COMMENTS

More on SUPPORT: the controversy continues

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The article by Sunita VS Bandewar in the January–March issue (1) does an excellent job of describing the controversy over informed consent in the SUPPORT clinical trial. As one of the authors of the duelling articles Bandewar cites, I commend the author's conclusions calling for disclosure not only of randomisation in so-called "standard of care" clinical trials, but also the comprehensive disclosure of risks in this type of research (also known as "comparative effectiveness research [CER]"). Bandewar surmises that the disclosure of randomisation could result in a "much higher chance of patients declining to participate in a randomised trial"; and that this may be one of the motives of those who argue for non-disclosure of randomisation. In fact, at least some supporters of limited disclosure of the risks in CER trials have expressly acknowledged their concerns about the recruitment of participants if all the risks of "standard of care" treatments are mentioned in the consent forms.

This goes to the heart of the controversy over the consent forms in the SUPPORT trial. Defenders of those consent documents argued that detailed disclosure of the risks of standard of care interventions is unnecessary since the research will not expose the subjects to any greater risk than those they would be exposed to even outside the study. Some even maintained that so-called standard of care research should be classified as "minimal risk", regardless of the risks posed by those interventions in the clinical setting. In this commentary, I expand upon the discussion in Bandewar's article, in addition to briefly describing a draft guidance document and some reactions to it.

The Institute of Medicine workshop

On December 2, 2014, the Institute of Medicine (IOM) of the National Academies of Science convened a workshop, entitled "Ethical Review and Oversight Issues in Research Involving Standard of Care Interventions". It was prompted by the issuance of draft guidance, entitled "Draft Guidance on Disclosing Reasonably Foreseeable Risks in Research Evaluating Standards of Care", by the Office for Human Research Protections (OHRP) on October 20, 2014 (2). The OHRP is the US governmental agency responsible for oversight of research involving human subjects. As described in Bandewar's article, it criticised the consent forms used in the SUPPORT trial and imposed a mild sanction on the investigators. That sanction was later withdrawn, following pressure by the National Institutes of Health (NIH), which had sponsored the SUPPORT study.

The leading protagonists in the SUPPORT controversy were invited to a meeting at the IOM, lasting a day-and-a-half, and participated as members of several panels. The agenda of the workshop and the list of participants are posted on the IOM website (3). I was one of the participants invited. The speakers were instructed *not* to focus on the SUPPORT study, but to address the issues that had arisen in the controversy in more general terms. Some speakers could not resist invoking SUPPORT, and referred to it as "the study that shall not be named". The OHRP called for comments from the public on its draft guidance, with the receipt of comments being due by January 22, 2015. The guidance reignited the controversy over standard of care research.

The draft guidance says: "OHRP's general position is that in research studies designed to evaluate the risks of standards of care: [1] the risks of standards of care that at least some subjects would be exposed to by participating in a research study that are different from the risks of therapies the subjects would be exposed to outside the study are risks of the research that the IRB must consider when evaluating the research; and, [2] the identified risks the research proposes to evaluate as one of the purposes of the study are reasonably foreseeable risks that generally must be disclosed to prospective subjects when seeking their informed consent." In other words, in a randomised, controlled trial studying two "standard of care" interventions, although some participants may receive the treatment they would get outside the study, others will not. An example is a clinical trial to compare a commonly used medical intervention with a standard surgical treatment for the same condition. In sum, I agree with the position of the OHRP outlined in its draft guidance, in opposition to its critics, who maintained – in the complete absence of evidence – that the need to disclose the reasonably foreseeable risks of "standard of care" interventions would cause this important type of research to grind to a halt.

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The comments made at the IOM meeting, as well as other reactions to the OHRP draft guidance, were predictably a restatement of the positions the proponents had taken in published articles and on blogs since the SUPPORT controversy arose.

Dr Michael Carome, Director of the Public Citizen's Health Research Group (the organisation that initially defended OHRP's proposed sanction against the investigators), maintained that the SUPPORT trial was not, in fact, a "standard of care" trial (4,5). As one example, Carome notes that "the use of the falsely reading pulse oximeters represented an extraordinary deviation from 'standard of care' in the non-research setting, particularly since oxygen saturation levels played a role in many important clinical decisions related to adjustment in the oxygen therapy and whether to intubate or extubate an infant" (4,5). Carome also drew the conclusion that "the oxygen interventions in the five trials, especially the low oxygen target range, resulted in substantial deviations from routine clinical practices and differentially altered risks in the two study arms". This objection goes beyond the controversy over the adequacy of the informed consent documents, as it claims, in essence, that the SUPPORT trial was mistakenly classified as a "standard of care" study. This point is relevant to the discussion of standard-of-care research, however, as it demonstrates the vagueness of the concept of "standard of care". When experts disagree on whether a research design constitutes the standard of care in clinical medicine, it challenges the notion that disclosure of risks in such research should be treated differently from what is normally required in all research.

Perspectives of potential research participants

The whole point of the requirement of informed consent is to disclose information that patients – potential research subjects – want to know in order to help them decide whether or not to participate in research. It is surely not what the investigators think people should be told. With this in mind, I recount here the presentation I made at the IOM workshop on "standard of care" research.

I begin as a patient who knows nothing about research, the *Belmont Report* and the US Federal Regulations for research involving human subjects, and I do not read the *New England Journal of Medicine*. As a patient, I may fall into one of at least three categories:

1) I have a personal physician who knows me and with whom I have a patient–doctor relationship, and my physician is *not* a researcher.
2) I have a personal physician who knows me and with whom I have a patient–doctor relationship, and my doctor conducts research on a condition for which I have been diagnosed and treated.
3) I am a patient who does not have a personal physician. I obtain my medical care at an urban public hospital, and I typically see a medical resident.

In situation 1, my doctor tells me the medicine he will prescribe for my condition, as well as the risks and benefits. My doctor tells me this information only for the treatment that he normally prescribes, without informing me of the risks and benefits of other treatments that other doctors prescribe for the same condition. He tells me that a colleague of his is conducting research, and asks whether I might be interested in participating to contribute to scientific knowledge. When I say "yes", he refers me to his researcher colleague. The researcher gives me a consent form to sign. The form says that I will be assigned "by chance" to one of two treatments that are "standard of care". One is the medical treatment my doctor has told me about. The other is a surgical treatment for the same condition. The consent form says only that both treatments are "standard of care" for my condition, so I will not be exposed to any additional risk by enrolling in the study. The consent form does not describe the risks of the treatments, so I am uncertain about whether I should agree to participate. I have no idea what the risks of the surgery are. I wonder why those risks are not described in the consent form.

In situation 2, my doctor is both my personal physician and also a researcher. Since I have been her patient, my physician has already explained the known risks and discomforts of the medicine she normally prescribes. These include headache and fatigue. But now she is a researcher inviting me to be a subject in a clinical trial. My doctor has read articles in the *New England Journal of Medicine* and decides that the only thing she needs to include in the informed consent document is a statement: that "The risks to you are the same as you would undergo if you did not enrol in the trial because whichever treatment you will get is the 'standard of care'." The consent form says I will be assigned "by chance" to one of two treatments that are "standard of care". I enrol for the study and after taking the medication, I experience nausea and fatigue, but no headache. I am surprised because I had no idea that the risks and side-effects of another "standard of care" medicine would be different from those of the one I've been taking. I can go to work when I have a headache, but I cannot work when suffering from nausea.

In situation 3, I am a patient who receives care in a public hospital provided by medical residents under the supervision of an attending physician. I have not yet been treated for my condition – a new medical problem for me – and, therefore, have not been told anything about the risks and benefits of the standard treatment. After the resident completes the work-up, a doctor I have never met approaches me and asks if I would be willing to enter a clinical trial. I do not know what that means. I ask, and the physician says that it is research and gives me a consent form that says: "This is a study to see whether one of two treatments that are the 'standard of care' for your condition is better than the other." When I enquire further, the physician-researcher says, "You will be under no additional risk if you participate in the research because the treatments are what doctors normally use to treat patients with your condition. Since there are no experimental treatments, the risks of entering this research are no different from what you would

experience if you decided not to enrol in this study." As this is a new medical condition for me, I have never received any "standard of care" treatment. I decide not to enrol in the study, hoping that the resident will explain the risks and benefits of the standard treatment that she will prescribe.

What is clear from the above three situations is that patients often do not know and have not been previously informed of the risks of treatments that may well be a standard of care for their condition. In some cases, they may be aware of the risks of an intervention they have previously been exposed to, but not those of the alternative in a randomised controlled trial. In another situation, a patient who gets an opportunity to participate in research may encounter a treatment option for the very first time. In the SUPPORT study, for example, unless the parents had previously had a severely premature infant, they would be unlikely to know what is typically done in the neonatal intensive care unit. The women were approached by researchers before they delivered, so it is likely that they had not had an encounter with the neonatologists who would be caring for their babies.

A fourth scenario raises the same problems as the above three, but illustrates the importance of disclosing potential differences in *benefits* among "standard of care" interventions, as well as the risks. I am a patient with a family history of colorectal cancer. I am a 55-year-old philosophy professor, and although I have very little medical knowledge, I know something about clinical trials. So I consult a gastroenterologist about a routine colonoscopy, and she asks me if I would be willing to enter a clinical trial to compare colonoscopy with another "standard of care" screening method. The consent form says, "This is a trial to compare two 'standard of care' screening methods for colorectal cancer. One commonly used procedure is colonoscopy. The other is foecal immunochemical tests (FITs). Given the invasive nature of colonoscopy, the associated small, but real risk of complications, and dramatically higher costs than other screening tests, it is especially important to determine the true comparative effectiveness of colonoscopy relative to other proven non-invasive options. Since both colonoscopy and FITs are 'standard of care' screening methods, there are no experimental treatments in this research. You will not be at any increased risk over standard treatments by entering the study. You will be assigned by chance to one or the other screening method."

I then go to the web, type in "clinicaltrials.gov", and use the search terms "standard of care comparative effectiveness" and find the study entitled "Colonoscopy versus Fecal Immunochemical Test in Reducing Mortality From Colorectal Cancer (CONFIRM)," processed by clinicaltrials.gov on November 27, 2014. Although the entry does not list the foreseeable risks of FIT, it clearly indicates that FIT is a proven, non-invasive screening method. My first inclination is to request FIT instead of colonoscopy because it is non-invasive; but then I read that the study "hypothesis is that colonoscopy will be superior to FIT in the prevention of colorectal cancer mortality measured over 10 years" (6).

I decide to enrol after asking the gastroenterologist for detailed information about the reasonably foreseeable risks of each treatment. My decision is based not only on the foreseeable risks of these alternatives, but equally importantly, on the potential for greater preventive benefits of the more invasive intervention.

Conclusions

With regard to the hypothetical scenarios described above, it would not be correct to assume that in the "real world", physicians would (or should) describe the risks of the alternative "standards of care" to their patients orally before inviting them to participate in research or referring them to a clinical researcher. They may or may not do so, especially when the treating physician is not also the researcher. The key point is what potential subjects want to know about the risks and potential benefits of the alternatives in so-called "standard of care" research. The underlying assumption is that the risks of routine procedures in medical care are "reasonably foreseeable", but of course, that assumption may sometimes be mistaken.

Potential research subjects may also want to know about the reasonably foreseeable benefits. As the scenario of the colonoscopy–FIT demonstrates, a prospective subject may prefer the risks of the non-invasive procedure, but at the same time, value the potential benefits of more effective colorectal screening. So the idea that potential subjects will be "scared away" from participating in research if significant risks of standard of care interventions are disclosed, is just silly. If people are not scared away from the same standard treatments when their doctors describe the risks to them, why would they refuse to participate in research that discloses the same risks? Moreover, if potential subjects are prepared to enter investigational research when the risks are described and the consent form mentions unknown risks, is there any evidence to suggest that they would be *more* reluctant to refuse "standard of care" research when the risks of the standard interventions were disclosed? Since we are promoting evidence-based medicine in conducting these "standard of care" clinical trials, should we not also practise evidence-based ethics?

The obvious solution is that the consent process and documents should disclose *all* reasonably foreseeable risks, clearly distinguishing the risks of experimental treatments, if any, from those of the procedures that the subjects would undergo in routine medical treatment. The reasonably foreseeable benefits of the standards of care, as well as the reasonably foreseeable risks, should be described. This is typical of consent forms for clinical trials in oncology and other areas in which the experimental intervention is an add-on to the standard of care intervention and the comparator is the standard treatment. There is no ethically sound reason for the failure to disclose the risks of standard of care interventions even in research that contains no experimental procedures.

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Conflict of interest in public health: should there be a law to prevent it?

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Abstract

"Conflict of interest", now being commonly cited, is a set of circumstances that creates a risk that professional judgement or actions regarding a primary interest will be unduly influenced by a secondary interest. Conflict of interest situations can be institutional or personal, and can stem from financial or other interests including post-employment opportunities or during public private partnerships. Conflicts of interest in the creation of public policy, especially health or nutrition related policies such as the vaccine policy, tobacco control, and research related to health, can have negative impact on the lives of millions of people. While the UN Convention Against Corruption, to which India is a signatory, identifies conflict of interest as often being a precursor to corruption, there is no serious action being taken in this direction by the Indian government, in spite of the fact there are instances of serious nature coming to light that affect our peoples lives. If conflict of interest situations are allowed to continue especially in health policy it could be detrimental to millions of people; therefore, it would be in public interest that India enacts a law to prevent conflict of interest in the making of public policies, comprehensive enough to include financial and institutional conflicts of interest.

Introduction

Most of us believe that we know what conflict of interest is, as the concept is old and has been used in an English proverb: "He who pays the piper calls the tune." Despite its long history, the term conflict of interest is a relatively new one. The first appearance of the term in ethics codes dates back to as early as the 1970s. Thereafter, the medical literature started to pay serious attention to the concept. Now the term is in common use throughout the world (1). Connected with the concept is the "Duty of Loyalty", a term used in corporate law to describe a fiduciary's "conflicts of interest" and according to which the fiduciaries must put the corporation's interests ahead of their own (2). Similarly, government officials/representatives can be considered to be in a position of trust due to their *duty of loyalty* towards the country's citizens. They are obliged to work in the interest of the public, which pays for them or has brought them to power, both ethically and legally. A round-table discussion on "Prevention and management of conflict of interest" was organised in Delhi on September 13, 2014, under the aegis of the Alliance Against Conflict of Interest (AACI) by the Breastfeeding Promotion Network of India (BPNI) /International Baby Food Action Network (IBFAN) Asia, in which several forms of conflicts of interest in public policy-making were listed. These included the inclusion of "experts" from industry in regulatory bodies; the revolving door phenomenon, which denotes the movement of policy-makers and government officials in and out of the industry that they regulate; incentives for policy-makers, regulators and monitors, including the payment of their salaries; ownership of stocks and shares of a company by its regulators; presence of private-sector experts in policy-making/recommendatory bodies, such as the National Technical Advisory Group on Immunisation (NTAGI); and institutional conflict of interest and public–private partnerships (PPPs) in general (3). Over the past few years, conflict of interest has become an important consideration in governance. Prime Minister Modi's 17-point agenda reflected the Indian government's recognition of the need to prevent conflict of interest (4). Most recently, the issue drew a great deal of attention when the Supreme Court observed that there was

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