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Arch. Dis. Child. 2009;94:651-654; originally published online 19 May 2009;
doi:10.1136/adc.2008.155317

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Compassionate and innovative treatments in children: a proposal for an ethical framework

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Accepted 6 May 2009
Published Online First
19 May 2009

Optimism is a good characteristic, but if carried to an excess, it becomes foolishness. Theodore Roosevelt¹

ETHICS AND INNOVATIVE THERAPIES IN CHILDREN'S MEDICINE

We would define an innovative therapy as any newly introduced treatment, or a new modification to an existing therapy with unproven efficacy and side effect profile, which is being used in the best interests of a patient, often on an experimental and/or compassionate basis.

Innovation in treating those who are suffering has been a driving force in the advancement of medical knowledge and treatment for many centuries. Many commonly accepted techniques, for example vaccination or transplant surgery, have developed from the use of innovation in response to human need. In critical care medicine, the need for innovation is driven by the obligation to rescue, often in circumstances that do not permit prolonged deliberation. In contrast there exists an obligation to protect the weak and vulnerable from interventions that are unlikely to achieve their intended benefits, but which may be accepted because they provide hope in the face of an otherwise bleak outcome.

When accepted and proven approaches are failing a critically ill or suffering child, and some promising experimental therapy exists, it may be argued that there is a moral obligation to strive to obtain that therapy for the patient. Whilst those using innovative therapies should remain mindful of that ubiquitous maxim associated with Hippocrates, *primum non nocere* (first, do no harm),² perhaps an alternative ethos might be equally pertinent. If, as Plutarch suggested, "the omission of good is no less reprehensible than the commission of evil,"³ it might plausibly be argued that failure to use a therapy that has some chance of benefit, in this context, can be interpreted as failing to avoid harm.

However, Silverman specifically expressed the contrary view in considering the "advances" in neonatal intensive care towards the end of the last century:

Why, for example, are neonates chosen to receive the hoped for benefits of an untried treatment during the period of initial "haphazard" exploration, not provided with the same safeguards recommended for others?⁴

Silverman decried the argument, advanced by the Institute of Medical Ethics Working Group, that there should be a limit on the number of times

innovative therapy should be tried on children without formal ethical review. He asked "Why is there not a mandatory pre-review of the initial explorations?" Some 22 years later, perhaps we are attempting to meet his request.

This balancing of the risk and benefits in the uses of innovative and compassionate treatment is becoming increasingly complex. While innovation has been at the forefront of the advance of medical science, we now live in an era in which the use of treatments that fall outside the clinical standard of best evidential practice is increasingly questioned. Indeed, the lessons of the ICU seem pertinent to clinical practice in general:

There is no room in the modern ICU for medical "cowboys," either in trying approaches that have little physiological or pharmacological support or in applying therapies in a situation beyond hope.⁵

IMPORTANCE OF APPROPRIATE ETHICAL REGULATION

In our modern regulated, and safety-conscious healthcare system the application of standardised performance indicators and clinical governance mean that we look less to innovation to solve clinical problems, and more to the scientific method to provide evidence on which to base treatments. In this paradigm, research studies are designed to answer questions of therapeutic efficacy and safety, by minimising factors such as chance while assessing statistically the degree to which the observed effects of studied treatments compare with standard therapy or those that might occur randomly.

Clinicians, who wish to use truly novel or compassionate treatments, face an increasingly complex system of guidelines, protocols and professional standards before they may embark upon them. They may perceive these as overly bureaucratic or even truly inhibitory. Furthermore, the often lengthy processes of application for research ethics review, with its increasingly laborious paperwork and stages of scientific and ethical review, may also be perceived as acting as a serious brake on innovation.

Although both innovation and research are experimental in nature, their aims and objectives differ. One of the primary aims of research is to accumulate a generalisable body of knowledge that can be used for the benefit of future patients. In this construct the benefits of inclusion in a research project for the patient may be incidental. In contrast innovative treatment is not usually based on an experimental protocol and is often tailored to specific individuals in unique circumstances. Its

primary purpose is the benefit of patients, and though information gathering is not the primary intention, it is possible that useful information that can be the genesis of future research is obtained. As such, it may represent the autonomous and altruistic choice of patients when other hopes fail.

In the UK, proposals for research involving human subjects are examined by Research Ethics Committees (RECs): the latter have specific governance arrangements and a regulatory function. However, UK RECs have very limited powers to consider requests for the use of compassionate or innovative treatments outside the context of clinical trials, even if the latter have been reviewed in other ethical systems, for example US Institutional Review Boards (IRBs). Increasingly, matters of this kind have been brought to Clinical Ethics Committees both in the UK and elsewhere for consideration, but the latter have no statutory basis and do not as yet operate within a governance framework. Moreover, not all trusts that wish to use innovative or compassionate therapies will have access to such bodies. Nevertheless there is demand for a forum for informed ethical debate over such issues in UK practice; this demand is likely to increase in the face of continuing desire to apply innovative technology to patient care. Whatever the proposed mechanism for review of requests for application of innovative therapies, it may be logistically impossible to organise formal meetings of RECs or IRBs in situations where there is an urgent clinical need for action. The Declaration of Helsinki recognises this by granting clinicians the freedom to use new or unproven treatments if they believe that such treatment offers hope of saving life, re-establishing health or alleviating suffering, provided that clinicians have the informed consent of the patient.⁶

INCREASING DEMAND FOR THERAPEUTIC INNOVATION

However, it is precisely the circumstances in which innovative or compassionate treatments are used that makes such consent difficult to obtain. Moreover, there is an increasing global demand from those in the greatest need for access to experimental therapies long before the basic standard animal and human safety trials are completed. Those with most to gain and least to lose, those suffering from diseases with otherwise severe, perhaps imminently fatal outcomes, are less interested in their protection and more willing to try high-risk treatments.⁷

Indeed, the entire field of antiviral therapy in the first years of HIV/AIDS was driven by sufferers demanding access to “experimental” treatments long before conventional evidence-based trial designs would have allowed this.⁸ To deny such therapies to those who request them on the grounds that their circumstances limit both their capacity for informed choices and their freedom to make them seems unduly paternalistic, even if it is understandable. The situation is more complex in paediatric medicine where parents have the ethical and legal right to make decisions on behalf of their child, provided that they act in their best interests. They may request innovative or compassionate treatment for their child, even when there may be doubt as to whether the best interests’ criterion can be fulfilled.

However, the compassionate use of experimental treatments is becoming a necessity in paediatric practice, not least due to the relatively high number of rare, and occasionally unique, diseases. The latter may well need truly novel therapies that may have a theoretical basis for their use, but lack research or experimental justification. Bone marrow transplantation and enzyme replacement therapy have revolutionised the outcome in the diseases for which they were developed. However, it is increasingly apparent that these techniques can be applied to

other diseases or used in children outside their published indications, leading clinicians to question how best to proceed in such circumstances. Is there a limit as to how speculative a treatment should be if its intended aim is to preserve a child’s life? How much residual morbidity is acceptable after such attempts, and acceptable to whom? Indeed, how should clinicians proceed when faced with a clinical situation in which further treatment may well be considered futile? Should they “try anything?” at any cost? Increasingly there is the possibility to choose high-quality palliative care that is directed to meeting the physical, spiritual and psychological needs of the child and their family, and it seems good practice that this option is sensitively explored.

DEVELOPING AN ETHICAL FRAMEWORK FOR EXAMINING PROPOSALS TO USE INNOVATIVE TREATMENT

If innovative treatment is to be used, it is necessary to ensure that it is conducted within an ethical framework. Referral of requests for compassionate or innovative treatment to the Clinical Ethics service at a tertiary referral Children’s hospital has led us to develop a mechanism for ethical review whose principles we outline here. This framework has been designed from the basic ethical considerations we detail, to provide an aid to clinicians in their consideration of the use of innovative therapy. We do not specifically recommend external review by a Clinical Ethics Committee/service, because in the UK at least there may be places where easy and timely access to such a service is not possible either such a service because does not exist or does not provide this particular service. However, where such an entity is available, then from our experience clinicians find its input and review valuable. We believe that an ethical framework for reviewing requests—whether by a clinical team or ethics service—should combine considerations of scientific justification, professional consensus, autonomy (in paediatric practice meaning parental assent and either child assent or consent), the role of the hospital and research institute, and crucially an agreement to disseminate the results of therapy whatever the outcome. In this way, in the context of innovative therapies, the balance between the paramount best interests of the child in question but also the overall interests of current and future children in general can be served.

The ethical framework we have developed encompasses these considerations:

- ▶ There is a clear clinical need for this particular child.
- ▶ There is a realistic and reasonable scientific basis for what is proposed, which may be verified by an independent second opinion or review.
- ▶ There is realistic expectation that the child is likely to benefit from the intervention, for example some evidence from adult medicine, laboratory or animal research that this is likely to be the case.
- ▶ There is consensus in the team that what is proposed is in the child’s best interests and that there are no other reasonable or feasible or safer alternatives that might achieve the same result.
- ▶ The child’s family, and the child if competent or able to understand, actually does understand that the procedure is experimental and what its possible risks, benefits and alternatives are. The information standard should arguably be that which this family need to make the decision in question (consent).
- ▶ Allowing for the pressures produced by the child’s clinical condition, there should be no coercion, and the family should be free to withdraw at any time.

- ▶ The resources utilised by offering the treatment must be justified against likely success.
- ▶ The results of the use must be reported, whatever the outcome.

WHAT IS THE ETHICAL STANDARD THAT SHOULD BE MET?

The initial standard to be met is that the proposed treatment or intervention is in the best interests of the child. Considerations of best interests are complex and value-laden, depending on the extent to which they consider potentially conflicting wishes preferences and values of the child, family and treating teams. In the context of innovative treatment, there may be genuine equipoise over what treatment is in the child's best interests. It has also to be acknowledged that those who seek to introduce innovation or are likely to adopt it early will have different views on best interests than those who adopt innovation late or only when it becomes mainstream practice.

DETERMINATION OF CLINICAL NEED

A fundamental principle in considering what is in the child's clinical best interests is that there should be reasonable and plausible scientific grounds for the use of this particular treatment in this particular clinical circumstance for this patient. For example, there may be evidence to suggest likely efficacy from animal and/or adult studies, even in the absence of formal trials. The child's clinical situation should be such that such treatment offers, on balance, a reasonable chance of efficacy, balanced with the likely risks of burden to this child in so far as they can be determined and as they relate to the context of the child's illness.

HOW MAY CONSENSUS BE ACHIEVED?

The professional consensus should involve all appropriate members of the team; indeed peer review is an absolute requirement for such therapies. It is likely that teams will include both those who wish to use innovative treatments early and those who feel comfortable only when such treatments have become established. It is important that these conflicting positions are recognised and, where possible, resolved before treatment is given, especially if it demands the cooperation of the entire team. Depending on time and available expertise, it might well be appropriate to consider an opinion from another institution. The nature of the required opinion should be explicit; it should be concerned with the clinical facts rather than ethical values. However, where the person providing the second opinion has considered the latter they should try to draw clear distinction between facts and values, for example the views preferences wishes and beliefs that they bring and those of the child and family.

WHAT INFORMATION IS NECESSARY?

A clear statement concerning the innovative nature of the treatment should be recorded in the clinical notes. This should include recognition that the treatment is not standard therapy but innovative therapy, and that it is being used in the absence of successful and accepted standard therapy, and represents a justifiable departure from whatever conventional management exists.

Although there is no legal imperative to give more information than a reasonable or prudent parent might want in these circumstances, we believe that there is an ethical duty to give the information which these particular families might want to make the decision in hand. There is of course the duty to answer

all the questions they might have in so far as answers can be given. They should have written information and the opportunity to reflect upon it, in so far as clinical circumstances permit.

HOW MAY DIFFICULTIES IN OBTAINING VALID CONSENT BE ADDRESSED?

The most fundamental ethical principle of the appropriate use of innovative treatments that are perceived to be in the child's best clinical interests is obtaining sufficiently informed voluntary consent from a person competent to give it. How can the clinicians who propose using such therapy to the parents of a seriously ill child resolve the obvious problems in obtaining consent? Can parents really understand what is being proposed? How can they rationally consider the balance between the risks and benefits of a treatment when little is really known of these risks and benefits? Does not the fact that this treatment may be the last possible curative option for the child produce extreme coercion?

This is especially so if there are concerns that the family's justifiable worry about a child's condition and their desperation might impair their ability or competence to understand what is being proposed. Above all they must clearly understand that this is an experimental treatment, which may have significant short- and long-term adverse effects. The extent to which the family might feel that they must accept any treatment, which might prolong their child's life, could potentially reduce the voluntariness of the choices they make and should be sensitively explored.

The nature of any other alternative treatments and the reasons that they are being rejected should also be recorded. The response to the offer of the option of palliative care rather than continuing aggressive treatment should also be recorded, as it should be in the obtaining of consent for any procedure.

WHAT SHOULD HAPPEN IF A CHILD OR FAMILY WISHES TO WITHDRAW?

In a standard research project there would be the option to withdraw at any time for any or no reason, and we suggest this should also apply to cases of compassionate use of experimental treatment. Arguably the threshold at which withdrawal might be honoured is lower for innovative treatments than it would be for established therapies.

WHAT ARE THE RESOURCE IMPLICATIONS OF THIS THERAPY?

A fundamental consideration that relates to the use of innovative therapy is one of resource allocation. Rationing is an unavoidable part of healthcare provision,⁹ and by virtue of their status, compassionate and experimental treatments are a challenge for those charged with allocation of healthcare budgets. Of course this requires consideration of a full account of all other resources potentially required to deliver the innovative therapy. The latter may include, but are not limited to, increased length of hospital stay, intensive care admission, theatre provision and other supporting therapies on top of the basic cost of both innovative and ongoing treatment. This does not mean such treatments must necessarily be limited. Nevertheless it must be made clear to all that financial factors are a component of the overall ethical debate and also clear what means are used to consider them. Indeed, it should be deemed unethical not to consider resources in these situations, because of the need to satisfy the fundamental ethical tenet of distributive justice.

DUTY TO REPORT OUTCOMES

Finally, there is a need for reporting of the results of innovative treatments used in compassionate situations. This should include the cases where outcome has been adverse or less optimal than envisaged, as well as those where the treatment has been successful. It is often the latter which are selectively¹⁰ reported in the literature, but if adequate information is to be available for those tasked with making decisions about similar therapies in the future reporting of all outcomes is necessary. We believe that this is keeping with the recommendations of the Bristol enquiry¹¹ and likely to satisfy the desirable criteria for ethical decision making of transparency, honesty and accountability. This may include development of a wider national/international reporting system.

CONCLUSION

We have suggested an ethical framework to facilitate the use of innovative therapy in paediatric practice. Although every such case will have many unique features, we hope this framework will be an aid to clinicians using treatment in this challenging context, facilitating their approach to the ethical considerations involved.

Funding: None.

Competing interests: None.

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