# THIS WEEK

## EDITORIALS



# Subject to question

*Even when conducting clinical trials to study widely used therapies, researchers must ensure that they disclose the full risks to patients.*

Full disclosure of the potential risks to people who volunteer to be test subjects for biomedical research has been a bedrock of ethical protections for decades. Now, a fresh question has come to the fore: how best to protect human subjects in trials that examine the effectiveness of existing therapies that are already in widespread use.

On 28 August, the US office charged with protecting human research subjects will hold an unusual public meeting in Washington DC to tackle this contentious, complex issue, which has polarized the biomedical community in recent months. The Office for Human Research Protections (OHRP), part of the Department of Health and Human Services, is asking for input on how institutional ethics committees — the advisory boards that decide whether proposed trials can go ahead — should assess the risks to people in randomized studies that investigate the risks and benefits of existing treatments for the same condition. Such 'standard of care' trials are likely to become more widespread after being mandated in the 2010 health-care law, so a lot is riding on what the OHRP decides. It might insist that these risks be spelled out on patient-consent forms, even though patients with a particular condition would be taking one or the other medication anyway. Those who argue for looser regulations of such research say that this move could put many volunteers off, because they might mistakenly think that the research itself is adding risk of harm.

The issue has been thrust into the spotlight by a protracted controversy over a study of extremely premature infants, funded by the US National Institutes of Health. From 2005 to 2009, the Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT) enrolled 1,316 infants born, on average, 14 weeks early and weighing less than a kilogram. Such infants struggle to breathe because of their immature lungs and so are given extra oxygen from birth. Those in the trial were assigned at random to one of two groups. In one, blood oxygen levels were kept at the higher end of the range used in US hospitals, with the attendant risk of causing an eye disorder called retinopathy of prematurity (ROP) — an abnormal growth of retinal blood vessels that blinds 400–600 US infants every year. In the other group, oxygen levels were kept at the lower end of the range, with the accompanying risks including neurodevelopmental disorders and, some experts in the field believed, death. The goal was to determine the effects of lower or higher oxygen levels on the infants' survival, neurological development and likelihood of developing ROP. In short, the trial sought the sweet spot — the level of oxygen supplementation that would lead to maximum survival without damage.

### RISK AVERSE

In 2011 the OHRP, responding to a complaint, began to investigate the informed consent forms signed by parents at the 23 SUPPORT sites. In March this year, it concluded that the forms failed to describe "the reasonably foreseeable risks of blindness, neurological damage and death". All but two of the forms failed to note, for instance, that infants in the group maintained at higher oxygen levels would have a greater chance of eye damage, yet more than half said that infants in the lower-level group could benefit from a lower risk of eye disease or less need for eye surgery. None noted the increased risks of neurodevelopmental disorders in the lower-level group. None listed death as a possible risk of the procedure, although the trial protocol (not seen by parents) did list death among the related adverse events "that may be related to the study". The consent forms did reassure parents that: "Because all of the treatments proposed in this study are within standard of care, there is no predictable increase in risk for your baby."

> ***"Transparency and respect for research subjects must be beyond reproach."***

Much of the biomedical establishment has rallied to support the trial investigators and the ethics committees that approved the informed consent forms. They argue that the babies encountered a set of grave risks inherent to being premature, not to being randomly assigned to one or the other arm of the trial. Because the trial administered treatment within accepted guidelines endorsed by the American Academy of Pediatrics, they say, the study added no risk and thus the consent forms were adequate.

The goals of SUPPORT were laudable and addressed a need for better information for physicians. And the study did produce illuminating findings: the infants who received lower levels (aiming to keep the oxygen saturation of their haemoglobin at 85–89%) were less likely to get severe eye disease — but more likely to die — than infants receiving oxygen at 91–95% saturation levels. But in an age in which it is more important than ever that transparency and respect for research subjects must be beyond reproach, the SUPPORT consent forms simply do not pass muster. And although it is true that, collectively, the infants enrolled in the study may have been at no greater risk of a negative outcome than infants who were not enrolled, it is not collectives who sign informed consent documents. It is individuals.

Put yourself in the position of a parent with an extremely premature infant. Would you make the decision to enrol your child in the trial if the consent form stated in simple language that babies assigned to one group were more likely to go blind, and that those in the other were at a higher risk of getting neurodevelopmental disabilities? Equally, would you decide to enrol if the form spelled out that, if you do not take part, your own physician and institution might keep your infant in the middle of the range, trying to avoid either outcome? Perhaps you might, but you would do so with full knowledge of the attendant risks. The parents in this case could not do so.

In June, under pressure from many sides, the OHRP said that it would not sanction the SUPPORT investigators and instead would hold next week's meeting. No matter the thorniness of the issues raised there, research is still research in whatever context, and the duty to protect human subjects must remain paramount. ■