ARTICLE

The SUPPORT controversy and learnings

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Introduction

Over the past year, the Surfactant, Positive Pressure, and Oxygenation Randomized Trial (SUPPORT) (1) has generated yet another rich debate relating to the study of treatments that fall within the standard of care. This was triggered by the investigational intervention – the compliance-oversight determination letter (2) – by the Office for Human Research Protections (OHRP) of the US Department of Human and Health Services (DHHS). A large number of bioethicists, researchers, members of ethics review boards, neonatologists and parents of those receiving care have contributed to this discourse. The amount of space created for the debate by some of the key journals – the *American Journal of Bioethics, Hastings Centre Report* and *New England Journal of Medicine,* to mention a few – demonstrates its salience.

The factors which have rendered the trial a fertile ground for such extensive and in-depth discourse on research ethics are the fact that the participants are prematurely born infants and this research is being conducted with a view to advancing neonatal care; the fact that the two treatments being investigated in the trial are being reported as part of the standard of care; and the growing recognition of and the interest of the US government in "learning healthcare systems" as sites for undertaking comparative effectiveness research (CER). Several issues have been raised and discussed, with some in favour of SUPPORT and others against it, and yet others in favour of a middle ground, particularly given the importance of CER. Central to the debate is whether the randomisation to different arms should have been disclosed to the guardians of the neonates. Some of the allied key questions raised in response to the DHHS investigational intervention are as follows. In the context of such trials, should disclosure standards be guided by the framework of clinical care ethics or research ethics? Should the risks be equated to those in the routine clinical care setting? What constitutes the "reasonably foreseeable risks" in the context of researching standard-of-care interventions? Should a different framework of research ethics be considered and applied? Finally, can such research at all be considered as "research studying standard of care"?

In this paper, I offer a brief overview of the debate so far and argue that the SUPPORT researchers should have met the obligation of disclosure of randomisation to the guardians of the participants, the neonates.

Overview of SUPPORT

SUPPORT was conducted as part of the Neonatal Research Network of the Eunice Kennedy Shriver National Institute of Child Health and Human Development, USA at more than 20 sites in the country. It was conceived in 2003, launched in 2005 and concluded in 2009 (3). It compared target ranges of oxygen saturation of 85%–89% or 91%–95% among 1316 infants who were born prematurely. Retinopathy of prematurity (RoP) is an important morbidity that causes blindness and other visual impairments in preterm infants. The SUPPORT study group mentioned that "… previous studies have suggested that the incidence of RoP is lower in preterm infants with exposure to reduced levels of oxygenation than those exposed to higher levels of oxygenation. However, it is unclear what range of oxygenation is appropriate to minimise retinopathy without increasing adverse outcomes" (1: p 1959).

The study concluded that a lower target range of oxygenation (85%–89% compared to 91%–95%) resulted in a slight but statistically significant increase in the incidence of death, but led to a substantial decrease in the incidence of severe RoP among the survivors. The SUPPORT research team felt that this finding was of significance for clinical practice because "a lower target range of oxygen saturation is increasingly being advocated to prevent RoP" (1). The SUPPORT study's findings have prompted the American Academy of Pediatrics to amend its guidelines and physicians treating very premature babies to opt for a higher range of oxygenation to reduce the risk of death, even though the risk of RoP is higher at this level of oxygenation (4).

SUPPORT was conducted in response to the need of neonatologists to respond effectively to the healthcare requirements of prematurely born infants, a global concern. One of the challenges neonatologists face is to know more precisely the level of oxygenation that would be appropriate to minimise RoP while still avoiding an adverse outcome. Given the global nature of preterm births and the necessity of ably meeting the healthcare needs of these infants, trials similar to SUPPORT were launched in other countries around the same time. These included the Canadian Oxygen Trial (COT), conducted in 25 institutes in Canada, the USA, Argentina, Finland, Israel and Germany, and the Benefits of Oxygen Saturation Targeting (BOOST) trials in the UK, Australia and New Zealand (5). The importance of the research problem and the need to address it have been universally acknowledged, whether by the OHRP, which made the investigational

intervention, or those who have been critical of SUPPORT due to the disclosure issue.

The OHRP's determination letter and the concerns

The OHRP, the apex regulatory oversight agency of the USA, is entrusted with the responsibility of protecting the rights, welfare and well-being of those participating in research conducted and/or supported by the DHHS. The key concern expressed by the OHRP in its 13-page letter, dated March 7, 2013, to the institutional review board (IRB) of the University of Alabama Birmingham (UAB), the lead site on SUPPORT, was "… 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 damage and death" (2: p 2). According to the OHRP, in violation of the requirements of 45 CFR 46.116(a)(2), the researchers did not mention the risks that the premature infants could face as a result of random assignment to the trial's two arms, ie the lower oxygenation (85%–89%) and higher oxygenation (91%–95%) groups. Furthermore, it stated that those subjected to the lower range could have faced a greater risk of death compared to the standard of care, and those subjected to the higher range could have faced a greater risk of RoP.

To support its claim that the regulatory requirements had been violated, the OHRP extensively cited the literature that had been published over a span of about five to six decades before SUPPORT was launched. It concluded by saying, "In short, the research and data analyses that had occurred prior to the SUPPORT study demonstrated that the use of higher versus lower levels of oxygen could significantly affect the likelihood of a premature infant developing RoP and other aspects of morbidity and mortality" (2:pp 3–4). The letter noted that "…above [literature quoted in the determination letter] are consistent with what the protocol of the SUPPORT study itself included about the use of oxygen and RoP in premature infants" (2: p 4).

Following the issuance of the determination letter, the scope of the intense debate so far has come to be defined by the OHRP's concern relating to the inadequate disclosure of reasonably foreseeable risks in the context of CER. The latter is increasingly being termed and viewed as "research studying standard-of-care interventions" by the peer community, including the OHRP (2, 6). This characterisation of SUPPORT has certainly been "a point of departure" in the SUPPORT-generated debate. Broadly speaking, commentators have raised substantive and/or procedural issues, ie the appropriateness of OHRP's intervention in relation to its official mandate.

In defence of SUPPORT

The SUPPORT team defended its informed consent form on the grounds that the two ranges under trial were in clinical equipoise at the time of the launch of the intervention (7) and that the informed consent, if seen in its entirety, addressed the prevalent knowledge fairly and reasonably (3). Other supporters highlighted that the informed consent form did spell out that differences with respect to RoP were anticipated between the two arms, although the matter was mentioned in a positive rather than negative way, and that the form template stated that "some unknown risks may be learned during this study" (5). Defenders of the study attributed the opposing views on SUPPORT's approach to disclosure to a confusion between the risks of the clinical treatment and the risk of the randomisation. They argued that there were well-understood risks involved in administering accepted oxygenation treatment to the premature babies, but there was no evidence that randomisation of one option over the other increased that risk (8).

The defence of SUPPORT hinges around the argument that the two ranges of oxygenation under trial had obtained clinical equipoise (3). Clinical equipoise is said to be obtained when the data available provide no reason to prefer one treatment over the other alternatives (9). One of the key points mentioned by those in favour of SUPPORT is that both interventions under trial were part of the standard of care (4). This being so, Hudson and colleagues wondered how the risk should have been conveyed when seeking informed consent. They argued, "The increased risk of death was a significant and unexpected finding of the study; if it had been known before the study began, standard clinical care would not have encompassed the lower oxygen range, and it would have been unethical to conduct the study" (4:p 2351)

Randomisation, risks and standards of disclosure

Wendler (10) situates his argument in the broader context of standards of disclosure in a clinical research setting such as that of SUPPORT. In his opinion, central to the SUPPORT controversy is the lack of consensus on standards of disclosure for informed consent. The question he discusses in depth is whether in the case of a study of standard-of-care options, the disclosure of information should be guided by the appropriate disclosure standards for research participation or by appropriate disclosure standards for patients? His thesis is that the informed consent process for clinical research should be designed to address the ethical concerns raised by the research. He suggests that only "net risks" – added risks that are not compensated by the potential for clinical benefit – need be disclosed in the clinical research setting. The rest, related to the standard of care, should be described in the consent form used for appropriate clinical care. He also argues that the disclosure of randomisation in clinical research studying treatments that have obtained clinical equipoise is unwarranted. The assumption behind the disclosure of randomisation is that it impacts the individualised treatment in the clinical care setting. Wendler argues that the disclosure of randomisation is required only if it increases the risks and/or decreases the potential benefits in comparison to what would have been the case in a clinical care setting. Also, drawing on the data, he argues that randomisation has not resulted in worse clinical outcomes compared to assigning interventions on the basis of clinical judgement of what is best for the individual patient.

For Resnik (11), the SUPPORT controversy is rooted in the varying interpretations of the notion of "reasonably foreseeable risk". Drawing upon the epistemology of risk, he argues that a risk is reasonably foreseeable if there is some evidence to expect that it may occur. The evidence could stem from empirical research, past experience, or scientific or mathematical principles. He makes an important distinction between probabilistic and possible risk. The former implies that there is enough evidence to assign an objective probability to the occurrence of harm, while the latter implies that there is not sufficient evidence to do so. SUPPORT defends itself on the ground that there was no evidence of there being any risk in assigning the infants to either of the ranges of oxygenation. Resnik (11) further argues that both the OHRP and SUPPORT defenders have made valid points, but "they were talking past each other because OHRP focused on the possible risks, whereas SUPPORT defenders focused on evidence for risks" (11). He points out that while the DHHS regulations require the disclosure of "reasonably foreseeable risk", they are silent on what it means. He underscores the need to distinguish between "probabilistic" and "possible" risks, and emphasises that the OHRP/DHHS should provide guidance on the same.

Yet another point raised by those in favour of SUPPORT relates to the comparative assessment of the outcome of any intervention in routine clinical practice and in a research setting. Many believe and have demonstrated via empirical evidence that the assumption that the administration of protocol-driven standardised treatment to patients enrolled in clinical research increases risk is unfounded (10, 12). For example, Wendler, sourcing the work of others such as Gross (13), Peppercorn et al (14), and Vist et al (15), argues that random assignment is not associated with worse clinical outcomes as compared to assigning interventions on the basis of clinical judgment of what is the best for individual patients. Wilkinson and colleagues (12), drawing on the work of Silverman on the topic that was subjected to empirical exploration by SUPPORT, point out that Silverman had concluded that "… in the absence of clear evidence, individualized titration of oxygen, based on physician judgment, led to blindness, death, and serious disability in thousands of premature infants in the 1950s and 1960s" (16). In the case of SUPPORT, it is noted that while the trial enrolled 1316 infants, 3053 eligible infants were not enrolled and had higher rates of death before discharge, together with various morbidities (17). However, Rich and colleagues (18) have demonstrated that the baseline indicators – demographic and clinical – were not comparable for these two groups. These factors predicted overall less favourable outcomes, ie higher mortality rates, for the babies not enrolled in SUPPORT than those enrolled in the study. Schmidt and colleagues (19) demonstrated that just being in the trial offered the patients a chance to have a better outcome. This has served as a basis to justify the stand that "disclosure regarding randomisation is not necessary in a clinical research setting, such as SUPPORT". However, this has been countered by those who have been critical of SUPPORT (20).

With regard to the issue of the disclosure of risks in the consent form, Binik and Sheehan (21) argue that the failure to disclose randomisation on the ground that the two treatments under trial had obtained clinical equipoise is not convincing. They argue that disclosure standards are guided by the broader moral requirement to respect persons and their autonomous decisions. This is aimed at enabling prospective research participants to make an informed and responsible decision relating to their participation in the trial. King (22) holds a similar position and argues forcefully that randomisation, indeed, alters the risks of harms and chances of benefits to the patient-subject compared to the ones s/he would be exposed to outside the research setting.

An answer to the question whether trials like SUPPORT ought to comply with research ethics framework/s or clinical care ethics lies in the Nuremberg code of 1948 (23) and the subsequent Belmonte Report of 1979 (24). These were the very first research ethics codes which established a distinction between a research ethics framework and a clinical care ethics framework. These codes came into existence in response to research scandals that took place when healthcare settings were exploited to double up as research sites. They underscored distinct primacies in medical practice and research. Protecting and advancing the best interests of patients is of the foremost importance in the case of healthcare settings, while advancing science and knowledge to benefit people in the future is of prime importance in the case of research sites. On the basis of this distinction between medical practice and research, Macklin and Shepherd (25) made three key points opposing SUPPORT's position with respect to standards of disclosure. First, they felt that random assignment of care receivers to one of the two ranges implied the possibility of more than minimal risk and, therefore, should have been communicated to the participants in the study. Second, they said that "… when what is being studied are the potential differences in risk of those harms, the risks of harm related to the research cannot be described as 'minimal'" (25:p12). Finally, they pointed out that reasonable people would have preferences between treatments in the different arms.

Further strengthening the critique of SUPPORT

Having briefly set out the issues that have been at the centre of the SUPPORT controversy, I shall go on to make a strong case in favour of the disclosure of randomisation to patient-participants in the context of trials of two or more regimens from within the standard of care. I would like to make three points. The first is that the individualisation of the provision of care in the clinical care setting is disrupted when clinical care sites double up as research sites for randomised trials. This disruption of individualised care warrants the disclosure of randomisation to the patient-participant, regardless of any other factors. Two, the fiduciary obligations of healthcare providers since they are rooted in broader moral and legal obligations, physician's participation in randomised controlled trials makes his/her consent-related obligations

more demanding. Three, empirical data indicate that patient-participants do not expect, and may not appreciate and accept, assignment to randomised treatment in a clinical care context which, I argue, warrants the disclosure of randomisation.

Disruption of individualisation of care and obligation to disclose randomisation

This argument flows from the empirical distinction between the care provided to patients during routine healthcare and that provided in any research setting, including settings such as SUPPORT. In the former case, the healthcare provider treats every patient's broader context as unique, and this context shapes the patient–provider relationship and the treatment prescribed to the patient. In-depth insights on this topic can be found in the literature that critiqued evidence-based-medicine (EBM). It is noteworthy that advocates of EBM speak of the insufficiency of evidence alone. Upshur (26) argued "… that at each level of decision-making, values are regarded as crucial components of appropriate healthcare" (26:pp113). It is thus rare to find value- or preference-neutral decisions being made in medicine and healthcare. Naylor (27) and several others underscored the importance of learning of and respecting the values of patients in clinical practice. For example, the *User's Guides to the Medical Literature* (28) recognises the importance of the patient's context, preferences and values in making clinical decisions. It sums up the matter in the following words.

… Knowing the tools of evidence-based practice is necessary, but not sufficient for delivering the highest quality of patient care. In addition to clinical expertise, the clinician requires compassion, sensitive listening skills, and broad perspectives from the humanities and social sciences. These attributes allow understanding of patients' illness in the context of their experience, personalities and culture. (28:p 1293)

Thus, the criticism of EBM focuses on the argument that modern medicine is not based on evidence alone. It is considered to be shaped by the contexts of the practice and experiences of practitioners, and the narratives and experiences of patients; the basic and clinical sciences; and values and societal perspectives. All these are conceived of as integral elements of the larger process of the provision of clinical care.

The implication of this critique of EBM is that the individualisation of care that is integral to and an inseparable, although somewhat intangible, aspect of healthcare would suffer in the case of patients receiving care while participating in trials, which are necessarily driven by stringent protocols. Therefore, the disclosure of randomised assignment of treatments is warranted even when they constitute standard-of-care regimens.

Broader moral and legal understanding of fiduciary obligations warrant disclosure

The view that research-related interference in healthcare settings causes disruption of individualized care is further supported by the broader understanding of the moral and legal foundations of the healthcare provider's fiduciary duties to his/her patients. The fiduciary obligations are rooted in the concept of equity in English law, which dates back to more than 250 years (29). It is inspired by a doctrine that acknowledges the need for special legal and moral obligations in a relationship between any two private entities/parties, such as patient–provider and client–solicitor, which is characterised by an imbalance in or inequality of knowledge and power; dependency; and trust. This doctrine is now well-accepted. The protection of the best interests of the weaker (beneficiary) party always rests with the stronger (fiduciary) party. In the context of clinical research, this has a bearing on the moral obligations of the provider-researcher. The obligation of full disclosure flows from the fiduciary obligations of healthcare providers who enter into research and thereby play dual roles. Fried, the proponent of equipoise, discusses how, in such situations, moral obligations of a fiduciary nature and the consent-related obligations of the healthcare provider-researcher become intertwined (30). Fried judged the consent-related obligations to be more demanding in cases in which the fiduciary relationship is potentially imperilled by the physician's participation in randomised controlled trials:

The very fact that the doctor acts in the dual capacity of therapist and researcher, and that his role as researcher to some degree does or may influence his decisions as a therapist, would argue that the fullest disclosure of all the circumstances relating to that dual role, and to the basis on which functions are exercised and decisions made would be required. (30: p 33)

Fried further argued:

Thus, whether in clinical practice or in clinical research, if fiduciary duties are to be discharged appropriately, the physician's focus must remain with the 'particular circumstances of the particular patient'." (30: p 53)

When seen from the broader moral and legal perspectives, it becomes clear how tightly fiduciary obligations are intertwined with research ethics obligations, particularly those related to consent, and how they warrant full disclosure of all matters that impact the therapist's role.

Patients' perspective on randomisation necessitates its disclosure

Empirical research on patients' understanding of randomisation and methods of randomisation, as well as on the acceptability of random allocation of treatment in randomised controlled trials, indicates that patients may understand the meaning of randomisation and appreciate the various methods of randomisation. However, they may not wish to be randomly assigned to study arms unless offered an acceptable justification for this (31). The findings of qualitative studies suggest that participants often struggle to accept randomisation in clinical trials (32,33). Ellis and colleagues (34) found that 74% of the patients in their study thought the doctor would ensure that they received the best of the treatments offered in a randomised trial. This indicates

that patients probably hold a "therapeutic misconception", a concept which was floated by Appelbaum and colleagues and according to which patients believe that every aspect of a clinical trial has been designed to benefit them (35).

These findings are of relevance in the context of the current debate in two ways. One, not all patients would necessarily like to be randomly assigned to treatment arms while seeking care in a healthcare system in which research is conducted. Two, it would be necessary to disclose randomisation to different arms and the purpose of such randomisation to patient-participants to enable them to decide whether being part of such trials is acceptable to them.

Disagreement on appropriateness of OHRP's intervention

There was a lack of consensus even on the count of procedural matters related to the OHRP's intervention. The disagreement was about whether the intervention was warranted or whether the OHRP had overreached itself. . The supporters of SUPPORT felt that the intervention had "overreached" itself (36) and some asserted that "… we strongly disagree with their [OHRP's] determination of inadequate informed consent …" (3). Among the concerns expressed by these critics was that such "overreaching", or going beyond investigating the impropriety of the manner of conducting research would have an adverse impact on any research studying standard-of-care treatments, particularly for health conditions such as preterm births which are widely prevalent across the globe. It is difficult to comprehend the position taken by these critics against the backdrop of the growing trend on research initiatives which have been faulted for failing to meet research ethics obligations towards the study communities and participants.. These include studies which have been initiated in the USA and implemented locally or globally.

Several commentators who supported the OHRP intervention felt that it discharged its responsibility of oversight effectively and according to its mandate (37,38). Hunter, Macklin and colleagues resolutely supported the intervention and considered that it was well within its mandate. According to them, the OHRP can and should look into substantive matters, too. They felt that the OHRP is not meant to limit its role to bureaucratising the process of oversight by merely assessing whether the institutional review boards have been constituted and are operating in compliance with the federal regulations; the OHRP should, in addition, provide leadership to ensure the protection of the rights, welfare and well-being of the participants.

Take-home message

By way of a take-home message, I may mention five points. First, the assessment and disclosure of the risks involved in a multi-interventional trial ought to be comprehensive and not confined to a subset of the study's interventions. SUPPORT consisted of two key interventions for experimental purposes. It reported the outcomes separately, which is often the case with complex trials for logical reasons. However, one of the major components of the "treatment approach" of SUPPORT (continuous positive airway pressure versus intubation/ surfactant), as per its own original protocol, involved not only risks which Macklin and Shepherd (25) argue were "not only reasonably foreseeable but foreseen" risks. (25:p 10) This warrants that the assessment of research ethics obligations by ethics review boards, entities for regulatory oversight, and the peer community of bioethicists be carried out in relation to the intervention in its entirety. Supporters of SUPPORT do not seem to have accounted for this major gap in disclosure, ie the failure to disclose the "reasonably foreseeable risks". This lesson learnt from the SUPPORT experience has global application.

Second, how should researchers, ethics review board members and other stakeholders assess when a particular research study is studying a standard-of-care intervention? What should be the sufficient and necessary criteria to firmly determine that two or more interventions under trial continue to be in clinical equipoise? Or what determinants should be used to decide that clinical equipoise has been sufficiently breached so that the interventions under consideration can no longer be viewed as standard-of-care interventions? Would insights based on clinical practice, which indicate possible differences in the outcomes of standard-of-care interventions, be sufficient or would insights from empirical research be required? What if the outcomes of different researches are inconclusive and/ or contradictory? These factors make it most challenging for researchers and members of ethics review boards to make a proper assessment and arrive at an understanding of whether a particular study is "researching standard-of-care" interventions. This issue is of relevance throughout the world.

Third, does CER really require different frameworks to meet research ethics obligations? Some of the major issues that have featured in this debate have stemmed from disagreement amongst bioethicists, researchers and others about what distinguishes CER from research of other kinds. The debate surrounding SUPPORT has highlighted that this question has direct and deep implications for how research ethics obligations are operationalised in the context of the "learning healthcare systems" and the research (CER) being conducted in these newly emerging trial settings. This has generated interest amongst bioethicists, who are deliberating whether there is a need for a new approach to research ethics (39). Before considering any changes in the existing regulations, it will be necessary to put the evolving frameworks of research ethics relating to CER to the test to ensure that they are applicable. Needless to say, there is no consensus on this view and while regulatory agencies need to consider it, they should be watchful that trade-offs aimed at optimising research resources for improving the quality of health services do not come at the cost of patient-research participants' safety.

Fourth, the debate generated by SUPPORT would be of specific relevance to India for more than one reason. In India, the main sites for the recruitment of patients are healthcare facilities. The private healthcare sector continues to dominate healthcare

services in India. When sites for the provision of healthcare double up as sites for recruitment, extra precautions need to be taken and there must be no slackening of research ethics obligations and in regulatory compliance. In such a context, an alternative framework of research ethics for CER , might be utilised, given the fact that it is less stringent. However, we must guard against any misinformed temptation to relax research ethics guidelines that would compromise the safety, welfare and well-being of patient-research participants.

Fifth, the critical role played by the civil society in pursuing the matter with the DHHS/OHRP underscores the need for and importance of a people's watchdog. For example, the Public Citizen's Health Research Group (HRG), which promotes research-based, system-wide changes in healthcare policy and drug safety, has made several interventions and appeals to the DHHS/OHRP. Several members of the HRG participated in the public hearing organised by the OHRP and presented their critique of SUPPORT (20). A review of the HRG's interventions shows that the force it wields stems from its detailed, well-researched and evidence-based arguments, which are hard to ignore. The HRG's ability to come up with such sound critiques seems to originate from the fact that it is constituted by academics, bioethicists and doctors. The HRG has set a very good example of how civil society-based groups can contribute to the ongoing bioethics discourse and more importantly, play a role in demanding ethical conduct not only from researchers, but also the apex oversight bodies.

I would like to draw attention to two other points that fall outside the scope of the discourse shaped by the DHHS determination letter. There is a need for continued deliberations on these points to avert controversies such as the SUPPORT controversy, and to find an alternative to randomised controlled trials without compromising on the validity and robustness of the evidence. First, over the past few decades there has been a substantial body of literature which has advocated breaking away from the strong tradition of employing the randomised controlled trial design and has argued in favour of searching for alternative methods of creating evidence. Besides the ethical quandaries that randomised controlled trials often raise, they also face challenges that originate from the fact that the trialed healthcare intervention needs to cross the trajectory from RCT tested "efficiency" to "effectiveness" in various populations, foundational to the usefulness of new intervention beyond the patient groups subjected to trial. The second point is that from the patients' perspective, there is no compelling reason to participate in researching treatments which constitute the standard of care at a given point in time. It is likely, then, that there will be a much higher chance of patients declining to participate in a randomised trial upon disclosure of randomisation, and this would adversely affect the recruitment and accrual rates and, thereby, the successful completion of the trial. This, in turn, will have implications in terms of the costs to be borne by the trial sponsors and/or investigators. This may end up being one of the motives, though not always conscious and perceptible, behind the non-disclosure of randomisation.

Post-script

In the post-script, I would like to mention that the diverse views on SUPPORT's approach to disclosure and the various issues raised in this context prompted the OHRP to issue another letter to the UAB IRB on June 4, 2013. While it largely defended its actions, it declared its intention to put all action related to compliance on hiatus until the process of producing appropriate guidelines was completed (6). As mentioned earlier, the DHHS convened a one-day public hearing on the topic on August 28, 2013(40), when it not only emphasised the significance of the issue at hand, but also spoke of the willingness of the government regulatory agency to engage with broader communities of various stakeholders. The purpose was to deliberate on issues relating to research studying standard-of-care interventions in the non-research context. These include seeking comments, via broader public participation, on how regulatory requirements should be applied to such a context; how IRBs should assess the risks of randomisation in such a context; what reasonably foreseeable risks of the research should be disclosed to prospective research subjects; and facilitating the development of guidelines on what constitutes reasonably foreseeable risk. On the procedural front, the DHHS declared that it was considering whether other processes should be incorporated into the OHRP's procedures for overseeing compliance.

Finally, despite some gaps, and disagreements over the OHRP's decision to intervene, it is heartening to read through its thorough determinations letter and to note its willingness to respond promptly and adequately to the concerns expressed by the communities of stakeholders relating to research enterprise in the clinical settings.

Interestingly, as this manuscript was being revised, the HRG, in its communication of May 20, 2014 to the DHHS/OHRP (41), presented evidence (drawing on e-mail exchanges) on the NIH's interference with the OHRP's investigation in the SUPPORT case. The communication reveals a conflict of interest and expresses shock on finding that the second letter issued by the OHRP on June 4, 2013 (6) was heavily redacted by the NIH. It notes that the OHRP has been silent since the issuance of this letter. The in-depth, informed and ongoing involvement of the civil society in this complex issue and the affairs of the oversight body seems to highlight that despite the existence of robust regulatory and oversight systems, the people at large have a big role to play in ensuring transparent, accountable and ethical advancement of medical research.

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