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With a Little SUPPORT from our Friends: Children, Trials and Bioethics.

Angus Dawson and Paul Baines

From the perspective of the other side of the Atlantic, it looks as if a new American Civil War has begun. Skirmish follows skirmish in an indecisive conflict in the blogosphere and on the letters page of the *New England Journal of Medicine*: two opposed camps of clinicians and bioethicists engaged on the field of battle. One group applauds the recent US Office for Human Research Protection's (OHRP's) judgment in relation to claimed inadequacies in the informed consent documentation in the Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT)[1], whilst the other suggests the OHRP was mistaken and that the judgment fails to consider the issues of risks fairly and fails to consider the implications for medical research on children more generally.[2] We know and respect bioethicists in both camps, and do not write simply to add force to one side or another. Instead, we wish to step back from details and make some broader points about the nature of research ethics, particularly relating to children. We start with the cultural observation that it seems odd that two groups of respected academics can disagree so profoundly on such fundamental matters. How could this come about, and what does it tell us about the nature of bioethics in the US? No doubt there are personal rivalries and antipathies between at least some members of the two groups, but this cannot explain the radically different conclusions about this trial. There are also perhaps different ideas at work here about the nature and purpose of bioethics. Is it academic (to explore concepts and arguments), collaborative (working with clinicians to improve medical practice and research), or should it have more of an advocacy role (focused on critiquing pharmaceutical companies and their influence in medicine and other current practices)? Given what we know about some of the signatories to the two NEJM letters, this is certainly one influence. However, we need to begin at the beginning. What was SUPPORT?

SUPPORT was conducted by a cross-US team of researchers supported by the Eunice Kennedy Shriver National Institute of Child Health and Human Development. For some time it has been appreciated that both too little and too much oxygen delivered to babies with breathing problems is harmful, but the optimal oxygen level was unknown. The SUPPORT trial was designed to answer this question for premature babies. In the trial conducted in the US from 2005 to 2009, published in 2010, severely premature infants (under 28 weeks gestation, but of at least 24 weeks gestation) were randomly assigned to oxygen saturation target levels within a range of either 85-89% or 91-95%.[3] Across the US and the

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[1] Macklin, R. et al. The OHRP and SUPPORT – Another View. N Engl J Med 2013;369:e3. DOI: 10.1056/NEJMc1308015

[2] Wilfond, BS. et al. The OHRP and SUPPORT. N Engl J Med 2013;368:e36. DOI: 10.1056/NEJMc1307008

[3] SUPPORT Study Group of the Eunice Kennedy Shriver NICHD Neonatal Research Network. Target Ranges of Oxygen Saturation in Extremely Preterm Infants. N Engl J Med 2010;362:1959-69

rest of the world, both of these oxygen saturation target levels were in widespread use within clinical practice and no definitive evidence existed about which was preferable.[4] Consent was obtained from parents or guardians before the birth of the child. The primary outcome was the development of damage to the eyes, often resulting in blinding, called retinopathy of prematurity (ROP) or death before hospital discharge. At the end of the trial, with 1316 infants enrolled, no significant difference was found between the two groups in the primary endpoint (found in 28.3% of those in the low saturation group and 32.1% of those in the high saturation group). However, the composite primary endpoint concealed a higher mortality in the low saturation group (19.9% contrasted with 16.2%) which was compensated by a lower incidence of severe ROP in the low saturation group (8.6% versus 17.9%).[5] Mortality remained higher in the low oxygen saturation group when the children were neurodevelopmentally assessed at 18-22 months (22.1% compared with a mortality of 18.2% in the high oxygen saturation group).[6]

That this was an important trial is beyond doubt. Severely premature infants have a significant chance of dying, and those that do not die are often left with severe impairment.[7] A large multinational (UK, Australia, NZ) trial, BOOST II, using the same oxygen saturation targets (85-89% and 91-95%) running from 2006 closed early following an interim analysis of 2315 enrolled infants (including the 1316 infants enrolled in SUPPORT) that demonstrated a very significantly higher mortality in infants treated with the lower oxygen saturation targets of 85-89%.[8] As a result of these studies, clinical practice in relation to the management of premature babies has changed.

This might have served as a paradigmatic example of how international, collaborative clinical research can benefit individuals and communities, if it ended there, but the US Office for Human Research Protection (OHRP), the organisation given the responsibility of enforcing US federal research regulations, pursued an investigation after allegations of inadequate consent procedures in the SUPPORT study. In a letter setting out their findings the OHRP reprimanded the researchers and claimed that 'the conduct of this study was in violation of the regulatory requirements for informed consent, stemming from the failure to describe the reasonably foreseeable risks of blindness, neurological

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[4] The study also (in a factorial design) allocated infants randomly to intubation with early surfactant administration, or early continuous positive airway pressure (CPAP). However, this part of the research was reported separately, and has not been the subject of any criticised, so we set it to one side.

[5] SUPPORT Study Group, op cit.

[6] Vaucher YE, Peralta-Carcelen M, Finer NN, et al. Neurodevelopmental Outcomes in the Early CPAP and Pulse Oximetry Trial. N Engl J Med 2012;367:2495-504. DOI: 10.1056/NEJMoa1208506

[7] Morley CJ. CPAP and Low Oxygen Saturation for Very Preterm Babies? N Engl J Med 2013 362;2024-5

[8] The BOOST II United Kingdom, Australia, and New Zealand Collaborative Groups. Oxygen Saturation and Outcomes in Preterm Infants. N Engl J Med 2013;368:2094-104. DOI: 10.1056/NEJMoa1302298

damage and death'. They state that the information sheet should have made clear that neonates participating in the study could have received a different level of oxygen from those not involved in the study and that this 'could increase the risk of brain injury or death'.[9] However, a number of clinicians and bioethicists objected to this judgment, suggesting that it required the researchers to notify the participants about risks that they could not possibly have known about until after the SUPPORT data was analysed. The danger, on this view, is that the informed consent process is judged in retrospect to be inadequate, because of the very findings of the research itself.[10]

As can now be fully appreciated, even determining the facts of this case is difficult. However, we don't think that the dispute merely relates to the complexity of the trial. The disagreement is ultimately a normative one. The bioethics supporters of OHRP argue that the parents of the children involved should have been told more about various aspects of the study. Their focus is on the need to obtain adequate informed consent and presumably this can be supported by appeal to the central role that autonomy is often held to have in research ethics. The bioethics opponents of the OHRP judgment suggest that the information sheet and informed consent procedures were adequate, given the knowledge at the time of the initiation of the trial. They focus on the existing standard of care at that time (that ran across the whole range of the two saturation levels), the existence of disagreements between clinicians about what treatment option was best, and that, given these facts, participants in the trial were clearly no worse off than those who were not.[11] The primary focus here is on benefit and harm. So, perhaps one source of disagreement between the two armies is a tendency to see different principles or values as being key to judging the appropriateness of this study, or indeed any research study.

It is interesting that those supportive of the OHRP's ruling do not seem to dispute that the research was prima facie necessary and worthwhile, they only focus on the issue of consent.[12] However, some others clearly do think that

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[9] http://www.hhs.gov/ohrp/detrm_letrs/YR13/mar13a.pdf (accessed 15/8/13). However, it is worth noting that a subsequent letter has tried to minimise the implications of the initial findings for other research, although they affirm their finding about the nature of the SUPPORT consent process: http://www.hhs.gov/ohrp/detrm_letrs/YR13/jun13a.pdf (accessed 15/8/13)

[10] Drazen, JM. Et al. Informed consent and SUPPORT. N Engl J Med 2013;368:1929-31 and Magnus, D. & Caplan, AL. Risk, Consent, and SUPPORT. N Engl J Med 2013;368:1864-5.

[11] Indeed, it is interesting to note, as John D Lantos points out, that in retrospect we can see that participants in the trial were actually at an advantage because we can compare the reported results of the SUPPORT trial with the routine data collected on all premature infants. http://www.thehastingscenter.org/Bioethicsforum/Post.aspx?id=6306&blogid=140 (accessed 15/8/13)

[12] Macklin et al, op cit.

conducting such research on children is problematic in itself.[13] But what is the alternative? Is it appropriate to require clinicians to make their decisions based upon their intuition or tradition instead? Isn't it better to obtain clear and systematic answers about the relative merits of treatment options? The researchers should not be presented as Nazi experimenters, wanting to perform gruesome and pointless research on children. This was therapeutic research, where the relevant harm threshold for research participation was met, and significant benefit from improvements in treatments for children as a group.

Given this disagreement, which value or principle should take priority? It seems odd to us to place such a focus on informed consent here. Indeed, one thing that the dispute perhaps reflects more than anything else is the curious prominence of informed consent in so much of the research ethics discourse. It seems to be forgotten that the actual participants were premature children, and therefore unable to consent themselves. So, those to be informed were the parents and guardians as proxy decision-makers for their children. Is it obvious that we should treat a parent's consent on behalf of their child in just the same way that we would if they were consenting for themselves? We think not. Protecting children from potential research abuse requires a stronger emphasis on other ethical aspects than just consent. Even if we think that competent adults can look after their own interests, and should be permitted to expose themselves to any harm they wish, it does not follow that parents should be able to do the same for their children. It, therefore, seems odd to place consent at the centre of the dispute. Can parental consent, alone, legitimate an action that puts a child at risk of harm? Do parents alone have a right to determine that their children should participate in any research? Surely not. The key issue in research on children is not that of consent, but rather the fair assessment of harm related to participation in the research versus standard treatment. Parents may be given more or less information, or they may understand more or less of the information that is provided. But the central issue is about risks and this assessment is to be made by IRBs as well as (in this case) parents. Indeed, it might be argued that the primary obligation of an ethics committee is to ensure that participants are protected from unnecessary harm.[14] We suggest that this obligation was clearly fulfilled in this case, and as far as we can make out, given the rather confusing expression of their views, the OHRP agree.

Another common option for justifying interventions (including research) on children is to appeal to the idea of best interests.[15] We presume that parents will act in the best interests of their children, but to what extent is best interests the relevant test here? Is it ever in the best interests of a child to be involved in research? This may be doubted, as it seems odd to think of the relative risks of

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[13] Public Citizen's letter: http://www.citizen.org/documents/2111.pdf (accessed 15/8/13)

[14] Garrard, E. & Dawson, A. What is the Role of the REC? Paternalism, Inducements and Harm in Research Ethics. J. Med Eth. 2005, 31:419-423.

[15] P. Allmark, S. Mason, A. Gill & C. Megone. Is it in a neonate's best interest to enter a randomised controlled trial? *J Med Ethics.* 2001; 27: 110–113.

participation and non-participation in this way. For SUPPORT it certainly seemed at the start of the trial that participation was *no worse* than non-participation or 'normal' treatment, but it is ~~a~~ stretching the everyday meaning of the term to call participation in the 'best interests' of a child.

There are important issues for us all to learn from the SUPPORT saga. One of the reasons this issue created such vociferous debate in the US is the role of the OHRP. This is a federal body with immense powers. The US's system of conducting research ethics is unusually in many respects. It is essentially a legal system, not one focused on ethics. By this we mean that law must follow the rules as laid down in the relevant statute, whereas ethical judgment can allow for more flexibility and response to individual cases, it can weigh different ethical values or principles against each other. If the law says that an informed consent must be obtained, then it must be obtained. Arguably, complex ethical judgments about the justifiability of research cannot be captured by such an absolutist approach. There is a warning here for all research ethics regulators.

The discussion of the SUPPORT trial brings out the fact that there is still no consensus on how research ought to be conducted on children, although it is almost universally held to be necessary. It is certainly the case that justifications for conducting research on children that appeal to the rights of the parents to decide or the idea of the 'best interests' of the child look grossly inadequate. Turning to the traditional magic bullet of bioethics, informed consent, hardly seems to be the answer either. Considerations of harm, is and ought to be, at the centre of the discussion. We don't see any early end to the new American civil war going on in bioethics, but perhaps its time to go back to fundamentals. If we accept that research on children is ever necessary, what is it that justifies it?