Dealing with the unknown: reducing the proportion of unvalidated treatments offered to children

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The frontispiece of Bill Silverman’s book *Retrolental fibroplasia: a modern parable* is an image of the 12th century Jewish Arab polymath Mūṣā ibn Māyaṃ (Moses Maimonides). Maimonides holds a book with the following inscription: “Teach thy tongue to say ‘I do not know’ and thou shalt progress.” What does it mean to declare “I do not know”? Famously, former US Secretary of State for Defence Donald Rumsfeld, distinguished three situations:

There are things we know that we know.
There are known unknowns. That is to say there are things that we now know we don’t know. But there are also unknown unknowns. There are things we don’t know we don’t know.

When, on the basis of up-to-date, well-conducted systematic reviews of relevant evidence, we know we do not know and yet we fail to act, people have suffered and died unnecessarily. For example, the consequence of decade-long delays in addressing uncertainties about the long-term effects of fetal exposure to antibiotics given to women in preterm labour is that many individuals are living today with cerebral palsy that could have been avoided.1

Paediatricians have been better than other medical specialists in acknowledging and addressing uncertainties.2 The longstanding integration of evaluative research as an expected element in paediatric oncology is rightly held up as a model of serial evaluation of proposals for new treatment regimens; and this feature of routine practice has been fundamental in transforming the outlook for children with disease that was formerly rapidly fatal. The way that the paediatric haematologists and oncologists have organised their practice has meant that inferior as well as superior new treatments have been identified more efficiently than they have been in other medical specialties. This is important because new treatments for cancers in children3 and for other conditions4 are as likely to be inferior as they are to be superior to existing, standard treatments.

More recently, neonatologists have also behaved in similar ethically and scientifically exemplary ways. When there has been uncertainty about the effects of new treatments for newborns, for example extracorporeal membrane oxygenation and head cooling for neonatal asphyxia, neonatologists have sometimes agreed that these inadequately evaluated new forms of care should only be offered within the context of randomised trials until more was known about their effects.5

What can be done to build on and extend this exceptional track record of professionally responsible development of paediatric practice?

**CONFRONTING THE DOUBLE STANDARD ON INFORMED CONSENT TO TREATMENT**

Illogically, and with no empirical evidence to support it, a mischievous view has been promoted that the interest of the vast number of patients involved in the poorly controlled experiments of informal medical ‘tinkering’ are less in need of protection than are those of the relatively small number of patients who are involved in planned, properly controlled clinical experiments.6

Other paediatricians have drawn attention to the double standard of informed consent to treatment within and outside controlled treatment comparisons. As the British paediatrician Richard Smithells noted decades ago, “I need permission to give a drug to half of my patients, but not to give it to them all.”7 Another British paediatrician, Edmund Hey, spelled out the problem very clearly: “If I can convince myself that some totally new treatment strategy must be good I am allowed take it into use without getting any prior ethics clearance, and without bothering to tell the patient that it is a new and untested treatment. If I am cautious enough to want to be able to compare the new strategy with the one previously used, then unsystematic clinical drift suddenly becomes ‘research’ and I become swamped by an unending deluge of bureaucracy. Sloppy medicine is considered ethical while careful, thoughtful, medicine is treated as potentially unethical.” (Personal Correspondence, IC) American paediatrician John Lantos observed two decades ago “This confusing real world situation seems to reflect a confused ethical analysis”.8

**A SALUTARY EXAMPLE OF THE NEED FOR MORE INFORMED PUBLIC DISCUSSION**

Between 2005 and 2010, in the USA, Canada, Australia, New Zealand and the UK, nearly 5000 extremely preterm infants were enrolled in five randomised controlled trials (RCTs) designed to resolve long-standing uncertainty about which blood oxygen levels should be targeted when infants were being treated with oxygen.9–13 In the trials, infants were randomly allocated to have oxygen titrated to either a lower or a higher range of saturation within the range widely respected in everyday practice.

Surfactant, Positive Pressure, and Pulse Oximetry Randomized Trial (SUPPORT), the first of these trials to be reported,12 was attacked after its publication by a US lobby group—Public Citizen. An investigation by the Office for Human Research Protections (OHRP) criticised the study on the grounds that it allegedly subjected infants to a foreseeable risk of death without informing parents about this risk.14–16

The ensuing controversy missed a much larger and more worrying problem. Over the period during which the trials were recruiting, in developed countries around the world more than 50 000 extremely premature infants died each year, and the long-term disabilities of those who survived included chronic lung disease, cerebral palsy, and blindness. It is the more troubling that the parent of one of the authors (DM) was an observer in the SUPPORT trial, and that he remembered his son sitting in the back of the car wearing a breathing mask, his mother holding his hand “as we were being driven to the hospital where he would die”.17

### References

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5However, as OHRP noted, the trial information leaflet appropriately disclosed (29 May 2008 version, p.5) that the CPAP (Continuous Positive Airways Pressure) or intubation or surfactant arm of this randomised 2x2 factorial trial carried a risk of resuscitation, chest compressions and even death. Every parent was thus informed, before random allocation of treatments, that the SUPPORT trial entailed this risk.
Table 1  Potential strategies for integrating clinical trials into routine care and reducing ‘known unknowns’

| 1. Provide accurate information about benefits and risks of RCTs and of standard care | Systematic reviews show that RCTs of new treatments pose no greater risk than established treatments. Could hospital websites, fact sheets, and research consent forms convey this information in neutral, non-coercive language? |
| 2. Establish ‘research friendly hospitals’ | Hospitals and other healthcare organizations could be encouraged to implement practices that support RCTs by achieving recognition and accreditation. Regulatory bodies could consider nominating some of these research performance indicators as mandatory criteria for continuing institutional accreditation. |
| 3. Build stronger partnerships between parents and clinicians | Jointly agree priorities for research and equip parents and non-professionals as effective partners with clinicians in trials. |
| 4. Implement evidence-based practice for recruitment into RCTs | For example, a Cochrane review of 45 (non-neonatal) trials with over 43,000 participants identified telephone reminders, opt-out procedures for contact, and open (non-blinded) designs as associated with higher recruitment. |
| 5. Adopt most efficient designs for research | For example, factorial, cluster, cross-over cluster RCTs. |
| 6. Build and sustain clinical trials networks | Assist clinicians in conducting RCTs, help policymakers and clinicians make better use of information from RCTs, share infrastructure, standardize study tools and metrics and develop best practices for creating sustainable collaboration. |

RCT, randomised controlled trial.

preterm infants were subjected to different ranges of oxygen therapy outside the trials. Their parents were not consulted. They received no information sheets or consent forms. Most were unaware that the correct range of oxygen saturation was unknown or that their infants were treated differently from others. Surveys showed huge variations in practice, reflecting the target ranges of arterial oxygen their physicians happened to have adopted. These infants received ‘random care’ rather than ‘randomly allocated’ care. In his moving testimony to a committee of enquiry, John Lantos drew attention to the flawed logic of the positions of Public Citizen and the OHRP. He had recently become a grandfather of two extremely premature twins who were ineligible for participation in the SUPPORT trial. One of the twins died and the other survived with visual impairment. He pointed out that, had the twins been eligible, and had their parents read a consent form that warned them of the potential risks and they decided not to enrol, no federal agency would have scrutinised the consent process and there would have been no public outcry. However, there should have been, because the risks of non-validated therapy are no less, and may be greater, than the risks of comparative effectiveness research studies like SUPPORT. He called on OHRP to require that potential research participants be given accurate information about the risks and benefits of research and of non-validated therapy.

An important lesson from the oxygen targeting trials is that well-intentioned variations in practice can lead to preventable morbidity and mortality. Many had concluded from various analyses of observational data, without evidence from RCTs, that lower saturation targets safely reduced the risk of severe retinopathy. Others judged the evidence so clear that it would be inappropriate to randomise infants to higher oxygen saturations. It now appears that many deaths might have been avoided had these infants participated in the neonatal oxygen trials.

MAKING A CHOICE: WELL-CONTROLLED OR POORLY CONTROLLED EXPERIMENTATION IN TREATING CHILDREN?

Many physicians attack experimentation, believing that medicine should be a science of observation; but physicians make therapeutic experiments daily on their patients so this inconsistency cannot stand careful thought. Medicine by its nature is an experimental science, but it must apply the experimental method systematically. Claude Bernard, 1865.

Translated Claude Bernard’s observation into the circumstances of the 21st century, what should be done to engage parents, carers and children themselves in choosing between well-controlled and poorly controlled treatment experiments? Once they have been made aware of the litany of adverse consequences of using inadequately evaluated treatments in paediatrics and in medicine more generally, what do patients want doctors to do when there is uncertainty about the relative merits of alternative treatments?

If it is, indeed, a professional duty to try to reduce the number and proportion of unvalidated treatments offered to children, what can be done to confront that situation that is clearly not in the interests of children or their parents and carers?

Several organisational changes could make it easier for paediatricians, parents and children to contribute to a reduction in unvalidated forms of treatment (table 1). Nothing less than a major shift in organisation is needed to promote the ‘integration of clinical trials … as a routine activity within clinical care.’ However, in the light of Public Citizen’s reaction to the SUPPORT trial, surely the most challenging agenda is to encourage much greater patient, parent and public involvement in understanding why it is important that treatment uncertainties should be addressed, and how they can play their part in shaping the research agenda.

CONCLUSION

It is important that research is performed safely, rigorously and transparently to high ethical standards. It is critical that community concerns about research are openly addressed. However, we must not lose sight of the risks and harms of not participating in research, and in failing to subject current treatment to careful evaluation. Partnerships involving patients, parents and researchers can help ensure that fewer children suffer and die needlessly because the number and proportion of unvalidated treatments offered to children remains too high.

We must change community culture so that one of the first questions asked by parents with a baby in newborn intensive care is “Are there any randomised trials my baby can join?” Melinda Cruz, parent.

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REFERENCES

20 Routine use of unvalidated therapy is less defensible than careful research to assess the effects of those treatments. http://www.testingtreatments.org/2014/05/13/non-validated-therapy-often-dangerous-careful-research/(accessed 16 Dec 2014).
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