there will be obligations to do whatever can feasibly be done to promote fetal development, with a view to the long-term interests of the child-to-be, so long as these are consistent with the interests of the mother. Such treatment, however, could not legally be imposed on a competent woman without her consent.

Given that, for both the one-patient and two-patient models, treatment that provides a direct benefit solely to the fetus is permissible but not obligatory, the issue becomes the ethical status of a trial of maternal gene therapy. The international ethical standard for clinical trials is the World Medical Association’s Declaration of Helsinki¹⁵. This relies on three central ethical requirements: the responsibility of the physician (as a matter of general medical ethics) for the wellbeing and safety of his or her patients; the centrality of informed consent; and the need for research to offer a fair and proportionate balance of risk and benefit to all participants. It makes no reference to the inclusion (or exclusion) of women (pregnant or otherwise) in research or to gene therapy. The key test for the ethical acceptability of research that is not therapeutic is that it should pose no more than minimal additional risk to the participants, over and above the risk of procedures they are ordinarily undergoing in their clinical care. If this is satisfied, then the next crucial test is consent. In the EVERREST trial, the key concern was the consent to a procedure that is for research, offers no guarantee of benefit and, in a context of FGR could be psychologically burdensome and unacceptable. The interviews in the study were designed to explore this question in more detail.

Semistructured interviews

Fifty-five stakeholder organizations were contacted, of which 34 agreed to participate (Table 1). The remainder either declined to be interviewed or referred the request to another organization (Table 2). There was considerable difficulty recruiting Spanish stakeholders; the two organizations that did participate would only agree to be interviewed in writing via email, with telephone follow-up to verify unclear answers, conducted in native Spanish (supervised by M.S.). Two German organizations, one medical and one parental, felt that a trial of gene therapy in pregnancy would be unethical. Unfortunately neither was willing to discuss their beliefs in more detail.

Twenty-one interviews were carried out with women who had had a previous pregnancy affected by severe early-onset FGR (UK, $n = 7$; Germany, $n = 7$; Sweden, $n = 3$; Spain, $n = 4$). Five of these women had experienced a mid-trimester miscarriage or stillbirth and two had chosen to terminate an affected pregnancy. Nineteen women had undergone at least one preterm delivery for FGR, between 24 and 32 weeks’ gestation, and two of these liveborn babies had subsequently died. In Spain there were a further three interviews with partners of women with a previous affected pregnancy. In one case this was because the woman spoke limited Spanish and in the other two because the husband attended the interview alone. It was not felt appropriate to refuse these respondents an interview after they had made the effort to attend, nor to remove their responses from the study. In Sweden there was difficulty in recruiting women as research had been conducted before in this same group of patients and many were reluctant to take part in a further study.

On the question of the moral status of the fetus, stakeholders expressed divergent views when asked whom they

Table 1 Key stakeholders interviewed about the ethics and social acceptability of the proposed EVERREST clinical trial, according to nationality and type of stakeholder

Country	Type of stakeholder			Total (n)
	Medical	Parental and midwifery	Disability	
International	European Critical Care Foundation (ECCF) International Stillbirth Alliance (ISA) European Society of Paediatric Neonatal Intensive Care (ESPNIC)	European Foundation for the Care of Newborn Infants (EFCNI)	International Federation for Spina Bifida and Hydrocephalus (IF Global)	5
UK	British Association of Perinatal Medicine (BAPM) Royal College of Obstetricians and Gynaecologists (RCOG) British Maternal and Fetal Medicine Society (BMFMS)	Antenatal Results and Choices (ARC) BLISS charity, for babies born too soon, too small, too sick Child Growth Foundation Stillbirth and Neonatal Death charity (SANDS) Tommy's charity Royal College of Midwives (RCM)	Liberation Network Alliance Alliance for Inclusive Education Inclusion London Disability Rights UK Disability Rights Commission British Council of Disabled People (BCODP) Bristol Disability Forum Scope charity	17
Germany	Deutsche Gesellschaft für Perinatale Medizin Deutsche Gesellschaft für Neonatologie	Bundesverband 'Das frühgeborene Kind' e.V. Frühstart München Deutscher Hebammenverband (German Association of Midwives)		5
Sweden	Swedish Society of Obstetrics and Gynaecology Swedish Society for Neonatology	Riksförbundet Svenska Prematurförbundet Prematurföreningen Mirakel Swedish Association of Midwives		5
Spain	Spanish Society of Obstetricians and Gynaecologists	Asociación Valenciana de Padres de Niños (AVAPREM)		2
Total (n)	11	14	9	34

Table 2 Distribution of stakeholder organizations that declined to be interviewed about the ethics and social acceptability of the proposed EVERREST clinical trial, according to nationality and type of stakeholder

Country	Type of stakeholder			Total
	Medical	Parental and midwifery	Disability	
International	3/6	0/1	2/3	5/10
UK	0/3	2/8	6/14	8/25
Germany	1/3	1/4	2/2	4/9
Sweden	0/2	1/4	0/0	1/6
Spain	1/2	2/3	0/0	3/5
Total	5/16	6/20	10/19	21/55

Data are given as number of non-respondents/number of stakeholder organizations contacted.

would consider a patient in the context of therapy for FGR. Although the majority held the view that the pregnant woman was the patient, several stakeholders viewed both the woman and the fetus as patients, whereas some saw the fetus as the patient, because it was the fetus that required treatment. The majority of women across all four countries considered the fetus to be a person, although there was some divergence as to at what timepoint in pregnancy this began. When asked whose interests should take priority, just over half of the women considered the interests of the unborn child as more important than those of the mother. A few thought that the interests of the woman and the child were of equal importance and a few considered the interests of the pregnant woman to be more important than those of the child. This was

particularly the case when the woman already had other children or when the fetus was not at a gestational age or weight at which it was likely to survive outside the womb.

On the issue of maternal treatment for fetal benefit, all women and all but one of the stakeholders felt that this was acceptable, providing the woman was in agreement and there were no major risks involved, or that she understood the risks to herself and the fetus. Medical stakeholders stressed that many current treatments already fell into this category, and both parental and medical stakeholders cited the possibility of fetal benefit being of indirect benefit to the woman.

'You do a Cesarean section in mothers because you want to save the fetus but the Cesarean section

is of no benefit to the mother... All of fetal therapy, in particular fetal surgery, is basically clearly dangerous for the mother and is only done because it is of benefit to the child.'

(Medical stakeholder, Germany)

Only a few women had experience of being asked to participate in a clinical trial during pregnancy. However, the vast majority of women could imagine taking part in such a trial as long as they were given sufficient information. Reasons advanced for participation included an attempt to improve the critical situation for their unborn child and helping other women in their situation in the future. For the majority of women the main concern about participating in a clinical trial was the potential for harm to the fetus. Only a few respondents expressed any concern about potential serious risk to themselves, particularly if this would mean that they might not be able to look after their baby. In this light, all respondents suggested that they would be more inclined to participate in a clinical trial if the treatment investigated was likely to confer a benefit to their unborn child rather than to themselves.

'It is my child. My love would be much too great to think of myself. I think it is more important to give something to the child in the last analysis. I already have lived my life so far. And she has not done that so far.'

(Patient, Germany)

In relation to the proposed EVERREST clinical trial, the majority of stakeholders and, in particular, non-medical stakeholders were concerned about the psychological burden that making a decision to take part, or taking part, may place on women at an already very stressful time. It was suggested that a woman may be uncertain and anxious that, whatever her decision, the outcome would somehow be her fault. Most stakeholders still felt that women would be able to make an autonomous decision in these circumstances and would not feel obliged to participate. However, some stakeholders expressed concern that the psychological state of a woman experiencing a pregnancy affected by severe early-onset FGR might not be conducive to making a rational decision. A few stakeholders questioned the decision-making capacity of pregnant women in general, suggesting that a pregnant woman would always wish to do the best for her child even if that acted against her own needs.

The majority of interviewed patients felt that they had been capable of making decisions regarding management options at the time of their diagnosis of severe early-onset FGR. Most women stated that they arrived at a decision about their pregnancy themselves, although they had discussed the options with their partners and listened to the advice of healthcare professionals. The majority of women acknowledged that it might be difficult to think clearly and rationally when faced with a decision regarding a new experimental treatment at the time when

their unborn child had just been diagnosed with severe early-onset FGR. However, this did not appear to be an insurmountable problem as long as they had some time to consider and someone with whom to discuss the intervention. All of the respondents thought that they would have been able to arrive at the decision freely and did not feel that they would be pressured to participate by healthcare professionals, although a few thought they might put themselves under emotional pressure.

'So in between this horrific experience you can have time when you are thinking clearly. I don't think you are necessarily out of control the whole time. I'm not.'

(Patient, UK)

'The pressure is not from the medics... but from oneself. That you fear that if you don't participate then the baby will stay small. I would then be without hope.'

(Patient, Germany)

A frequent concern among non-medical stakeholders was that it would be difficult to obtain valid informed consent for participation in the EVERREST clinical trial, as it would be difficult for lay people to understand the intervention and its possible outcomes. Added to this was the limited public understanding of gene therapy and prejudice against it. In contrast, medical stakeholders were not concerned as they felt that obtaining informed consent would be no different from many other trials. Stakeholders agreed that trial participants should be given independent advice, e.g. from psychologists, midwives, or parental organizations. They highlighted the need for informed consent to be a continuing process rather than a single event and for women to be given time to consider whether or not to participate in the trial. The woman or couple would need printed, clearly written information to take away so that they could discuss participation without any pressure being exerted by the healthcare team.

'I think the most important thing in this trial as with all trials is that one explains it at the level of the patient and not at an academic level... you need to use simple vocabulary and you need to keep on repeating it because these parents... are in a certain state of shock.'

(International parental organization)

Information, support and time were also raised by the patients as important factors when deciding whether or not to participate in a clinical trial. The need for accurate and adequate information was mentioned by all the patients and most preferred this to be given by the treating doctor rather than a doctor involved in the trial. Almost all patients would involve their partners in the decision regarding trial participation, although the final decision would be the woman's. They would also want

to speak with someone who was independent of the trial, including other pregnant women who had experienced a similar situation.

Almost all patients spontaneously expressed a positive reaction to the proposed EVERREST clinical trial, with some stating that they wished it had been available at the time of their pregnancy. A minority of patients had a negative response, suggesting that the trial was intervening in nature, that any first-in-human trial may be risky and that it may have harmful consequences for participating women. When patients who were initially positive were probed about any potential problems with the trial, the main concerns, expressed by a minority, were that the treatment may be ineffective or may cross the placenta, potentially resulting in unknown effects on the fetus. Some women were also concerned that it may have harmful long-term consequences for the woman and/or child or that the administration procedure might be risky.

'I think you would need to be hopeful, but you would also need to be realistic that it might not work. But that hope might be that it's what you're looking for, I suppose. If it didn't work, I think my husband would worry about how I would pick myself up from that again, having gone through what I've gone through ...'

(Patient, UK)

'It's not the treatment that worries me, but the potential consequences that it could have for the baby. In this case I would not be worried about me at all ... it's not knowing how it could affect the baby.'

(Patient, Spain)

Two potential issues raised by the literature review were that the trial may either be seen as discriminating against people with a disability or, in contrast, may result in the birth of babies with severe disabilities who would otherwise have died *in utero*. Most stakeholders, including disability rights groups, did not consider that the proposed trial would be discriminatory as the primary aim was not to eliminate disability. A minority of stakeholders felt that some people within the disability movement might be concerned about the trial intervention, particularly because of the use of the term 'gene therapy'.

'I can't see from a disability perspective anyway that there's any problem with this at all ... because it's not, you know, like a search and destroy operation which I think, you know, the Downs syndrome tests are.'

(Disability movement stakeholder, UK)

Over half of the patients were very clear that it was acceptable to them to have a disabled child, as long as the disability was not caused by the trial intervention itself. Several respondents stressed that it was preferable to have a disabled child rather than a dead child. A minority of

the patients did not find it acceptable to have a disabled child who would have died without the trial as they felt that the disability would harm not only the life of the child but also affect the lives of their other children. One respondent expressed the concern that the trial might lead to societal and economic problems if the net effect was to produce many more severely disabled children.

'I think it is still better to have a disabled child than a dead child ... because in the last analysis I had decided to have a child. My [child] could have been born with a disability. I decided to have [him or her] and I will stick with that. And therefore rather this way than not to have [him or her] at all.'

(Patient, Germany)

The majority of stakeholders and patients were not concerned by the novelty of maternal gene therapy. The main exception was a German stakeholder who felt that the negative societal view of gene therapy in Germany would make the intervention unacceptable. Interestingly, this view was not shared by the German patients. Several stakeholders highlighted the importance of communicating to the public what maternal gene therapy would entail, and some patients suggested it would be preferable to avoid the term 'gene therapy' to eliminate any misunderstanding regarding the purpose of the treatment.

'The term gene therapy causes fear because you think that it causes genetic changes to the baby ... Because the term gene therapy is used you think as a lay person that ... maybe one should use a different term ...'

(Patient, Germany)

All but one of the patients were in favor of the trial taking place and the great majority would have wanted to participate in such a trial. The patients who would have declined participation cited concerns about the unknown risks of the intervention or the possibility of a child surviving with severe disability. Stakeholders also had a generally favorable view of the ethics and social acceptability of the trial. They mostly felt the ethical issues were those raised by any clinical trial in pregnancy, including the psychological burden on women and the challenges of obtaining informed consent. Assuming the intervention was effective, the main concern for stakeholders was the risk of harm.

'[I would be in favor] on the condition that long term data is shown about safety and on the condition that experts who are completely independent, i.e. who have no reason to be in favor of this trial starting, will say that they consider it safe, that they consider it acceptable to treat the fetus via the mother.'

(Medical stakeholder, Germany)

'I would have wanted to participate in the trial even if one would not know whether it would work or not.'

(Patient, Sweden)

'There has to come a time when the intervention is trialed and, and that obviously has its challenges, its sensitivities etc. But if it's handled carefully and ultimately we have an improvement in outcome for these very high-risk pregnancies, then, for us as an organization, that's a positive outcome.'

(Parental organization, UK)

DISCUSSION

The findings of this study indicate that a trial of maternal gene therapy to treat severe early-onset FGR is ethically acceptable to many key stakeholders and women who had had a previous affected pregnancy. Although participants expressed varying views on the personhood of the fetus, the concept of a maternal intervention for fetal benefit was acceptable to all but one of the interviewees. In relation to the proposed trial of maternal VEGF gene therapy, information, independent advice and sufficient time for decision making were highlighted as important issues by patients and stakeholders. Although the psychological burden of trial participation was a concern for stakeholders, most interviewees felt that pregnant women would be capable of making an autonomous decision about whether or not to take part. Almost all patients viewed the proposed trial positively and most felt that they would have wanted to participate.

The aim of this study was to identify any fundamental or insurmountable ethical objections to a trial of maternal gene therapy for severe early-onset FGR. It did not aim to either quantify the distribution or provide an in-depth characterization of societal attitudes towards the proposed trial. Purposive and theoretical sampling were used to try to identify a diversity of opinion, not to provide a statistically representative sample. Similarly, a thematic analysis conducted in light of the narrative literature review aimed to identify discordant and outlier views, rather than develop an overarching conceptual model. Triangulation of the findings from the literature review, stakeholder interviews and interviews with patients demonstrated consistency of opinion, supporting the credibility of the results. Independent, internal peer review of the results was provided by the EVERREST Independent Ethics Advisory Board³ comprising experts in ethics and law, philosophy, social sciences and disability rights.

One important limitation of this study is that the attitudes and beliefs of women with a previous affected pregnancy may not have been the same at the time of interview as they were at the time of diagnosis. We judged that it would not be appropriate to undertake interviews with women currently experiencing an affected pregnancy, as it raised the possibility of an intervention when no current treatment is available. It should also be noted

that the majority of stakeholders were from Northern Europe, especially the UK and this may have affected the range of views expressed. This was partly because of the greater number of parental support and disability rights groups in the UK, many of which are organized on a professional basis. This is in contrast to the organizations in many other European countries, which generally receive less funding and are often staffed by unpaid volunteers.

Although the views of the stakeholder groups were broadly positive, two exceptions should be noted. One was that some German stakeholders felt strongly that a gene therapy trial of this kind would be unacceptable because of the history of eugenics in the Nazi period. It is not clear how widely held this view would be, or what the connection is between the eugenic practices referred to and the trial here with its goal of supporting and promoting fetal survival and welfare. The other view was shared by some midwives who felt that this trial was part of a tendency to 'overmedicalize' pregnancy. We had no evidence that this view was shared by any of the interviewed patients.

The views expressed by the women in our study echo the findings of other qualitative studies exploring women's experiences of obstetric research. Four studies carried out interviews with women who participated in ORACLE¹⁶ (randomized controlled trial (RCT) of antibiotics in preterm labor) and Magpie¹⁷ (RCT of prophylactic magnesium sulfate for severe pre-eclampsia), and women who were approached to participate in PLUTO¹⁸ (RCT of percutaneous shunting in fetal lower urinary tract obstruction) and eight other clinical obstetric trials¹⁹. They found that key reasons for participation were the possibility of benefit for the woman or fetus and altruism, which were potential motivations suggested by women in our study. As anticipated by our interviewees, women who took part in these trials described feeling free to make their own decision about participation, with varying degrees of input from their partners^{16,17,19}. However, they also described limitations in the consent procedures, including a lack of information and explanation^{17,18} and a lack of time for discussion with research staff¹⁹. As suggested by patients in our study, women who considered participation in PLUTO said it would have been useful to speak to someone with personal experience of their clinical situation¹⁸. Only one other study has investigated women's attitudes to a potential clinical trial. The strong opposition that women voiced to the idea of an RCT of Cesarean section *vs* vaginal delivery in first-time mothers²⁰ is in stark contrast to the generally positive reaction of patients towards the proposed EVERREST trial.

It is clear from the review of the regulatory literature, the opinions expressed by our interviewees and the reported experiences of women who have participated in other obstetric trials that obtaining valid informed consent will be a key issue for a trial of maternal gene therapy. As well as providing sufficient information and time, it will be important to bear in mind and strive to minimize the psychological burden for potential participants. However, the women interviewed in this study also felt that they

would have been capable of reaching an autonomous decision, even at a very difficult time, and most would have wanted the option of participating in the proposed EVERREST clinical trial.

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SUPPORTING INFORMATION ON THE INTERNET

The following supporting information may be found in the online version of this article:



Appendix S1 References included in the literature review.