Clinical trials in neonates: ethical issues

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Abstract

Clinical trials in neonatology often raise complex ethical problems. This paper suggests that in tackling these it is useful to identify and separate out those elements of the problem that are genuinely ethical (e.g. can I enter a child into a trial if I am not in personal equipoise?) from those that are empirical (e.g. what is the evidence for a treatment's effectiveness?) and those that are formal (e.g. what do codes or the law permit?) The genuinely ethical elements are examples of philosophical problems and must be tackled in a way appropriate to such problems. In practice this usually means some form of systematic argument. This is often frustrating to clinicians who are more used to the assuredness of empirical research. The paper next examines two ethical problems that arise frequently in neonatal trials. The first is equipoise and the related issue of recruiting parents who are not in equipoise because they strongly desire that their baby get the active treatment. We briefly defend the recruitment of such "desperate volunteers". The second is informed consent. We discuss the nature and value of informed consent and suggest that clinicians can often obtain worthwhile consent even in very difficult trials. The final section of the paper uses the example of clinical trials for brain injury to illustrate the difficulties.

Key words

Neonatology; clinical trial; ethics; equipoise; consent.

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Introduction

If neonates are to receive the best possible treatment, clinical trials involving them must take place. However, doing such trials raises complicated ethical issues. These issues are not unique to neonatology but some of them may be more common or acute than in other areas of medicine. This paper focuses on two issues in particular, equipoise and informed consent. These issues themselves arise as many different types of problem in practice. The paper begins, however, with the question, "What is an ethical issue?" This is of importance as sometimes, issues that are not ethical are mistakenly thought to be so and *vice versa.* Furthermore, once we recognise what type of problems are ethical we can also recognise the correct means to tackle them.

What is an ethical issue?

Isaiah Berlin usefully distinguished three types of questions: empirical, formal and philosophical.[1] Empirical questions are those that are, in principle at least, answerable by reference to sensory experience: observation, experiment and the like. Similarly, empirical science is that which tackles such questions. Formal questions are answerable by reference to a man-made system, such as mathematics, games or law. Questions such as "What is the square root of 9?" or "How does the knight move in chess" are answerable by applying the relevant formal system, not by observation of the world. Clearly many questions will combine both types. "How many chairs are there in the room?" is empirical and formal. However, it is primarily empirical.

Finally, there are philosophical questions. These are those that have no obvious empirical or formal method for answering them but which nonetheless appear to make sense. They belong academically within

the discipline of philosophy. However, just as the empirical questions of medicine impinge on our lives, so do philosophical questions. Chief amongst these belong to the branch of philosophy that concerns itself with questions of right and wrong conduct, good and bad character, and the like: that is, ethics. Hence a question such as whether a particular neonate, faced with a short life of severe handicap, should be given treatment aimed at keeping him alive, is primarily an ethical one. This then gives us a definition of an ethical issue. It is one in which an ethical question or questions will play a large part in its resolution.

Berlin's distinction is useful because it helps us think more clearly about the type of problem we face and the appropriate means for resolving it.[2] Neonatologists, like most clinicians, have a background that is primarily in the empirical sciences; their means of resolving problems is usually through recourse to evidence. Where the problems faced are primarily empirical this is entirely correct. In deciding whether surfactant is the appropriate treatment for a neonate, empirical evidence is the standard to choose. Where clinicians may err is in attempting to resolve, or believing they can resolve, ethical issues empirically.

An example may help illustrate this; a paper entitled, "Is venepuncture in neonatal research ethical?"[3] The researchers do a questionnaire study assessing parents' report of their feelings about the test and of doctors' perception of parents' feelings. They conclude that "venepuncture in neonates seems to be acceptable to most parents and is associated with a favourable risk: benefit ratio …" This, however, does not answer the question posed by the paper. That question cannot be answered empirically as it is a philosophical/ethical question. What is required is some notion of what would make venepuncture ethical. In the paper, the authors seem to imply something along these lines: venepuncture will be

ethical if it accords with guidelines of the British Paediatric Association and if it is acceptable to parents (in the sense that it doesn't upset them too much). However, in order fully to answer the question posed by the paper the authors need to state this explicitly and, perhaps, to defend it.

How, though, would the authors go about mounting such a defence? Here it is useful to return to Berlin's distinction. An empirical question is answered through observation and experimentation; a good answer to such a question is one that is obtained systematically and which can be replicated. A formal question is answered through application of the formal system; a good answer is one which can be replicated. A philosophical question is answered through some kind of systematic argument. There are many types of argument; dialectic is one example.[4] A good answer is one that is convincing (or, more precisely, should be convincing to one who is rational). So, the authors would defend their definition of what counts as an ethical intervention through some kind of argument attempting to convince the rational reader.

For many clinicians, philosophical argument is immensely frustrating. Used to the certainty of evidence based medicine, with its gold standards, philosophy seems to present answers that only ever hold tenuously, until the next, better argument comes along. It is tempting, therefore, to try to answer philosophical questions empirically; but this cannot be done. It is tempting also to try to answer them formally. In ethics, particularly, one might do this by recourse to the law or to codes of conduct. Ultimately, though, the success of such an enterprise will depend on whether the law or codes themselves have answered the ethical questions well. For example, researchers have criticised the data protection law for preventing epidemiological research. One way of describing their criticism is as a philosophical argument: the law places too much value on consent (to

the use of data) as opposed to the value of what could be done with this data.

Many of the problems we face in clinical trials may be a combination of empirical, formal and philosophical questions. In tackling them we should try to be clear about what type of question we face and, therefore, the appropriate method for resolving it. It seems unlikely that clinical trials in neonatology face any unique problems. However, there are a number of features of neonatology that result in certain problems occurring particularly frequently or acutely. These features include: that neonatology is a relatively new discipline, resulting in a need to trial many interventions; the incompetence of the research subject, resulting in difficulties relating to proxy informed consent; the immensely fragile nature of the research subject, resulting in potentially large benefits and harms from experimental interventions and, therefore also, difficulties in assessing equipoise; and the fact that clinical trials are quite often done in situations of urgency, resulting in questions of whether or not informed consent is possible and whether a consent waiver should be given.

In the rest of this paper we shall consider some of these issues. We focus on two in particular, although we shall brush against other issues in our discussion (such as the desperate volunteer problem). The first is equipoise, the second, informed consent.

Equipoise

As an example, the issue of equipoise arose in setting up the UK collaborative trial of extracorporeal membrane oxygenation (ECMO).[5] At the time it was set up, two studies had been performed the results of which, it was argued, might have undermined equipoise.[6-8] The trial organisers argued, however, that the unconventional design of the previous studies undermined their credibility and that, therefore,

equipoise remained about ECMO as a treatment for pulmonary hypertension: a proper randomised controlled trial (RCT) was justified.

We do not take issue with this conclusion. However, it is a good example from which to illustrate the complexity of equipoise (a concept on which there is a vast literature). At the heart of this complexity is the way equipoise combines both empirical and philosophical judgement. Equipoise is not simply a matter of whether or not we know that a treatment works or doesn't work.

Clinical trials are set up to avoid error to a certain degree. At the end of a trial we may typically be able to say that we can conclude that a treatment is effective with a certain level of certainty: if we have p=0.01 we can say that drawing such a conclusion will be wrong on one occasion in a hundred. This is not the same as saying we know with absolute certainty; very little in medicine is known to this degree. What is important is that we believe it is certain enough to act upon. And it is the link to action that makes equipoise particularly difficult.

When a clinician says he is in equipoise he means he does not know whether he should or should not give a certain treatment to his patients: an action. However, deciding whether or not to act is not simply a matter of empirical knowledge. We act on the basis of what we know but also of our values. If someone knows there is a pound coin on the road, whether or not she picks it up will be a function of how important the money is to her compared to other values, such as how important her time is or how important her well-being should there be traffic on the road. When a clinician decides to give a treatment it is because she knows it has been shown to be effective (to a certain level of certainty) and she values the outcome of palliation or treatment. In most cases this is straightforward and clinicians will hardly notice the value judgement running alongside the empirical one.

The times when it is not straightforward are where decision-makers disagree either over the empirical or the value judgement. Our concern here is with the latter. A good example is the judgement of whether or not to treat very premature infants. The disagreement between clinicians is not usually empirical: they all know the relevant empirical evidence. Rather it is ethical, of values: they disagree over whether the small chance of survival, and the quality of life of those who do survive, is worthwhile both in terms of resources and in terms of the best interest of the infant itself.

In that equipoise concerns a decision to act, to give a treatment, it follows that whether or not one is in equipoise regarding treatments will also be a function of values. A clinician may not share the equipoise of her peers not because she disagrees about the empirical evidence but because her values differ from theirs. She may, for example, think that a side-effect is particularly undesirable and that a new treatment which risks it should be avoided.

In setting up clinical trials, therefore, the question is not simply whether there is equipoise but whose equipoise should matter. In many trials this is not a problem as all relevant parties are either in equipoise or are, at least, indifferent between treatment arms in a trial. This will be the case most commonly when there is not too much at stake, as in some feeding trials. Controversy is more likely where the trial is into an intervention that is a potential treatment for a dangerous or debilitating condition for which current treatment is unsatisfactory, such as perinatal asphyxia. Here, whilst there may be equipoise across the clinical community, it may be that parents do not share it. Qualitative research involving trials in just such situations (the ECMO and TOBY studies)[9;10] found that many parents who gave consent for their neonate to take part in such studies were far from indifferent between treatment arms; they wanted their child to receive

the new treatment. Why should clinicians' equipoise, and therefore values, take precedence over parents' in this situation?

An alternative way of phrasing this question is to ask whether, in order for it to be ethical to set up and run a clinical trial, equipoise must obtain amongst all relevant participants, clinicians and parents. Such a stipulation would result in it being impossible to run randomised trials of treatments for the most debilitating and dangerous conditions. One would, instead, have to run non-randomised trials using, say, historical controls. As a result, one might argue, the areas most in need of strong evidence for treatments would have only weak evidence. However, where one runs randomised trials one runs into the problem of desperate volunteers. These are parents who agree to take part in the randomised trial only because it offers them a 50/50 chance of getting their child the treatment they want, rather than no chance at all outside the trial.

This desperate volunteer problem will perhaps be fairly common in neonatology. A recent paper attempts to defend the use of clinicians' equipoise in the setting up of trials and the recruitment of desperate volunteers.[11] This uses the notion of collective clinical equipoise based on the decisions of the Trial Steering Committee (TSC) and the Data Monitoring and Ethics Committee (DMEC). The paper argues that the reason these committees' notion of equipoise, and the related values, should take precedence, is because they reflect widely held social values. Given the complex nature of equipoise and the reams written on the subject this paper is unlikely to be the last word, however.

Informed consent

We turn now to informed consent. In any discussion of this topic it is useful to have three questions in the back of one's mind:

What is informed consent?

Why does it matter?

How much does it matter?

These are philosophical/ethical questions. The first is about the nature of informed consent, the second and third are about its value. Typically one finds that controversies about informed consent may involve some confusion between the two areas. Take the question of whether or not a thirteen-year-old girl can consent to the pill. Disputants may argue that such a girl is unlikely to have the maturity to make such a decision (a dispute about the nature of consent); or they may argue that the girl's decision should not be allowed to override her parents' views (a dispute about the value of consent). And often the argument will confuse the two areas; it pays to keep them separate. Using the nature/value framework, let us turn to the topic of informed consent in relation to clinical trials in neonatology.

Nature of informed consent

The most obvious point is that the research subject can never consent him or herself; the parents must do that. In order for the parental consent to be ethically sound and/or legally valid it should probably meet the standards applied to all other consent.[12] In other words, it should meet various criteria. First, those giving consent should be competent to do so; second, those giving consent should have adequate information and understand that information; and, finally, those giving consent should do so voluntarily, without coercion.

The main concern in neonatology has been that consent to clinical trials falls short of one or more of those criteria. This is particularly so in trials on very ill neonates and where the time available in which to consent is short. Such circumstances could undermine all the criteria. In relation to competence, the mother may have had a traumatic birth involving drugs that render her unable to think

clearly; she may even be unconscious. The father may be emotionally overwhelmed by the circumstances. In relation to information and understanding, parents may struggle to understand concepts such as randomization, particularly in the short time available. In relation to voluntariness, parents may feel pressured to consent to research studies knowing that the clinicians have their child's life in their hands. Furthermore, the consent of desperate volunteers can hardly be said to be voluntary.

At least two studies have suggested that at least some of these problems do eventuate in practice.[13;14] There is also evidence that parents who give consent for a trial in the early neonatal period later forget having done so.[15] One response of neonatologists has been to look to ways of improving the consent process, particularly in urgent and emergency trials. An example of this is the TOBY trial, assessing the effectiveness of whole-body cooling in the treatment of neonatal asphyxia. This is precisely the sort of trial where one might expect consent to be compromised: the treatment is for a life-threatening condition; the parents are usually unaware of any problem pre-natally; the trial is randomized; and the time available in which to decide about trial entry is short.

Aware of these problems, the TOBY TSC took pains to develop what it hoped would be an effective means of obtaining informed consent. This has two elements. The first is clinician training in the process of obtaining consent for the TOBY study, including role-play. The second is continuous consent: parents are given initial information about the trial, then further information if they are interested; finally, while the baby is getting the trial treatment, a clinician goes through the study with them again, checking understanding and ensuring they are happy for the trial to continue. A recent qualitative study of parents who gave consent to this trial suggests that these measures have had a good effect.[9]

Perhaps, then, clinicians should not be too hasty in believing it is impossible to get informed consent to some neonatal trials. They should also beware the "counsel of perfection". Informed consent should not be viewed as an ideal to which we aspire but which we can never obtain. Every decision in life is made against the backdrop of human frailties and uncertainty. There is no reason to aspire for to a standard of consent that is above this. Nonetheless, there may be situations in which it is impossible to achieve informed consent: the mother is unconscious and the father absent; there is extremely limited time available; the parents both have a learning disability. There may also be situations in which obtaining informed consent comes at a great cost. This may be in time and effort, as in epidemiological studies where it is now difficult to trace the parents to ask for consent. Or it may be emotional cost to the parents. In both ECMO and TOBY, there was evidence from qualitative studies that parents who gave consent and whose babies were then randomized to receive the control treatment were disappointed, sometimes bitterly. Are there times when we should forego consent? Answering this question requires that we look at the value of informed consent.

Value of informed consent

In considering the value of informed consent we need to think about what it is for. The standard reason is that its purpose is to respect people's autonomy. As Dworkin puts it:[16]

"All discussions of the nature of informed consent and its rationale refer to patient (or subject) autonomy" (p.5)

However, this sits a little awkwardly in neonatology. The term "autonomy" means, literally, "self-rule". Clearly the neonate cannot self-rule; and the decisions of the parents on its behalf are, to borrow Kant's term, heteronomous. What, then, is the role of their consent?

To answer this question is to call into question Dworkin's suggestion. Informed consent as a doctrine in medical research did not originate primarily as a method to safeguard autonomy; it was, rather, to safeguard well-being. Both the Nuremberg Code and the Helsinki Declaration emphasise the consent of research subjects/participants. Their origin was in the exposure of the horrific research performed in Nazi Germany.[17-19] The thought is that people do not usually put themselves into trials that expose them to unreasonable risk and harm.

This, then, may be one of the purposes of proxy parental consent on behalf of neonates; to safeguard them from harm. However, in this role it may be of fairly limited use. Clearly, parents will wish to safeguard their neonates. However, so do Research Ethics Committees, TSCs and DMECs as well as clinicians themselves. It is unlikely that parental consent contributes much to the protection of the neonate in clinical trials. So perhaps it has another role, one that we might express in terms of social recognition of the importance of families and parents. Our society is organised in such a way that children are brought up primarily within families. Parents take on the main responsibility and are required to make decisions on their behalf. They may not do so perfectly; but our respect for that system manifests itself in a respect for parental decision-making albeit imperfect.

This seems to give us a better handle on why parents should be asked their permission for neonates to be entered into clinical trials. If it is correct it helps us also in relation to what to do about consent that is of poor quality. For, faced with the difficulty of getting a reasonable quality of informed consent in some studies, some have argued we should waive the requirement for it.[20] Perhaps, though, if we think in terms of obtaining the best consent possible in the circumstances,

rather than informed consent of the type one would hope for in usual circumstances, we would be less concerned. If the role of parental consent is primarily to acknowledge the parental role then "best possible consent" does this job well enough.

We are still left, though, with difficult cases and difficult choices. Manning's point is not simply that getting informed consent to emergency neonatal research is difficult (or impossible); it is also that it is costly. It will inevitably take some time. One might test an intervention that is effective but only if performed very quickly. A requirement for consent of any kind might result in our never knowing this. Another cost is in the distress caused to parents.

It is perhaps possible to deal with Manning's point about distress to parents. The research available thus far suggests that even though parents recognise the difficulty and emotional pain caused through involvement in decisions about research and treatment, they do not wish to be excluded.[15;21] Similarly, the argument that Zelen randomization be used to protect the parents whose babies are randomized to the control group[22] is undermined by research suggesting that these are precisely the parents who would find such randomization objectionable.[23] This is evidence of the importance of the parental role from parents' own perspectives.

Manning's problem of the cost to emergency neonatal research itself of the consent requirement is not so easily dismissed. The argument here has shown why parental consent is very important, why it should not be put lightly to one side. However, is it so important that some research cannot be done, that some important evidence about effective treatment cannot be unearthed? Or, rather, should we view parental consent as important but defeasible?

What can we do?

However, this suggestion of defeasibility runs into problems when one considers the example of clinical trials and the treatment of brain injury. The aetiology of brain injury in human newborns is multifactorial and hypoxic-ischemic insults, genetic factors of susceptibility, growth factor deficiency, oxidative stress, maternal stress and infection, cytokines, have all been implicated in the pathophysiology of brain lesions associated with cerebral palsy.[24] The links between infection, cytokines and neurotrophins are complex and can have deleterious effects.

Some types of neuroprotective agents, such as NMDA receptors antagonists, are precluded because of a potential massive apoptotic cell death following the intervention. [25] In contrast, blockade of alpha-3-amino-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) and kainate receptors by drugs such as Topiramate or AMPA antagonists may not produce such deleterious effects on neuronal survival and neuroprotective effects were observed.[26] Positive allosteric modulators of AMPA receptors (S 18986) have been shown to be neuroprotective in neonatal animal models, by causing release of neurotrophins such as brain-derived neurotrophic factor (BDNF).[27] The role of cytokines, induced by infection, is predominantly deleterious in extending neuronal damage and a useful reduction of neurological deficit with tianeptine was shown to block the deleterious effects of inflammatory cytokines on neonatal excitotoxic lesions in a mouse model.[28] Tianeptine is a well-tolerated antidepressant drug used in human adolescents and adults. Trophic factors, such as IGF-1 and BDNF, which have anti-apoptotic properties, can prevent asphyxic or excitotoxic neuronal death in animal models of perinatal damage.

However, these drugs are experimental, or not used for neonates, and so there is great difficulty involved in testing drugs in neonates and children, which urgently requires an open and in-depth debate.[25] This is particularly the case as longitudinal development profiles have

been mapped out for brain maturation, allowing clear definition of where children may lie in their developmental trajectories.[29] While it is accepted that there is desperate need in some cases there is also great difficulty in obtaining potentially useful drugs for trials.

For financial and ethical reasons, the pharmaceutical industry has difficulties in making substantial investments in this area. Drugs may leave markers in development which are not necessarily due to the drug, but secondary to a combination of the modified lesion and the development stage when the drug was administered; such markers may appear in patient cohorts, leaving the doubt that the effects were due to the drug. Adolescents might therefore sue drug makers, where their lives have been saved, but where such developmental markers might, rightly or wrongly, point to the action of the drug. Thus the pharmaceutical industry has difficulties in supporting this difficult area. Society must have some willingness to accept benefit associated with risk. It follows that parental consent has a further role: to protect those conducting clinical trials from litigation. Furthermore, parental consent must be very strongly worded, even in difficult situations.

Clinical practice points

- When tackling ethical problems it is useful to distinguish between empirical, formal and philosophical elements of the problem.

- The philosophical elements must be tackled using techniques appropriate, such as systematic argument.

- One cannot answer philosophical questions empirically; this lack of empirical assuredness can be frustrating for clinicians.

- In neonatal randomised trials, clinicians sometimes recruit parents who are not in equipoise between the different treatment arms; they are desperate volunteers. Such recruitment is an ethical problem but may be defensible provided there is equipoise in the clinical community.

- Circumstances can make it difficult to obtain good quality informed consent to neonatal trials. This problem can be reduced to some extent through strategies such as continuous consent.

- Clinicians should avoid a "counsel of perfection" - obtaining the best consent in the circumstances is often good enough.

Research agenda

- Research into ethical issues will involve different methodologies from standard empirical research. Some empirical work is usually helpful but at some point it is always necessary to undertake philosophical work.

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