# Research on Perinatal Patients

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## Introduction

In the last couple of decades perinatal medicine has seen dramatic changes in what it is capable of achieving, due to the emergence of new technologies. There have been immense leaps forward in diagnostic powers, for example in the area of genetic testing, and, to a lesser degree in the art of prognosis. Therapeutic interventions have also undergone huge changes in areas such as foetal surgery, and the care of pre-term babies. None of these advances would have been possible without vigorous research programmes in the field. Advances in knowledge and technology in the earliest stages of the development of human beings have raised major questions about whether it is right to do what it is technically possible to do. Similar questions might be asked of perinatal medicine as defined by the World Health Organisation, though they have not enjoyed such a high profile.

In this paper I propose to look at the areas of research and therapeutic intervention and ask whether there are limits to what should be attempted.

## Research

There are safeguards which have to be built into any responsible research activity in medicine with respect to the research subjects. Since the publication of the Nuremburg Code the insistence that no unnecessary or aimless research be carried out on human subjects, that no undue suffering be involved and that proper consents be obtained has characterised all research guidelines concerning research involving human subjects. However, some of these requirements present problems in principle for research on some patient populations. The most obvious difficulty is presented by the requirement for a proper consent from the reseach subject. There are patient groups which, by definition, lack competence to give a proper consent. Sometimes the lack is an intrinsic lack where the mental and/or emotional

faculties to frame a consent are absent. The result is that where disease conditions have a peculiar application to such groups the requirement for consent makes research into those conditions very difficult. These groups include the elderly confused, psychiatric and perinatal patient amongst others. We might feel, nevertheless, that it is imperative that such patient groups be allowed to benefit from advances in care which are dependent on research. In order to make such research possible we might adopt a number of approaches.

## Research by Stealth[1]

Many advances in knowledge in medicine come about in the course of clinical practice. It would be irresponsible to practice medicine without employing adequate systems of audit and evaluation of outcomes. The current emphasis on evidence-based medicine reflects this concern and it would be incorrect to understand such attention purely in terms of economic frugality. To carry out invasive and often dangerous procedures on patients without reasonable grounds for doing so cannot be ethically justified.

Good clinical practice is innovative in that new situations which present themselves to practitioners in the daily round call for responses which traditional practice might never have addressed. This is evident, for example, in surgery where things do not always turn out as predicted and instant solutions are called for. These might take the form of the performance of a minor technique for the first time which turns out to be successful. Though it was not premeditated in detail it is thought worthy of repeat. Its second application is importantly different from the first. It has now been subject to review and has shown itself to be promising. The second patient therefore receives a planned procedure. So it progresses until a cohort of patients are subjected to it. Together with other incremental changes it might develop into a distinctive therapeutic intervention without ever being subjected to independent trials.

Naturally, the innovator is committed to the procedure as he is its inventor and this does not place him in the best position to evaluate it. So the question arises as to how many patients in the conduct of clinical practice should be subjected to new therapeutic interventions before proper trials are designed and executed. How should we design such trials where clinical equipoise is undermined by the experience of the innovator who has developed the necessary expertise to carry out the procedure? In perinatal care where sea changes are occurring in surgical intervention on foetuses caution is called for in developing responsible checks and balances of innovative practice. Lines should be drawn at small numbers of patients subjected to innovative procedures until agreed methods of independent assessment are applied. Some simple rules can be applied immediately. For example, thorough case notes of patient states prior to intervention should always be available against which improvements can be measured to provide historical controls from the earliest intervention. Any devices employed should be subjected to adequate mechanical testing before their first application. Only small numbers of interventions should be allowed before inde-

pendent assessments are designed. All patients' families should be informed, where possible, that the procedures are innovative before they are employed so that proper consent can be achieved. More work is called for on the methodology of prospective studies.

## Therapeutic/Nontherapeutic Research

The execution of research on perinatal patients in the course of therapeutic intervention affords a way around the problem of consent. In most countries parents are authorised to provide a consent for their child to be subjected to therapeutic interventions as the child itself is not in a position to provide the same. The parents are assumed to have the child's interests at heart and therefore to be the best proxies for the child. There are some problems in employing this assumption in the case of prenatal patients as we shall discuss below. However, even if we do not question the assumption for the moment, it is important to note that it should not provide an open door to research on perinatal patients. There are difficulties in parents providing consents to non-therapeutic research on their children because, ex hypothesi, those procedures are not performed explicitly in the interests of their children, thus undermining the rationale for their parents' authority to act as proxies.

Arguments have been made to question the distinction between therapeutic and non-therapeutic research on the grounds that if the procedure is a research procedure then improving the health of the subject cannot be its primary aim and benefit cannot be used as an incentive for the subject because the question of possible benefit is the one which the procedure is setting out to answer.[2] Nevertheless in the context of innovative practice, often last ditch intervention, experimental procedures might benefit the subjects. This is not so for healthy controls which are employed in research. Without healthy perinatal controls it will often be difficult to assess the needs of sick children and derive explanations and possible therapeutic interventions for their conditions. So what are the possibilities?

### *Tacit consent*

The fact that the perinatal patient is presented for investigation and treatment might imply that tacit consent for research has been provided. Investigations are called for which might by their very nature suggest advances in understanding of the human condition. Further, insofar as every therapeutic intervention in individual lives is something of an experiment – medicine being an art rather than a science – every patient is by definition a research subject. Finally, it might be argued, each patient stands on the shoulders of many other patients who have gone before in that, without the knowledge and experience gained from other patients, therapeutic understanding of the presented patient would be poorer. In this sense the presented patient owes a debt which can be repaid by providing similar advantages to future patients.

Interesting though these arguments might be they do not justify experimentation upon presented patients without seeking explicit consent from parents or guardians of the patients. They are being presented for examination and treatment in their interests not in the interests of others. The latter interests are beyond the remit of the parents to consider over and above the interests of their child for it is not they on whom the experimentation is to be conducted and their role in the consent procedure is strictly circumscribed. The debt analogy is not persuasive either for the alleged debt is not one which was incurred voluntarily by the patient. The patient cannot be considered as a party to a contract made with yet unknown patients as it would be a contract between the unknowing and the unknowable.

### *Life policy*

We might endeavour to open the door to the use of perinatal patients in research by adopting a prospective judgement on the part of the patient. This will be seen to be an important proposal in terms of determining what constitutes a successful outcome in perinatal medicine, but will it help us to resolve the problem of the use of these patients in research?

There is an analogy to be found elsewhere in clinical research, viz. in psychological research where it is often necessary to deceive the subjects about the nature of the research in order to protect the integrity of the research procedures and results. Thus no proper consent is achieved from the subjects. The useful rule of procedure used to justify the practice – thus facilitating psychological research – is that on completion of the project the subjects must be debriefed and told of the deceit. If it is anticipated that such a procedure would be particularly difficult or distasteful for, or offensive to, the subjects then the research should not proceed. We might adopt a similar approach in perinatal research by imagining the response of the child later in life when told of the decision of its parents to enter it into a research project. If we could imagine without difficulty the child's thinking it a most worthwhile thing to have done, albeit unwittingly, then we should be prepared to proceed.

What might militate against such a view being taken by the developed child? The obvious consideration is whether by volunteering the child's participation considerable risks were taken with respect to the child's welfare. Even though they might not have been realised the awareness that such risks were imposed on him by his parents might be met with great disbelief and resentment. Such a prospect would be sufficient reason to decline participation. Similarly if the character of the research was either worthless or morally objectionable – for example imagine that it had racist overtones – then the subject might complain when it was old enough to comment.

These considerations offer us useful guidelines for designing research involving perinatal subjects. First, the research should be worthwhile and its goals realisable, second, it should involve only minimal risk to the research subject. The latter idea is a difficult one in that there are no absolute standards to determine minimal risk. However a workable definition has been devised.[3] It is proposed that where the research is avowedly non-therapeutic then it might be regarded as presenting minimal risk when the procedures involve no more forseeable harms than those encountered in the everyday life of a child – though these are notoriously variable between countries, neighbourhoods and even families. Certainly the risks could be spelled out in these cases where, for example, one venepuncture was involved, or non-invasive physical examinations and so on. Once procedures proceed beyond the unthreat-

ening and are identifiably potentially harmful in specifiable ways, such as the catheterisation of healthy children to measure their pulmonary artery pressure in order to compare it with that of children with congenital heart disease, we cannot justify the risk, useful though the information might be.[4] The principle of primum non nocere will always outweigh the principle of beneficence in non-therapeutic research.[5]

In therapeutic research we can find a more acceptable definition of minimal risk. Here the risk posed by the intervention must be no greater than that posed by standard methods of treatment or by non-intervention, where the consequences of the latter would be harmful.

Thus the possibility of perinatal research is not closed, but it is, nevertheless somewhat circumscribed by the inability of the patient to provide a consent.

## Therapeutic Interventions

We have already discussed the vagueness of the line between research and practice in perinatal medicine and proposed that the interests of the patient should always be decisive in any decision to engage in innovative treatments. There might be radical disagreement about what are the best interests of the patient. There is always the possibility of a conflict between the narrative of the clinician and that of the patient. The clinician might be eager to test a new hypothesis, evaluate a new technique, initiate a new practice and so on, all of which are justifiable aims in a professional career. Parents' concerns may often be called in aid of such agendas when the prospect of losing their child is apparently intolerable. However these considerations must always be weighed against the cost to the patients who should not be left to drop out of the decision procedures simply because of their dire needs or their inability to frame and voice opinions about their treatment. Hindsight is, of course, a fine thing but we can identify some procedures which, on reflection, we might feel did not take such concerns seriously enough where extraneous considerations dictated practice. Such was the case of four-year-old Laura Davies who had been refused transplantation surgery in the UK because clinicians felt that it was not in her best interests given the suffering involved and the extremely gloomy prognosis. Her gut was not functioning and she had been kept alive by intravenous feeding until liver failure occurred. Survival depended on liver and bowel transplantation – very experimental surgery with too few historical cases to estimate reasonable chances of survival. Eventually she endured multiple transplantation of seven internal organs spending the last months of her life undergoing harrowing heroic procedures. This raised the question of whether some paediatricians felt there was no point at which to call a halt to innovative practice.[6]

This paper has argued that there are limits to both research and therapeutic intervention in perinatal medicine, difficult though they might be to determine. Ethics committees can best play a valuable role in identifying these limits where the distinction between research and practice is not used as a mechanism for evading independent ethical review. In New Zealand the remit of ethics committees makes such evasion theoretically impossible but elsewhere, such as in the United Kingdom, the review of clinical practice is not part of the brief of Local Research Ethics Committees. Nevertheless even in New Zealand the proportion of innovative procedures reaching ethics committees is very low as yet. This is a matter of concern which is currently a focus of attention.

## References


1 For a discussion of this difficult area see Donald Evans and Martyn Evans, *A Decent Proposal: ethical review of clinical research*, John Wiley and Sons (1996), Chapter 4 'Experimental Clinical Practice', pp. 51-61.

2 Alderson, P. 'Did children change or the guidelines?' *Bulletin of Medical Ethics* 80 (1992), pp. 21- 28.

3 Nicholson, R. (ed.) *Medical Research with Children*. Oxford University Press (1986), Chapter 5.

4 Howell, Rodney R. 'The importance of research on children', in *Research on Children*, Jan van Eys (ed.) University Park Press (1978), Baltimore, p. 35.

5 Jonas, H. 'Philosophical reflections on experimentation on human subjects', *Daedalus* 98 (1969), pp. 219-47.

6 Nicholson, R. Editorials, *Bulletin of Medical Ethics* 78 (1992) and 91 (1993).


*Interview continued from Page 2*

In the early days of the Centre there was, I think, an expectation that it would be doctors and lawyers who would come and do postgraduate study in bioethics. But we have discovered that many different people come to study ethics – some young, some older with lots of professional expertise, people from a range of health sciences, and people coming from the humanities. There have been some great challenges in designing courses that can meet the educational needs of such a range of students.

I've also enjoyed being part of the development of the new undergraduate medical curriculum. That has been fun because of working with the different people across the medical school, thinking through how we can best do this. It's been an opportunity to try out new ideas. And it has been exciting to see it come to fruition and be part of the changes to ethics education as we move into a new curriculum at Otago.

**OBR:** What about some of the research that you have been involved in?

**BN:** Some of my research has focused on ethics education: what we do, why we do it, what we are hoping to achieve both in terms of working with medical students and with graduates. I really enjoyed being part of the Feminist Pedagogy Research Group, an interdisciplinary group looking at how feminist pedagogy could inform our teaching. Again this was the stimulus of working with people across the different disciplines and the excitement of dealing with different questions.

My more recent research has been looking at the implications of the new genetics and the issues for scientists as they generate new knowledge and present society with new choices about how we are going to deal with these technologies. This is a field that is going to need continuing work.

**OBR:** What will you miss most about leaving the Bioethics Centre?

**BN:** What I am going to miss most are some of the people associated with the work of the Centre, and the excitement of students discovering new ways of thinking about things, gaining confidence in the ability to think things

*Continued on page 16*