Ethical issues arising from the INTERGROWTH-21st Fetal Growth Longitudinal Study

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The INTERGROWTH-21st Project presented a complex set of ethical challenges given the involvement of health institutions in geographically and culturally diverse areas of the world, with differing attitudes to pregnancy. This paper addresses how the research team dealt with some of those issues.

Keywords INTERGROWTH-21st, ethics, fetal growth, nutrition, standards.

Introduction

The design and implementation of the International Fetal and Newborn Growth Consortium for the 21st Century (INTERGROWTH-21st) Project, involving eight study sites, four continents and almost 60 000 women, presented a complex set of challenges to achieve consistent and endurable ethical approval. It was neither possible nor desirable to formulate a set of guidelines that could meet the differing issues raised by cultures as diverse as the UK and Oman, USA and China; what those guidelines might offer in terms of ethical rigour, they would lack in cultural sensitivity. What was pre-eminent in the initial design meetings was to acknowledge and appreciate the plethora of advice contained in the national and international guidelines, declarations and regulations, and synthesise it into a workable framework for international use. I was invited to participate in the INTERGROWTH-21st Project Steering Committee in the capacity of a voluntary lay member, in view of my background working in a similar competency on Research Ethics Committees and participating as a volunteer in other medical research projects.

Background

Any international ethical framework takes as its starting point the principles identified by the World Medical Association Declaration of Helsinki. All ethical frameworks exist within constantly evolving situations that take into account the context of the research, moral imperatives, ethical principles and the law. There was unilateral agreement amongst the members of the INTERGROWTH-21st Project Coordinating Unit that the principles of respect for human dignity, individual autonomy, truth (veracity) and justice were to be acknowledged and adhered to in every study site. Beyond this, it was apparent that each study site should work within the guidelines of their own local ethics committee and adhere to all stringent requirements set nationally. It was agreed that no ethical, legal or regulatory adjustment or requirement of any country could reduce or ignore any of the protections for human subjects identified by the World Medical Association.

All medical research is driven by the desire to further knowledge and understanding and to identify potential future benefit. Some medical research involves the participation of healthy individuals who offer their time, at least, and their bodies, at most. The whole project is dependent for its very existence on the goodwill of almost 60 000 pregnant women from the populations involved, of whom approximately 4500 in the Fetal Growth Longitudinal Study (FGLS) were completely healthy and not in need of any special medical attention other than routine antenatal care. In addition, INTERGROWTH-21st relies upon the dedication of a vast number of committed professionals. Therefore, the purpose of the ethical framework was to ensure that the rights of all those involved were respected and acknowledged,
and that the benefits of the project outweighed any present or future harm. The principles of academic freedom bring with them responsibilities to remain honest, open and accountable to everyone participating in the research. Alongside this is the requirement to recognise the social impact on the participants, to respect their autonomy and to accept their individual and cultural differences.

**Information to participants in FGLS**

Participants were to be kept informed in a comprehensible manner at all times and would be given a Patient Information Leaflet outlining the study aims, the level of commitment required, the address and phone number of the local research team, and the route to take in the event of a complaint. They were to be given the study website address and reassured of their right to withdraw from the study at any time with no impact on their ongoing care. They would also be offered the opportunity to request a copy of any published research papers. The focus in a longitudinal study is to recruit the appropriate number of subjects and then maintain their involvement without offering any inducement other than the altruistic benefit of future good. This was a challenge in its own right and was dependent on the generation of goodwill and altruism.

**Cultural issues**

Crucial to all research studies that involve human participation is consent. Given the multinational nature of FGLS, the challenge of devising a consent form that took into account all possible cultural differences was considerable. Some questions in the study questionnaire also presented difficulties. For some cultures, questions referring to an individual’s economic status were considered to be rude and inappropriate; for others, the criteria identified to ascertain a particular standard of living or education were improper and/or unsuitable. The direct, accurate and accessible translation of the questionnaire into the many different languages was dependent on the trust and commitment generated by regular visits from members of the Project Coordinating Unit to participating sites. This was a time-consuming but essential responsibility, for both the integrity of each individual involved and the ensuing data. Again, study sites referred the questionnaires to local ethics committees for approval and/or revision, using the original edition as the template. All questionnaires were approved in their original form, which included contributions from the local investigators.

**Other ethical issues**

One particular and challenging issue that arose in the design of this study was gender identification during ultrasound examinations. In some countries, this can be a value free communication, but it soon became evident that, in others, it is ethically value laden. Thus, in India, the identification of gender is illegal; in Brazil, it is a given. In some countries, antenatal care is determined by open market forces and competition is intense. In this circumstance, the possibility of gender identification offered a marketing advantage for the study site over other clinics. It would be impossible to create an overarching ethical guideline that would straddle these conflicting positions. The acceptance of these totally different ethical standpoints confirmed the importance of delegating ethical approval to local sites, with an overall adherence to the integrity of the international guidelines and the responsibility to do no harm.

A further challenge arose with regard to inducements. In nontherapeutic research, where the focus is on future generations rather than any specific benefit to individuals, once again the ethical issues focusing on respect for dignity, autonomy, truth and justice are pre-eminent. At the heart of this issue is the tension between the protection of human rights and the generation of knowledge. This issue is complicated by the variability of healthcare facilities in different countries and the potential for alternative interpretations of inducement. It could not be ignored that some participants would agree to be involved in the belief that they might be offered improved, perhaps more personalised, care throughout their pregnancy. Equally, it became apparent that, for some, the offer of extra ultrasound scans during the pregnancy could be interpreted as an inducement in itself. The focus on the altruistic purpose of this study, to benefit future generations rather than any specific or immediate benefit to an individual, was important to emphasise. Study sites were encouraged to communicate this message through their ongoing verbal appreciation of the women’s participation and by giving very small gifts that emphasised the global nature of the study and the feeling of being part of a large multinational team. Cotton shopping bags and a T-shirt for the newborn, of insignificant value, imprinted with the study logo, together with ‘thank you’ cards, were distributed to all sites, to be given to women already participating. The issue of these small offerings was referred to local ethics committees to ensure that they did not breach national standards. No actual inducements were offered to join the study.

A significant concern identified during the set-up of FGLS was how to address the issue of any clinical problems identified during the extra ultrasound scans. In a study of this size, it was acknowledged that some pregnancies could end in miscarriage, others could have fetal problems identified by ultrasound, and a few might result in severe morbidity or mortality. As stated previously, it is a prerequisite of all research studies involving human participation to establish whether the observations carry the potential for harm. Scans
themselves present no known risk to maternal or fetal health, and so the study observations themselves would cause no physical harm. (It is important to note here that researchers and participants may not always view the harms and/or benefits in the same light; for example, whereas the researchers may view the additional scans as value added, the participant might experience them as a drain on her time, and it is for this reason that design and implementation committees have lay members).

Pregnancy, however, does carry risks and care should be provided when those risks materialise. The identification of health institutions to participate in the study was driven by the requirement that they meet high standards of antenatal and postnatal care. In addition, clinical manuals (including internationally recommended, evidence-based care) were prepared and all institutions agreed to implement them. It was also agreed that any clinical problems found should be handled with thoughtfulness and sensitivity, and the mother should be referred for ongoing care consistent with the highest local standards. Whilst receiving the necessary care, she would remain in the study. No preferential treatment was given, except inasmuch as the problem may have been identified more quickly as a result of the slightly increased number of scans, or, in some cases, by scans being performed earlier than was customary locally. As this concerned the management of a future unknown, it could not be interpreted as an inducement.

The remaining issue addressed in the design and implementation of FGLS was the storage and retrieval of information generated by the study. Rigorous guidelines determine the participants’ right to withdraw at any point, to request destruction of personal data, to know that all data will be stored in an anonymous and protected manner, and that good records will be kept. This ensures the rights and welfare of the participants, whilst validating and protecting the integrity and reputation of the research institutions. Scrutiny at all points of the process was essential and remains so. No controversial points relating to this issue have been raised.

As outlined, the lay member’s principal purpose in any study is to represent the interests of the people who will participate and to ensure that they are treated with dignity and integrity. With volunteer status and giving considerable amounts of time for altruistic purposes, the lay member will obtain a sense of the value accorded to those future volunteers by the way they are welcomed and listened to on the committee. Achieving ethical approval can be both lengthy and onerous; the lay member can be a vexatious reminder of the demands involved in acquiring approval and of acting within the scope of that approval. This can be manifest in a frustration with the naïve nature of some of the questions or the challenge to an accepted status quo – the aforementioned reference to benefits and/or harms is a case in point, as was the painstaking questioning about the structure and layout of the Patient Information Leaflet – but the lay member brings the perspective of the ‘ordinary citizen’ and helps the researchers to understand the way they may be viewed by the public.

Conclusion

The design of a comprehensive, prospective project, such as INTERGROWTH-21st, is a lengthy and challenging process. Ethical approval was achieved in all the participating sites, and consistently high standards, as far as they are reported to us and evaluated during site visits, have been maintained throughout the implementation of the project. In FGLS, in particular, a not insignificant factor in achieving the high levels of recruitment and retention of women was the trust, goodwill and energy generated by members of the Project Coordinating Unit in their initial visits to participating sites, and the ongoing background work to ensure that all sites were accorded a consistently high level of care and were subject to rigorous standards for quality control. Participant involvement has been high and sustained and, although the knowledge generated by the study may be of benefit to future generations, we must never forget the contribution of the many thousands of women who gave their time to ensure the existence of the study and the progress of knowledge. Maintaining these good standards of care and ongoing respect for the rights of the individual have ensured high levels of participation and goodwill towards future research. Rigorous adherence to the World Medical Association Statement for Ethical Principles for Medical Research involving Human Subjects proved effective in designing and implementing this multinational study, and provided an effective template for local and international ethical approval. It is now up to the investigators and related institutions to complete the project, including data analysis, to the highest standards, and make the results available to be used at all levels of pregnancy care worldwide.

Disclosure of interests

None.

Contribution to authorship

F. Burton wrote the manuscript.

Details of ethics approval

The INTERGROWTH-21st Project was approved by the Oxfordshire Research Ethics Committee ‘C’ (reference: 08/H0606/139), and the research ethics committees of the individual participating institutions and corresponding health authorities where the Project was implemented.
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A full list of Members of the International Fetal and Newborn Growth Consortium for the 21st Century (INTERGROWTH-21st) and its Committees appears in the preliminary pages of this supplement.

References