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Quality Improvement Ethics: Lessons From the SUPPORT Study

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Abstract

The Office of Human Research Protections was not justified in issuing findings against the SUPPORT Institutions. Our community can learn from the evolving healthcare transformation into learning health systems by thinking about the novel ethical issues about standard of care research raised by the SUPPORT with the same spirit of quality improvement. The current regulatory framework and the concept of foreseeable research risks is insufficient to advance the debate about the ethics of randomization of standard clinical interventions. This article uses the example of the Wisconsin cystic fibrosis randomized clinical trial for newborn screening trial to explore the distinctions between risks of research and clinical care and waivers of informed consent for randomization. Collaborative exploration of these complex policy issues is needed and further deliberation, community engagement, and social science research will be critical to advance novel approaches for informed consent.

Keywords

comparative effectiveness research; informed consent; neonatology; IRB; randomization

I first became aware in April 2013 of the finding by the Office for Human Research Protections (OHRP) against the University of Alabama, Birmingham, and other institutions that the Surfactant Positive Airway Pressure and Pulse Oximetry Trial (SUPPORT; Carlo et al. 2010) failed to meet regulatory informed consent requirements, in particular regarding reasonably foreseeable risks of study enrollment. I read several commentaries that raised concerns that the finding by OHRP represented a precedent with far-reaching implications for valuable patient-centered outcomes research (Drazen et al. 2013; Magnus and Caplan 2013). My first thought was that this was a complex issue and it would be interesting to consider in more detail; I was not sure why OHRP came to the conclusion that the process and the approach were so far below threshold of standard practice to warrant the finding.

But I was already overcommitted at work with current projects, committees, and so on, and I was on my way to spend a week with my mother who was moving out of her apartment and into an assisted care setting. As I was helping my mother go through her belongings, I came across a clipping that she had saved from my college newspaper. It was a story about how a

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classmate and I had organized a petition that was eventually signed by 50% of our student body regarding the decision to deny tenure to a history professor. The professor was one of the most academically rigorous and intellectually stimulating teachers I had encountered. The newspaper story was told from the vantage of how unusual it was for students to spend their free time organizing a petition. In the story, I was quoted as saying something like I was not expecting the college to reverse its decision but that I thought it was important for this professor and for the administration to know that we were concerned that the decision did not make sense from our perspective. Looking at the news clipping, I contemplated that I no longer had time for such quixotic quests.

Over the following weeks, I thought more about SUPPPORT trial and was troubled by it. I appreciated that I did not know the full details of the study and any additional concerns behind the decision by OHRP (one of the lessons from my history professor was that there was more than one way to tell any story). I also reflected on my experiences as an institutional review board (IRB) member and the challenges of making balanced decisions. I also thought of ethics research projects that I had participated in that illustrate the arbitrariness of IRB judgments about key issues (Churchill et al. 2003; Miller et al. 2003; Shah et al. 2004; Whittle et al. 2004) and the variability of consent forms (Hull et al. 2004; King et al. 2005). My impression is that IRB decisions and consent forms are imperfect, and one of the goals of my scholarship is to contribute to improving that process. I became concerned that well-intended efforts for improvement by OHRP may have adverse consequences for children, as well as for researchers and institutions.

So I thought about my college petition, talked with colleagues who were leaders in the Association of Bioethics Program Directors, and decided that OHRP and the researchers should know that some in the bioethics community did not agree that what happened during SUPPORT justified the response from OHRP. A letter was circulated, with countless drafts and revisions, and was sent to OHRP. The main message was that the OHRP decision was over-reaching, and that more deliberative discussion of the issues raised by research involving standard interventions was necessary. The letter was published (Wilfond et al. 2013) along with a commentary by NIH officials, who disclosed that OHRP had decided to suspend its finding and hold a public hearing. I soon learned that other colleagues whom I respected had come to a different conclusion about the OHRP findings (Macklin et al. 2013). The next section of this article includes some comments to these respected colleagues as to why I think OHRP was misguided.

THE SUPPORT STUDY AND IMPROVING ETHICS QUALITY

The balance between risks and benefits is a central ethical issue in research involving children. The prospective determination of risk is a complex judgment, reflected by a substantial literature for which consensus remains elusive (Shah et al. 2004; Wendler 2004; Wendler and Emanuel 2005; Wendler and Varma 2006). It is not clear that the SUPPORT study posed risks to infants beyond the general nature and frequency of risks of standard care. An IRB could have evaluated this study as either 46.404 (minimal risk) or 45.405 (prospect of direct benefit). This study was reviewed by 23 IRBs and deferral to IRB judgment for attribution of risk and review of consent language was appropriate.

Substantively, while the assignment of level of risk or harm from participation in this study is ambiguous, a reasonable case can be made that enrollment in this project entailed minimal risk. The risks to these children were from their underlying lung disease and the standard interventions. Clinically, the fraction of inspired oxygen in NICUs was routinely titrated to keep oxygen saturations measured by pulse oximetry to a range between 85% and 95%. This was believed to provide an appropriate range of blood oxygen content sufficient to ensure adequate gas exchange, while avoiding the harmful effects of high blood oxygen content; the chosen range was based on expert opinion and inferential data, and was standard practice.

It is important to appreciate the lack of precision of these measurements. Blood oxygen saturation represents a range of blood oxygen content, and pulse oximetry only approximately measures oxygen saturation. However, the pulse oximeter routinely is used because it does not require the direct measurement of arterial blood for oxygen content. It is important to learn more about how to use pulse oximetry to safely and effectively manage infants in the NICU with lung disease. As a pulmonologist who routinely gets consulted in the NICU, I long for data that would enable me to make better recommendations based on data rather than my clinical impressions.

In the SUPPORT study, supplemental oxygen was titrated using a *research pulse oximeter* that indicated the measured oxygen saturations in the blood to be between 88 and 92%, even though the actual range was 85–95%. Depending on the arm to which the infant was assigned, using a correction of 3%, these numbers corresponded to clinical saturations of either 85–89% or 91–95%.

This study design was necessary to obtain population data to learn how best to titrate supplemental oxygen. However, individual clinical management decisions were not likely to be affected by a 3% difference in displayed oxygen saturations. Clinical management decisions are made using additional data, including measured blood CO₂ content, clinical evaluation of the lungs, radiographs, the patient's response to other clinical interventions, and the perspectives of the nurses, respiratory therapists, and the parents.

Thus, it is not clear that children would be harmed by participating in the study per se. However, the hope was that the study would help us learn whether one approach was better and another approach was worse. Quality improvement is central to developing learning health care systems and as such it can improve patient outcomes, but it can also cause harm. Thus, oversight and patient/public awareness of quality improvement are necessary (Faden et al. 2013; Kass et al. 2013). The SUPPORT trial exceeded the rigor of oversight and patient awareness used with most projects designed to learn how best to use standard approaches, interventions, and monitoring to improve health (Rich et al. 2010).

There was less parental awareness and oversight of the care of the other children who were not enrolled in the SUPPORT study in these NICUs, who were essentially enrolled in observational research that was reported in 2012 (Rich et al. 2012). In this context, the baseline harms associated with standard care were demonstrated to be worse than those in either arm of the intervention study. Parental permission was not obtained for infants in the

NICU whose data were used for the observational project. It is typical to waive consent or permission for such studies. While the intervention study used a detailed approach to obtaining permission, its appropriateness was debated in the literature as the risks associated with the study were considered to be minimal (Whitney 2012).

There is an irony about our confidence in the quality of our ethical analysis about research to improve health care quality. Quality improvement and learning health care systems represent a worldview that acknowledges that the delivery of quality health care is undermined by our limited knowledge of what is the best care and limited capabilities of individuals to provide the best known care. This world-view relies on two foundational approaches to improve health care: (1) using empirical data (research methods) to improve quality and (2) acknowledging systems contributions to problems and seeking to improve systems rather than blame individuals for systems failures. OHRP could adopt a similar approach to look to systems improvements to improve the ethics of standard of care research.

CONSIDERING THE ETHICS OF STANDARD OF CARE RESEARCH FROM THE PERSPECTIVE OF MEMBERS OF THE CTSA CONSORTIUM

One of the consequences of the decision by OHRP to suspend its finding and engage in public discussion is that it created more opportunity for stakeholders to consider the broader issues raised. Members of the Clinical and Translational Science Award (CTSA) Consortium, from of the Clinical Research Ethics Key Function Committee (CRE) and the Child Health Oversight Committee (CC-CHOC), held a conference call in July 2013 to discuss SUPPORT and the issues raised by OHRP. The comments that follow are informed by that discussion and input by leaders of these groups and formed the basis for a response to the questions raised by OHRP.

The CRE accomplishes much of its impact through working groups, two of which highlight useful approaches to the questions posed by OHRP: (1) The *Ethics and Community Engagement Working Group* is committed to community involvement in all aspects of research. Input from the public, including potential research subjects, will be critical to interpreting federal policy for the protection of human subjects in ways that are acceptable to all and that further the public interest. Community engagement can provide important insights into specific research projects on standard of care when traditional approaches to informed consent prove challenging. (2) The *Consultation Working Group* is a network of individuals who provide research ethics consultations to researchers and IRBs at CTSA institutions. The working group's experience is that sustained deliberation over time with input from all relevant stakeholders can be useful when navigating novel moral terrain. OHRP could consider how to routinely convene content experts when new issues arise.

The CC-CHOC members are committed to improving child health using the scientific method. The traditional exclusion of children from clinical research has resulted in an even larger proportion (when compared with adults) of clinical practice provided without an evidence base. The great majority of drugs, devices, and clinical approaches used to treat infants and children have not been studied adequately for safety and efficacy in those

populations, so the deliberations here are particularly germane and standard of care research is critically important.

The comments that follow, submitted on behalf of CTSA consortium leaders, focus on three of the five questions posed by OHRP for the August 28, 2013, hearing. The comments are prefaced by two overarching comments and a vignette to help frame the responses to the questions.

The first overarching comment is that there is growing appreciation that the current approach to informed consent has serious flaws. Informed consent documents are lengthy and difficult to understand (Paasche-Orlow et al. 2003). Numerous studies show that people can participate in the informed consent process and yet retain misunderstandings about the most basic facts about the research for which they have given consent (Flory and Emanuel 2004; Kinnnersley et al. 2013). Further, while the informed consent process is meant to inform, engage, and empower potential research subjects, consent forms serve other goals (i.e., administrative and legal) as well. As we think about ways to improve the process of giving information and seeking consent, it is important that we think about the underlying rationale behind the consent process and about the range of approaches to engaging participants respectfully and meaningfully. We are skeptical that patient engagement can be accomplished simply by appending additional information to consent forms that are already too long and too complex (Horng et al. 2002; Hull et al. 2004; King et al. 2005). Alternative means of engagement using the Web, video, graphic communications, and social media may be more useful than 10- to 20-page consent forms, especially with participants or surrogates who face highly stressful circumstances (Nishimura et al. 2013). Focusing on the information needed to make a decision to join a specific study should be prioritized. Additional information can be provided separate from the primary decision-making materials, such as (1) general information about standard research issues like confidentiality and injury, (2) reference information with details about the study necessary for ongoing participation, (3) supplemental information about the study that some might want to know, and (4) information that is intended to address administrative and legal concerns and is written in precise legal language.

The second overarching comment is that the concepts used to guide our standard approach to informed consent—that is, risks related to research, foreseeable risks, minimal risk, and waiver of informed consent—are intrinsically connected to the regulatory framework. As illustrated by the Advanced Notice of Proposed Rulemaking in 2011, the regulatory framework is being reconsidered. Although the comments that follow uses this regulatory language, the issues related to “standard of care research” or “comparative effectiveness research” transcend this framework.

The vignette, to which the remaining comments refer, is an example of a randomized clinical trial related to standard of care. In the early 1980s, several countries and Colorado implemented newborn screening (NBS) for cystic fibrosis (CF) as a “standard of care.” Researchers in Wisconsin decided to study this new intervention with a randomized clinical trial (Fost and Farrell 1989). From 1985 to 1994, 650,000 newborns were screened for CF in Wisconsin. Half of the results were returned within 6 weeks, while the results for the other

half were disclosed at 4 years of age. This study underwent NIH and IRB review as well as extensive community engagement and ethics consultation. It was conducted with a waiver of informed consent for screening, but a more detailed informed consent process was used for diagnostic testing and for treatment of identified CF patients with standardized treatment protocols (Taylor and Wilfond 2004). The study yielded important information and could not have been done logistically without a waiver of consent. In 2004, a CDC Workshop concluded that newborn screening for CF was justified (Grosse et al. 2004). Today, all states screen newborns for CF.

There were unforeseen harms during the study. Some children in the group whose positive screening results were revealed at 6 weeks had worse pulmonary outcomes than those diagnosed at age 4 years. The children identified with CF at 6 weeks were sent to a specialty clinic for treatment, where some were unintentionally exposed to *Pseudomonas* bacteria from other children (Farrell et al. 1997). Children diagnosed at age 4 years avoided that early exposure. Measuring *Pseudomonas* acquisition was one of many surveillance aspects of the protocol, but *Pseudomonas* acquisition was not an identified risk and participants were not told that infection was a risk of being in the study. This was not expected because of limited knowledge of appropriate infection control procedures.

Some lessons from the CF newborn screening study are: (1) There can be unforeseen risks in standard-of-care research. (2) Some of these risks are the risks associated with standard treatment. The harm in the CF research was also a harm of standard therapy, and the study led to reduction of risk and improvements in care for all the children of Wisconsin, as well as around the country. (3) Many parents of newborns did not understand the study. Efforts at community engagement and public education need to be improved. (4) Sometimes waivers of consent for randomization are ethically justified. Given next are comments on the first three questions raised by OHRP.

How Should IRBs Assess the Risks of Standard of Care Interventions Provided to Subjects in the Research Context?

The risks of standard practice can be quite significant, particularly for seriously ill newborns and children. Efforts to provide and improve care can be helpful or harmful whether or not these efforts are within the context of research. It is important that patients and parents be informed of specific risks and benefits of proposed treatments. When reviewing proposed standard of care research, IRBs should be aware of these risks and ensure that the balance between clinical benefits and harms is favorable. The risks and benefits of clinical treatments are *not* risks of research. The risks of research are only those risks associated with the portions of the research protocol that are not part of conventional clinical practice. IRBs also should consider their role in conjunction with institutional bodies responsible for clinical quality improvement planning and implementation. It is important to help patients understand the risks and benefits of standard treatments, but this will not be accomplished by including substantially more information in consent forms. Failure to include risks associated with standard interventions in the consent forms does not necessarily mean that informed consent was not adequately obtained. In some cases, the same outcome can be

inversely described as a benefit or a risk, and it is not clear how best to communicate this to participants.

It is important to remember that in a clinical context, there often are numerous conversations about the risks and benefits of conditions, treatments, and alternatives. During the treatment phase of the CF newborn screening trial, the potential risks of having a diagnosis of CF included hospitalizations, intensive care unit (ICU) admissions, and even death. These were not considered to be risks *of* the research even though these risks were present *in* the research; the purpose of the research was to learn whether newborn screening would improve the health of children with CF and thereby justify a significant public health effort.

What Factors Should IRBs Consider in Determining That the Research-Related Risks of Standard-of-Care Interventions (Provided to Research Subjects in the Research Context) Are Reasonably Foreseeable and Therefore Researchers Should Be Required to Disclose Them to Subjects?

The critical aspect of this question focuses on what should be disclosed to subjects. The expected risks of research should be disclosed to subjects (or their parents/legal guardians) to help them make decisions about research participation. Expected risks are those that reasonably can be foreseen and that are related to research. As stated earlier, some risks are not expected and other risks are not related to research. When death is a potential outcome, such as in the ICU, or with life-shortening diseases, it may be necessary to measure death rates, but it does not necessarily follow that death is a *foreseen* outcome of the research. In the Wisconsin newborn screening study, for example, death rates were measured during the screening and treatment phases, but death was not a foreseen risk of the research nor disclosed as a risk of the research.

In standard-of-care research, where the goal is to see whether one approach will be better than a different approach, it remains unclear how best to frame this for patients. One could say that the objective is to see whether one approach is *better* or whether one is *worse*. These outcomes are inverses. We need to learn more about how best to convey this, and without further empirical research on the issue, we would be reluctant to conclude that simply listing the inverse of benefits as risks will promote such understanding.

How Should Randomization Be Considered in Research Studying One or More Interventions Within the Standards of Care? Should the Randomization Procedure Itself Be Considered to Present a Risk to the Subjects? Why or Why Not?

The concept of randomization is complex, and much social science research has suggested that participants often are confused about what it means and why it is done—in spite of substantial efforts to explain it. Further effort to learn how best to explain and communicate the meaning and purpose of randomization is important. How to explain randomization, however, is distinct from whether it should be considered a risk. Explicit randomization to two different approaches offers no more risk than relying on random, unscientific reasons for selecting different treatment approaches. Using our CF screening example, in 1993, all babies in Wisconsin were randomized to one of two schedules for reporting screening results; while in Colorado all babies were screened, in Maryland no babies were screened,

and in Connecticut, babies in a few hospitals were screened (Wilfond and Gollust 2005). While the risks and benefits of screening were unknown at the time, we do not believe that randomization itself introduced any additional or unique risk.

Under the current regulatory framework, IRBs are able to “waive informed consent” for randomization of standard of care research in certain circumstances. However, there are ethical obligations to consider about how best to communicate and engage patients in this process. Although consent was waived in the CF newborn screening trial, all parents were notified about the study and parents could “opt out” by requesting their results. (As the study was designed, parents could not opt out of testing; they could only opt out of being blinded to the results.) One crucial lesson of the CF trial was that most parents remained unaware of the study (Tluczek et al. 1992). Clearly, better efforts at public engagement are essential in every study but particularly in studies done with waiver of consent. This context raises the prospect of using people without their knowledge for purposes they may not value or agree with, in a setting where they may assume that they will be receiving safe and effective medical treatment. Thus, public engagement is required to recommend specific practices that create respectful, transparent, and productive research partnerships. Patients at hospitals where such studies are being conducted should know that:

- Standard-of-care research with randomization is occurring.
- The research design has been carefully reviewed before being implemented.
- The research involves treatments that are in routine clinical use.
- The safest and most effective ways to use these treatments are not known.
- This is an important effort to improve care for future patients.

We think that such awareness has the potential to improve patients’ confidence in our health care systems and promote public trust in biomedical research. Requiring explicit patient consent forms for each randomization activity creates an administrative burden on patients and researchers that is not likely to promote such confidence. More social science research is necessary to determine how best to engage patients.

CONCLUSION

The risks of standard treatments are *not* risks of research. Research comparing two standard treatments is the best way to identify those risks. We need new approaches to the informed consent process that are more flexible, are more focused on helping prospective study subjects truly understand the most crucial elements of research, and are developed in conjunction with the relevant patient communities. Sometimes consent can be waived—but this, too, requires active and innovative community engagement and alternative ways to reach those individuals.

These issues are complex, and iterative deliberation among researchers, scholars, regulators, patient advocacy groups, patients, and the public will be necessary. In addition, more empirical social science research must be conducted regarding public views and concerns about research and experiments with novel approaches to informed consent and the

engagement of patients. The primary goal remains to improve the health of the nation through quality health care and research.

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