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

Short Title: Ethics of gene therapy

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Funding sources: This research was funded by the European Commission Seventh Framework Programme (FP7) and supported by researchers at the National Institute for Health Research (NIHR) University College London Hospitals Biomedical Research Centre (ALD, DMP).

Conflict of Interest: ALD and DMP are consultants for Magnus Growth, for which they receive a token consultancy payment and shareholding in the company. ALD is director of Magnus Growth, part of Magnus Life Science, which is aiming to take to market a novel treatment for fetal growth restriction. IZ is a consultant for Magnus Life, part of Magnus Life Science for which he receives a token consultancy payment and shareholding in the company.

Key Words: Ethics, fetal growth restriction, gene therapy, translational medicine, pregnancy, qualitative, interview study

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Abstract

Objectives: 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 and in particular of advanced therapeutics. Issues which were identified informed the interview guides for semi-structured, qualitative interviews, which were carried out in four European countries with key stakeholders (disability groups, professional bodies, and patient support groups, n=34) and with women/couples who have experienced pregnancies affected by severe early onset FGR (n=24).

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 directly benefit, and is it ethical to treat this 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 was no ethical or legal objection 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 where these conferred a potential benefit to their unborn child. The risk of disability for the premature child was a concern, but not considered a major stumbling block for maternal VEGF gene therapy.

Conclusions: Maternal gene therapy to treat severe early onset FGR appears to be ethically and socially acceptable.

Introduction

Fetal growth restriction (FGR) is a serious obstetric condition, in which defects in placental development and function result in chronic fetal hypoxia and under-nutrition, and thus a failure of the fetus to reach its growth potential.[1] There is currently no treatment for FGR; management involves regular monitoring of the mother and fetus, often culminating in the need for iatrogenic preterm delivery.[2] When severe FGR is detected relatively early in pregnancy, for example before 28 weeks of 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 is a multinational, multidisciplinary collaboration which 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 FGR.[3] 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 vasodilated the uterine arteries of pregnant sheep over days [4] and weeks 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 velocity.[7]

The EVERREST Clinical Trial would involve administration, via interventional radiology, of a VEGF gene therapy into the maternal uterine arteries in pregnancies affected by severe FGR between 22 and 26 weeks of gestation. The trial centres will 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 potentially the first clinical use of gene therapy during pregnancy, it raises important ethical questions.

Through reviewing the relevant published and regulatory literature and undertaking qualitative semi-structured interviews with key stakeholders and patients, this study aimed to establish whether there were any fundamental ethical or societal objections to the use of maternal gene therapy.

Methods

Literature Review

A thematic review of the literature was conducted, 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 care (RA).{Hutton, 1998 #3227} 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 (UNESCO), the International Committee on Harmonisation (ICH), and federal regulations of the United States of America, including guidance from the National Institutes of Health (NIH) and Food and Drug Administration (FDA).

Stakeholder Interviews

The issues raised by this literature review were used to develop an interview guide for semi-structured 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 around 30 to 40 minutes. 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 organisations, parental support groups, and disability rights groups. In response to ongoing data analysis, theoretical sampling of midwifery organisations and additional disability groups was also undertaken. Responses from midwifery organisations were analysed with

105 those from parental support groups, reflecting the self-expressed role of these respondents as providing
106 support and advocacy for pregnant women.

107 Interviews in the UK and Germany were performed by one bilingual, native language speaker (MS).
108 Interviews with Swedish stakeholders were conducted in English by the same interviewer, as all
109 potential respondents had a good command of English. These interviews were mainly via telephone or
110 Skype, with some face-to-face interviews with UK participants. Interviews in Spain were conducted by a
111 Spanish speaking bilingual interviewer (MYA) who was briefed and debriefed in detail by the lead
112 interviewer (MS). Interviews were recorded and transcribed, either verbatim for interviews in English, or
113 translated and transcribed into English for interviews in German and Spanish. Transcription and
114 translation was carried out on an ongoing basis during the study, allowing the refining of some of the
115 questions and pursuing specific avenues of enquiry in more depth. The interviews were content
116 analysed on an ongoing basis from the beginning of the research (MS) to improve the collection of
117 information in subsequent interviews. The data was coded manually, with sections of data labelled with
118 a summative phrase and then analysed thematically to identify patterns within the data.[8]

119 ***Patient Interviews***

120 The results of the stakeholder interviews, together with the findings of the literature review, were used
121 to design the interview guide for semi-structured qualitative interviews with patients. Fetal medicine
122 specialists from London, Hamburg, Barcelona, and Lund identified potential participants whom they had
123 previously managed for severe early onset FGR. Women and their partners were eligible to participate if
124 they were between 18 and 65, spoke the native language of the country in which they were recruited,
125 and had had a pregnancy affected by severe early onset FGR which ended between 3 months and not
126 more than 5 years before recruitment. The upper age limit was included as part of the application for
127 proportionate ethics review in the UK. Women were contacted and informed about the study by a
128 healthcare professional from their original treatment centre. In the UK women were only approached
129 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 (MS in UK and Germany, AML in Spain, PL in Sweden), either in the patient's home or at the original treatment centre, 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 to 90 minutes, 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 the University College London Comprehensive Clinical Trials Unit (UCL CCTU). 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 for 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

One fundamental issue raised by the literature review was the ethical status of offering a potentially risky medical treatment to a pregnant woman which confers no benefit to maternal health, but which 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.[9-13] Here "moral status" refers to the moral value inherent in "personhood". Although moral status is sometimes (especially in neonatology ethics) considered gradually acquired 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.

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

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

172 Given that, for both the one patient and two patient models, treatment which provides a direct benefit
173 solely to the fetus is permissible but not obligatory, the issue becomes the ethical status of a trial of
174 maternal gene therapy. The international ethical standard for clinical trials is the World Medical
175 Association's Declaration of Helsinki.[14] This relies on three central ethical requirements: the
176 responsibility of the physician (as a matter of general medical ethics) for the well-being and safety of his
177 or her patients; the centrality of informed consent; and the need for research to offer a fair and
178 proportionate balance of risk and benefit to all participants. It makes no reference to the inclusion (or
179 exclusion) of women – pregnant or otherwise – in particular in research or to gene therapy. The key test
180 for the ethical acceptability of research which is not therapeutic is that it should pose no more than
181 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 which is for research, offers no guarantee of benefit, and in a context of fetal growth restriction could be psychologically burdensome and unacceptable. The interviews in the study were designed to explore this question in more detail.

Semi-structured Interviews

Fifty five stakeholder organisations were contacted, of which 34 agreed to participate (Table 1). The remainder either declined to be interviewed or referred the request to another organisation (Table 2). There was considerable difficulty recruiting Spanish stakeholders; the two organisations which 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 MS). Two German organisations, 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 pregnancies previously affected by severe early onset FGR (UK=7, Germany=7, Sweden=3, Spain=4). Five of these women had experienced a mid-trimester miscarriage or stillbirth and two of them had chosen to terminate an affected pregnancy. 19 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 who had had affected pregnancies. 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 to be appropriate to turn these respondents away after they had made the effort to attend the interview, 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 would consider a patient in the context of a therapy for FGR. While the majority held that the pregnant woman was the patient, several stakeholders viewed both the woman and the fetus as

patients, while some saw the fetus as the patient, because it was the fetus that required treatment. A majority of the women across all four countries considered the fetus to be a person, although there was some divergence as to what time point 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 their own. 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 where the woman already had other children or where the fetus was not at a gestational age or weight where it was likely to survive outside of the womb.

On the issue of maternal treatment for fetal benefit, all of the 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.

> *"One does a caesarean section in mothers because one wants to save the fetus but the caesarean 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 of the patients 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 be somehow 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 the diagnosis of severe early-onset FGR. Most women stated that they arrived at a decision themselves about their pregnancy, although they had discussed the options with their partners and listened to the advice of healthcare professionals. A 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 one fears that if one does not 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, for example from psychologists, midwives, or parental organisations. 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 … one needs to use simple vocabulary and one needs to keep on repeating it because these parents … are in a certain state of shock" International parental organisation

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 respondents 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 what 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 disabilities, 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 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." UK disability movement stakeholder

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, would 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, while 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 one thinks that it causes genetic changes to the baby …Because the term gene therapy is used one thinks as a lay person that …maybe one should use a different term..." Patient, Germany

All but one of the patients were in favour 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 favourable 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 favour] 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 favour 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 trialled 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 organisation, that's a positive outcome."* Parental organisation, 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 have had previously affected pregnancies. While 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 characterisation, of societal attitudes towards the proposed trial. Purposive and theoretical sampling was 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 Board[3] 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 previously affected pregnancies 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 organised on a professional basis. This is in contrast to the organisations in many other European countries, which generally receive less funding, and are often staffed by unpaid volunteers.

While 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 "overmedicalise" pregnancy. We had no evidence that this view was shared by any of the women interviewees. 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 ORACLE [15] (randomised controlled trial [RCT] of antibiotics in preterm labour) and Magpie [16] (RCT of prophylactic magnesium sulphate for severe pre-eclampsia), and women who were approached to participate in PLUTO [17] (RCT of percutaneous shunting in fetal lower urinary tract obstruction) and eight other clinical obstetric trials [18]. They found that key reasons for participation were the possibility of benefit for the woman or fetus and altruism - 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 [15, 16, 18]. However, they also described limitations in the consent procedures, including a lack of information and explanation [16, 17] and a lack of time for discussion with research staff [18]. 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 situation [17]. 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 Caesarean section versus vaginal delivery in first time mothers [19] 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 minimise 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.

Acknowledgements

With thanks to all of the interviewees for their participation; Pia Lundqvist (PL), Department of Child, Family and Reproductive Health, Lund University, for conducting the Swedish patient interviews; Maria Yoya Alvarez (MYA) for conducting the Spanish stakeholder interviews; Alberto Merino Lefenda (AML) for conducting the Spanish patient interviews; and the members of the EVERREST Consortium, for their advice and help with recruitment outside of the UK. ALD and DMP receive funding from the UCL/UCLH NIHR Biomedical Research Centre.

Preliminary findings and summaries of this work have been presented at the British Maternal and Fetal Medicine Society Perinatal Medicine Conference 2014[20], the International Fetal Medicine and Surgery Society Conference 2014, and the Fetal Growth Conference 2014.[21]

References

1. Spencer RN, Carr DJ, David AL. Treatment of poor placentation and the prevention of associated adverse outcomes - what does the future hold? *Prenat Diagn* 2014.

2. Marsal K. Obstetric management of intrauterine growth restriction. *Best Pract Res Clin Obstet Gynaecol* 2009;**23**:857-70.

3. EVERREST Consortium. EVERREST: Maternal growth factor therapy to improve fetal growth. Available from: www.everrest-fp7.eu [updated; cited 2nd July 2014]

4. David AL, Torondel B, Zachary I, Wigley V, Abi-Nader K, Mehta V, Buckley SM, Cook T, Boyd M, Rodeck CH, Martin J, Peebles DM. Local delivery of VEGF adenovirus to the uterine artery increases vasorelaxation and uterine blood flow in the pregnant sheep. *Gene Ther* 2008;**15**(19):1344-50.

5. Mehta V, Abi-Nader KN, Peebles DM, Benjamin E, Wigley V, Torondel B, Filippi E, Shaw SW, Boyd M, Martin J, Zachary I, David AL. Long-term increase in uterine blood flow is achieved by local overexpression of VEGF-A(165) in the uterine arteries of pregnant sheep. *Gene Ther* 2012;**19**(9):925-35.

6. Mehta V, Abi-Nader KN, Shangaris P, Shaw SW, Filippi E, Benjamin E, Boyd M, Peebles DM, Martin J, Zachary I, David AL. Local Over-Expression of VEGF-DDeltaNDeltaC in the Uterine Arteries of Pregnant Sheep Results in Long-Term Changes in Uterine Artery Contractility and Angiogenesis. *PloS One* 2014;**9**(6):e100021.

7. Carr D, Wallace JM, Aitken RP, Milne JS, Mehta V, Martin JF, Zachary IC, Peebles D, David AL. Uteroplacental adenovirus VEGF gene therapy increases fetal growth velocity in growth-restricted sheep pregnancies. *Hum Gene Ther* 2014;**25**(4):375-84.

8. Pope C, Mays N. *Qualitative Research in Health Care.* 3rd ed. Oxford: BMJ Publishing; 2006.

9. Dickenson DL. *Ethical Issues in Maternal-Fetal Medicine.* Cambridge: Cambridge University Press; 2002.

10. Chervenak FA, McCullough LB. An ethically justified framework for clinical investigation to benefit pregnant and fetal patients. *Am J Bioeth* 2011;**11**(5):39-49.

11. Mahowald MB. *Bioethics and Women: Across the Lifespan.* Oxford: Oxford University Press; 2006.

12. Mason J. *The Troubled Pregnancy: Legal Wrongs and Rights in Reproduction.* Cambridge: Cambridge University Press; 2007.

13. Hervey TK, McHale JV. *Health Law and the European Union.* Cambridge: Cambridge University Press; 2004.

14. World Medical Association. Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects. *JAMA* 2013;**310**(20):2191-4.

15. Kenyon S, Dixon-Woods M, Jackson CJ, Windridge K, Pitchforth E. Participating in a trial in a critical situation: a qualitative study in pregnancy. *Qual Saf Health Care* 2006;**15**(2):98-101.

16. Smyth RM, Jacoby A, Elbourne D. Deciding to join a perinatal randomised controlled trial: experiences and views of pregnant women enroled in the Magpie Trial. *Midwifery* 2012;**28**(4):E478-85.

17. Morris RK, Malin GL, Quinlan-Jones E, Middleton LJ, Diwakar L, Hemming K, Burke D, Daniels J, Denny E, Barton P, Roberts TE, Khan KS, Deeks JJ, Kilby MD. The Percutaneous shunting in Lower Urinary Tract Obstruction (PLUTO) study and randomised controlled trial: evaluation of the effectiveness, cost-

461 effectiveness and acceptability of percutaneous vesicoamniotic shunting for lower urinary tract
462 obstruction. *Health Technol Assess* 2013;**17**(59):1-232.
463 18. Oude Rengerink K, Logtenberg S, Hooft L, Bossuyt PM, Mol BW. Pregnant womens' concerns
464 when invited to a randomized trial: a qualitative case control study. *BMC Pregnancy Childbirth*
465 2015;**15**(1):207.
466 19. Lavender T, Kingdon C. Primigravid women's views of being approached to participate in a
467 hypothetical term cephalic trial of planned vaginal birth versus planned cesarean birth. *Birth*
468 2009;**36**(3):213-9.
469 20. Sheppard M, David A, Spencer R, Ashcroft R. Ethics and ethical evaluation of a proposed clinical
470 trial with maternal uterine artery vascular endothelial growth factor gene therapy to treat severe early-
471 onset fetal growth restriction in pregnant women. *Archives of Disease in Childhood - Fetal and Neonatal*
472 *Edition* 2014;**99**(Suppl 1):A85.
473 21. Sheppard MK, Spencer RN, David AL, Ashcroft R. Evaluation of the ethics and social
474 acceptability of a proposed clinical trial using maternal gene therapy to treat severe early-onset fetal
475 growth restriction in pregnant women. *Hum Gene Ther* 2014:A98.

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477 **Table 1: Key stakeholders interviewed about the ethics and social acceptability of the proposed EVERREST Clinical Trial by country and type of stakeholder**

Nationality	Type of stakeholder			Total
	Medical	Parental and Midwifery	Disability	
International	1. European Critical Care Foundation (ECCF) 2. International Stillbirth Alliance (ISA) 3. European Society of Paediatric Neonatal Intensive Care (ESPNIC)	1. European Foundation for the Care of Newborn Infants (EFCNI)	1. International Federation for Spina Bifida and Hydrocephalus (IF Global)	5
UK	1. British Association of Perinatal Medicine (BAPM) 2. Royal College of Obstetricians and Gynaecologists (RCOG) 3. British Maternal and Fetal Medicine Society (BMFMS)	1. Antenatal Results and Choices (ARC) 2. BLISS charity, for babies born too soon, too small, too sick 3. Child Growth Foundation 4. Stillbirth and Neonatal Death charity (SANDS) 5. Tommy's charity 6. Royal College of Midwives (RCM)	1. Liberation Network Alliance 2. Alliance for Inclusive Education 3. Inclusion London 4. Disability Rights UK 5. Disability Rights Commission 6. British Council of Disabled People (BCODP) 7. Bristol Disability Forum 8. Scope charity	17
Germany	1. Deutsche Gesellschaft für Perinatale Medizin 2. Deutsche Gesellschaft für Neonatologie	1. Bundesverband "Das frühgeborene Kind" e.V. 2. Frühstart München 3. Deutscher Hebammenverband (German Association of Midwives)		5
Sweden	1. Swedish Society of Obstetrics and Gynaecology 2. Swedish Society for Neonatology	1. Riksförbundet Svenska Prematurförbundet 2. Prematurföreningen Mirakel 3. Swedish Association of Midwives		5
Spain	1. Spanish Society of Obstetricians and Gynaecologists	1. Asociación Valenciana de Padres de Niños (AVAPREM)		2
Total	11	14	9	34

Table 2: Distribution of non-respondents for stakeholder interviews, by country and type of stakeholder (numerator = non-respondents, denominator = number of stakeholder organisations contacted).

Nationality	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