Published in final edited form as:

Am J Bioeth. 2013 ; 13(12): 3–8. doi:10.1080/15265161.2013.851578.

What Should Be Disclosed to Research Participants?

David Wendler

Department of Bioethics, NIH Clinical Center

Abstract

Debate surrounding the SUPPORT study highlights the absence of consensus regarding what information should be disclosed to potential research participants. Some commentators endorse the view that clinical research should be subject to high disclosure standards, even when it is testing standard-of-care interventions. Others argue that trials assessing standard-of-care interventions need to disclose only the information that is disclosed in the clinical care setting. To resolve this debate, it is important to identify the ethical concerns raised by clinical research and determine what consent process is needed to address them.

Keywords

informed consent; research; disclosure; risks

There has been significant debate regarding the ethical and regulatory appropriateness of consent forms used in the SUPPORT study, which randomized preterm infants to two different levels of oxygen saturation, one at the low end of the range of standard of care and one at the high end (Hudson et al. 2013; Office for Human Research Protections [OHRP] 2013; SUPPORT Study Group 2010). Much of this debate traces to conflicting views regarding salient facts about the trial, especially the risks it posed (Macklin et al. 2013; Wilfond et al. 2013). Was there good reason to believe that one of the arms was riskier than the other? Was there good reason to believe that both arms were inferior to maintaining oxygen-saturation levels in the middle of the range of standard care? The first lesson of the SUPPORT study, then, is the unsurprising one that in order to evaluate the ethical appropriateness of the consent forms used in a given study, one needs to know the risks it posed.

The second lesson is the somewhat more surprising fact that it can be difficult to determine which practices constitute appropriate clinical care, and what risks they pose and potential benefits they offer. The fact that clinicians titrate treatments based on their clinical judgment of what is best for the individual patient in light of ongoing assessment does not imply that this approach benefits patients, nor that its absence poses increased risks. At the same time, one does not always need a randomized clinical trial (or two) to reasonably conclude that a

Address correspondence to David Wendler, PhD, Department of Bioethics, NIH Clinical Center, Building 10, Room 1C118, Bethesda, MD 20892, USA. dwendler@nih.gov.

The author has no competing interests with respect to this article.

⁶In some cases, and for some participants, it may be unclear whether a different set of risks poses greater risks.

given practice is beneficial and that its absence in the context of clinical research poses increased risks.

The disagreement over what risks SUPPORT participants faced has obscured the related question of what information should be disclosed to potential research participants. Do the competing recommendations for what should have been disclosed trace to different understandings of the facts, or different standards for what investigators should disclose? For example, are recommendations that more information should have been disclosed regarding the (limited) degree of individualized treatment in the study based on the assumption that this approach poses increased risks, or the claim that it should be disclosed whether it poses increased risks or not?

Identifying the appropriate standards for what information should be disclosed is complicated by the fact that the SUPPORT study compared different approaches within the standard of care. Roughly, when conducting a study of standard of care options, should the information disclosure be based on appropriate standards for disclosure to research participants or on appropriate standards for disclosure to patients? Given the increasing importance of research conducted in the context of clinical care, and on standard-of-care interventions, this question is likely to be the focus of research ethics for many years to come (Casarett, Karlawish, and Sugarman 2000; Faden et al. 2013; Largent, Joffe, and Miller 2011; Olson, Aisner, and McGinnis 2007).

The thesis of this article is that the informed consent process for clinical research should be designed to address the ethical concerns it raises. To this extent, the analysis agrees with those who emphasize the fact that, by collecting data to benefit others, clinical research raises important ethical issues. Yet commentators sometimes conclude from this fact that clinical research is pervasively problematic, suggesting that high standards of disclosure should apply to all aspects of a given study. In contrast, I argue that clinical research raises specific ethical concerns, and consent forms and processes should be tailored to address these concerns. Once these specific concerns have been addressed, disclosure to potential participants regarding the procedures included in a given study should be based on appropriate disclosure standard for those procedures in the context of clinical care.

In making this argument, I focus on what is required for ethically valid informed consent, by which I mean consent that satisfies the conditions on it being ethically acceptable to enroll potential participants in a given trial.¹ This is not to imply that initial consent is all there is to valid consent, nor that valid consent is all there is to consent in general. Ongoing consent is often important and, depending on the circumstances, there can be moral reasons to disclose to potential participants information beyond what is required for valid consent. Nonetheless, limiting the discussion to initial consent and to valid consent will help to clarify the analysis and focus it on the most important issues. Commentators should not spend much time attempting to identify, and investigators should not devote time to discussing, the information that would yield something closer to ideal consent until it is clear

¹For present purposes, I assume that potential participants need to understand the information that must be disclosed for valid consent. And I will have nothing to say about the conditions under which the requirement to obtain informed consent can be altered or waived.

that we have identified and potential subjects have understood the information needed for valid consent.

BACKGROUND

Allogeneic hematopoietic cell transplant offers a potential cure, and is now standard of care, for some leukemias and primary immune deficiencies (National Institutes of Health [NIH] 2013). These transplants vary somewhat, but they are all complex. They involve conditioning agents, premedications (e.g., meperidine, hydrocortisone), infusion of donor cells, and medications (e.g., cyclosporine, methylprednisone) against graft-versus-host disease (GVHD). Most patients nonetheless experience at least some symptoms of GVHD, and are treated with additional medications depending on their site and severity, including growth factors for prolonged neutropenia, blood products for low platelets, and antibiotics for infections. Finally, hematopoietic cell transplant is associated with a number of procedures, including central line placement, blood draws, and tests of various sorts.

Current research on allogeneic hematopoietic cell transplant often involves minor alterations to standard care procedures to assess whether it is possible to reduce their significant toxicities, without undermining their efficacy. For example, a study might split the dose of one of the drugs in two and perform two research blood draws to determine the associated blood levels of the drug. For the purposes of evaluating the risks and potential benefits of this study, the federal regulations are fairly clear:

In evaluating risks and benefits, the IRB should consider only those risks and benefits that may result from the research (as distinguished from risks and benefits of therapies participants would receive even if not participating in the research; Code of Federal Regulations 2005, 45 CFR 46.111.2).

The idea here is the reasonable one that the risks and potential benefits of research involve those risks and potential benefits that participation adds to participants' lives. Thus, the potential benefits of the present study include the chance that this approach may be less toxic. The research risks include the slight chance that splitting the dose will make it less effective, as well as the risks of the two extra blood draws.

With respect to disclosure, one might assume that investigators should inform potential participants of the same research specific risks. Instead, the regulations mandate the disclosure of any "reasonably foreseeable" risks (45 CFR 46.116 a.2). Based on this requirement, the consent form for an allogeneic hematopoietic cell transplant protocol of this type listed the potential risks for all of the treatments and procedures included in the protocol. The resulting risk section was 10 pages long and listed 188 risks (I counted them).² This, everyone can agree, is not ideal. It makes little sense for a document designed to help potential participants (or their surrogates) make informed decisions to list 188 risks. And it makes little sense for the regulations that govern such documents to require this level of disclosure.

²For this purpose, I chose the most recent and similar stem cell transplant protocol that I came across. I have not disclosed the source for sake of confidentiality. A second protocol that I consulted at random for comparison had a risk section of 7 pages and listed 139 risks.

This conclusion is reinforced by the fact that at least 182 of the listed risks are identical to the risks potential participants would face if they chose to pursue standard treatment instead. Hence, to the extent that potential participants are choosing between research and standard care, this approach likely undermines rather than promotes their decision making. Listing all 188 risks obscures the differences between research and care; it obscures the 6 risks that the research adds to standard clinical care. In addition, given that the vast majority of the 182 common risks likely are not disclosed in standard clinical care, this approach to risk disclosure makes research seem more risky than it really is.

The most obvious response would be to argue that the *disclosure* of research risks should be governed by the same qualifier that covers the *evaluation* of research risks. Specifically, the regulations might be amended to mandate disclosure to potential participants of only the risks that research adds to standard clinical care. Or one might argue that this is in fact the way that the current regulations should be interpreted. While the limitation to “research” risks is not stated explicitly in the standards for disclosure, the earlier use of that qualifier suggests that this is what the drafters of the regulations had in mind. This approach gains support from the fact that interpreting “foreseeable” risks as referring to all foreseeable risks yields a practice that undermines rather than promotes the primary goal of the disclosure standard, namely, helping potential participants make a decision.

On this proposal, the consent form for the hematopoietic cell transplant protocol should have disclosed the 6 research added risks and perhaps disclosed the remaining 182 risks in an appendix that is provided to, but not routinely discussed with, potential participants. This approach represents a clear advance over current practice, and should be encouraged. At the same time, it fails to address the problem of excessive risk disclosure in a range of cases. Consider a study assessing whether hematopoietic cell transplant might be effective for a serious condition for which there currently are no treatments. In this case, the potential participants would not face the risks of hematopoietic cell transplant outside of the research setting. Hence, even on the proposed account of what risks should be disclosed (i.e. the risks that research adds to participants’ lives), the consent form for this study should disclose all 100–200 risks of allogeneic hematopoietic cell transplant. The thought that this result is also problematic suggests that the current proposal is not tailored sufficiently to what should be disclosed to potential participants. One way to try to identify a better approach is to consider what ethical concerns are raised by clinical research and what consent form and process are needed to address these concerns.

THE POTENTIAL FOR EXPLOITATION

Clinical research exposes participants to various tests and procedures, and systematically collects data on the results, in order to identify improved methods to treat, cure, and avoid illness and disease. In this way, clinical research raises concern regarding the potential for exploitation: Participants are exposed to risks and burdens to collect data that might benefit others (Emanuel, Wendler, and Grady 2000).³ One way to characterize this concern is in

³Typically, the benefit in question involves identifying better methods to prevent, treat, and cure disease and illness. In the case of industry-sponsored research, the benefit also might involve making money for shareholders and employees.

terms of the view that clinically research is pervasively problematic. By exposing participants, often ill ones, to risks for the benefit of others, the very enterprise of clinical research is ethically suspect. Support for this view comes from the assumption that clinicians are obligated to always do what is best for the patient in front of them (Angell 1993; Fried 1974; Hellman and Hellman 1991), whereas investigators' goal is to advance the scientific goals of the study in question. This assumption suggests that the situation of research participant is a particularly parlous one. Individuals with an illness who receive treatment in the context of clinical care can essentially trust their physician to do what is best for them because physicians are trained and expert, and have no relevant interests other than helping the present patient. Enrollment in research changes things fundamentally by introducing a primary competing interest, with the result that participants cannot rely on investigators to protect them.

This characterization of the ethical concerns raised by clinical research supports the view that consent forms should provide a fairly exhaustive description of most, if not all, aspects of the study in question. If participants cannot rely on investigators to protect them, they must protect themselves. And to do this they need to be well informed regarding all aspects of the study. To get away from excessive descriptions of the risks of clinical research, we need to figure out what is wrong with this analysis.

The primary problem is that clinicians are not obligated to always promote the best interests of the present patient. Clinicians have a number of appropriate interests that can compete with providing the best care possible, including earning a living, helping other patients, conserving the resources of the institutions where they work, and training new clinicians (Wendler 2010). To take just one example, data reveal strong correlations between clinician volume and patient outcomes (Halm, Lee, and Chassin 2002). For many procedures, patients do better if they are treated by a clinician who has comparatively more recent experience treating the condition in question.

These correlations imply that if physicians were obligated to always promote the best interests of the present patient, less experienced physicians often would be obligated to decline to treat the patient in front of them, and instead refer the patient to someone more experienced. In fact, clinicians often are not obligated to do this, even when an experienced colleague is available, because they have other legitimate interests, including obtaining experience and earning a living.

The second problem with the present characterization of clinical research is that research participants tend to be monitored more closely than patients, and the monitoring is done by individuals who often are expert on the condition in question, often have greater resources at their disposal, and are themselves fairly closely monitored. This is all not to say that patients in general are at greater risk than research participants, although that is likely often the case. The point is that clinical research is not a pervasively problematic divergence from the morally pure context of clinical care. Rather, both clinical care and clinical research raise important ethical concerns that their respective consent processes should be tailored to help address. Thus, to develop a better approach to consent for clinical research, we need to

identify the specific ethical concerns that clinical research raises, and tailor the informed consent process to help address them.

SPECIFIC ETHICAL CONCERNS

A second way to understand the ethical concern raised by clinical research focuses on the fact that it exposes participants to procedures to collect data that might benefit others. In this way, individuals who are invited to enroll in a clinical trial are being invited to contribute to the goals of the study in question, and to enter into a research relationship with the investigators. In addition, the procedures used in research studies sometimes expose participants to net risks, that is, added risks that are not compensated by an increased potential for clinical benefit.

This analysis suggests that, at a minimum, investigators typically should disclose to potential participants that they are being asked to contribute to a research study designed to collect information to help others, and disclose any added net risks to which they will thereby be exposed. Because individuals who understand that they are being asked to contribute to a project to help others will have some understanding of the nature of the proposed relationship with investigators, there frequently will be no need to add anything to consent forms to address this issue explicitly. Finally, the fact that research participants agree to take on added risks and burdens for the benefit of others suggests that we owe them a measure of gratitude. This seems especially clear when they are not obligated to participate and the added net risks are greater than minimal. Thus, it makes sense at some point during the consent process to thank those who agree to participate and highlight the contribution they are making.

Disclosure of this information serves to address the ethical issues that clinical research in particular raises.⁴ Hence, the decision of what other information to disclose should be based on appropriate standards for obtaining consent for the procedures in question. In particular, what is disclosed regarding clinical procedures that are included in the protocol should be based on appropriate standards for disclosure regarding those procedures in the context of clinical care.⁵

For the aforementioned hematopoietic cell transplant protocol, the consent form should disclose that potential participants are being invited to help try to identify improved transplants methods, the risks involved in splitting the dose of one drug, and the two added blood draws and their risks. For the other standard-of-care procedures in the protocol the consent form should describe them in the detail that is used for appropriate clinical care. Presumably, these standards focus primarily on explaining the overall risk/benefit profile of the best option or options and the level of certainty or evidence supporting these judgments, as well as disclosing any additional information that is important for subjects to know (e.g., this hurts or will take 5 days), and then soliciting any questions.

⁴There are of course non-research-specific concerns, such as the possibility for deception and manipulation, that need to be addressed in some cases. The present assumption is that these concerns will be addressed by the standards for disclosure in the clinical setting, discussed later.

⁵By the standards for appropriate disclosure in the clinical care setting I have in mind clinical care that does not raise any of the specific ethical concerns mentioned earlier, such as physician training.

IMPLICATIONS

Risk Disclosure

The potential for exploitation traces to the fact that research participation poses added net risks to participants, not to the fact that it poses different risks. The mere fact that research participation poses one set of risks while standard clinical care poses a different set of risks does not raise ethical concern. It depends on whether the research set is less favorable for the potential participants in question.⁶ With respect to the example considered previously of a study assessing whether standard hematopoietic cell transplant might be effective for a serious condition for which there currently are no treatments, the principle that potential participants should be informed of all of the foreseeable research risks suggested that all the risks of transplant need to be disclosed. In contrast, if there is good reason to think that the risk/benefit profile of standard hematopoietic cell transplant is favorable for eligible participants compared to the available alternatives, it does not pose any net risks to them. Hence, the disclosure of the risks of the procedures should be based on appropriate disclosure in the clinical setting. For the transplant, this might involve explaining that it poses serious risks, including a risk of acute pain and mortality, that the potential benefits are thought to justify the risks, and an estimate for the degree of certainty associated with these judgments.

Randomization

The view that all aspects of clinical care are designed to promote the best interests of the present patient suggests that all deviations from the methods of clinical care raise important ethical concern and potential participants need to understand them. On this basis, it is widely assumed that randomization (as well as the relative lack of individualized treatment that characterizes most studies) is inherently problematic and needs to be disclosed by investigators and understood by potential participants (Appelbaum, Lidz, and Grisso 2004; Kupst et al. 2003). The present analysis suggests, in contrast, that whether randomization (and protocolization) needs to be disclosed (and understood) to obtain valid consent depends on whether its use increases the risks (or decreases the potential benefits) for participants.

Recent data suggest that, in the setting of clinical equipoise—when the available data provide no reason to prefer one treatment over the alternatives—random assignment is not associated with worse clinical outcomes compared to assigning interventions based on clinical judgment of what is best for the individual patient (Gross et al. 2006; Peppercorn et al. 2004; Vist et al. 2005). Given these data, there is no reason to disclose randomization for the purposes of describing net research risks. In addition, understanding randomization is not necessary for understanding that one is participating in research, nor necessary for understanding that the investigators, unlike clinicians, will be relying on the participants' efforts to gather information that might help others. This suggests that investigators do not need to disclose randomization, and participants do not need to understand it, to address the specific ethical concerns raised by clinical research in the setting of clinical equipoise. Is disclosure of randomization supported by appropriate standards for disclosure of treatment assignment in the setting of clinical care?

It seems widely accepted that, in the setting of equipoise, clinicians do not need to explain to their patients the basis on which treatments will be selected. Indeed, in the setting of clinical equipoise, clinicians may not know why they prefer one treatment over another. This suggests that appropriate standards for disclosure in clinical care do not provide reason to disclose randomization. In response, one might argue that randomly choosing treatments for individuals with an illness is itself ethically problematic, and hence should be disclosed. However, in the absence of evidence regarding which treatment is better for the individuals in question, it is unclear why choosing treatments randomly is ethically worse (especially when randomization promotes an ethically valuable goal) than choosing treatments based on other factors that are similarly not correlated with promoting the patient's clinical interests, such as what one has given in the past, or what one intuitively thinks is best, or where one went to medical school.

What Participants Want to Know

I have argued that consent forms for research should disclose the fact that enrollment involves contributing to a project to help others, and any net risks to which participants are thereby exposed. Otherwise, disclosure of information concerning the procedures included in a study should be based on appropriate standards for disclosure in the clinical setting. Against this proposal, one might argue that investigators also should be required to disclose information that potential participants want to know regarding the study in question, even if it is not relevant to any added risks and goes beyond what is appropriately disclosed in the clinical setting.

This view makes sense to the extent that one assumes that research should have higher standards for disclosure because it raises significant ethical concerns not raised by clinical care. In contrast, the present analysis is based on the claim that clinical research raises different ethical concerns than clinical care. Once these ethical concerns are addressed, standards for disclosure regarding the procedures involved in a study should be based on what is appropriate to disclose to individuals regarding the procedures themselves, in a context that does not raise additional ethical concerns. Given that many of the procedures used in research are clinical procedures, the appropriate standards for disclosure often will be the standards that are appropriate for disclosure in the clinical setting.

With that said, there can be good reason to disclose additional information that individuals want. First, in some cases, individuals will want to know additional information because it is relevant to their particular values. Second, when it is known that individuals want to know certain things, failure to disclose them can constitute manipulation or deception. Third, all else being equal, understanding more about the activities in which we are involved is typically better. Fourth, simple respect provides a reason to disclose things that individuals want to know. Importantly, these considerations apply to both the research and care settings and it remains important to distinguish what individuals need know for valid consent versus what it would be nice for them to know provided there is time and resources. Finally, what it would be nice for individuals to know should be disclosed only to the extent that it does not detract from their understanding what is needed to give valid consent.

CONCLUSION

The SUPPORT study and other trials that assess different approaches within the standard of care have raised anew the question of what information should be disclosed to potential research participants. Some argue that clinical research raises significant ethical concerns that necessitate extensive disclosure, even when assessing standard of care interventions. Others argue that research on standard of care interventions raises no ethical issues beyond those present in clinical care. Hence, what is disclosed to potential participants in these cases need be no different than what is disclosed in clinical care. The present analysis suggests something of an intermediate approach. Clinical research raises specific ethical concerns and the informed consent process should be tailored to address them. Once this is done, disclosure regarding the interventions used in the study should be based on the standards for appropriate disclosure in clinical care.

Acknowledgments

This work was funded by National Institutes of Health (NIH) intramural research funds. However, the views expressed are the author's own. They do not represent the position or policy of the NIH, the PHS, or the DHHS.

REFERENCES

- Angell M. The doctor as double agent. *Kennedy Institute of Ethics Journal*. 1993; 3(3):279–286. [PubMed: 10127995]
- Appelbaum PS, Lidz CW, Grisso T. Therapeutic misconception in clinical research: Frequency and risk factors. *IRB: Ethics and Human Research*. 2004; 26(2):1–8. [PubMed: 15069970]
- Casarett D, Karlawish JK, Sugarman J. Determining when quality improvement initiatives should be considered research: Proposed criteria and potential implications. *Journal of the American Medical Association*. 2000; 283(17):2275–2280. [PubMed: 10807388]
- Code of Federal Regulations. [accessed October 28, 2013] Title 45. Public welfare. Part 46. Protection of human subjects. Department of Health and Human Services. 2005. Available at: <http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html>
- Emanuel EJ, Wendler D, Grady C. What makes clinical research ethical? *Journal of the American Medical Association*. 2000; 283(2):2701–2711. [PubMed: 10819955]
- Faden RR, Kass NE, Goodman SN, et al. An ethics framework for a learning health care system: A departure from traditional research ethics and clinical ethics. *Hastings Center Report*. 2013; 43(S1):S16–S27. [PubMed: 23315888]
- Fried, C. *Medical experimentation: Personal integrity and social policy*. New York, NY: American Elsevier; 1974.
- Gross CP, Krumholz HM, Van Wye G, Emanuel EJ, Wendler D. Does random treatment assignment cause harm to research participants? *PLoS Medicine*. 2006; 3(6):e188. [PubMed: 16719548]
- Halm EA, Lee C, Chassin M. Is volume related to outcome in health care? A systematic review and methodologic critique of the literature. *Annals of Internal Medicine*. 2002; 137(6):511–520. [PubMed: 12230353]
- Hellman S, Hellman DS. Of mice but not men: Problems of the randomized clinical trial. *New England Journal of Medicine*. 1991; 324(22):1585–1589. [PubMed: 2027362]
- Hudson KL, Guttmacher AE, Collins FS. In support of SUPPORT—A view from the NIH. *New England Journal of Medicine*. 2013; 368(25):2349–2351. [PubMed: 23738511]
- Kupst MJ, Patenaude AF, Walco GA, Sterling C. Clinical trials in pediatric cancer: Parental perspectives on informed consent. *Journal of Pediatric Hematology and Oncology*. 2003; 25(10):787–790.

- Largent EA, Joffe S, Miller FG. Can research and care be ethically integrated? Hastings Center Report. 2011; 41(4):37–46. [PubMed: 21845922]
- Macklin R, Sheperd S, Dreger A, et al. The OHRP and SUPPORT—Another view. New England Journal of Medicine. 2013; 369:e3. [PubMed: 23803134]
- National Institutes of Health. [accessed July 23, 2013] Hematopoietic stem cells. 2013. Available at: <http://stemcells.nih.gov/info/scireport/pages/chapter5.aspx>
- Office for Human Research Protections. [accessed May 7, 2013] Determination Letter from the Office for Human Research Protections to University of Alabama at Birmingham. 2013. Available at: http://www.hhs.gov/ohrp/detrm_lettrs/YR13/mar13a.pdf
- Olson, L.; Aisner, D.; McGinnis, JM. The learning healthcare system: Workshop summary. Washington, DC: National Academies Press; 2007.
- Peppercorn J, Weeks JC, Cook EF, Joffe S. Comparison of outcomes in cancer patients treated within and outside clinical trials: Conceptual framework and structured review. Lancet. 2004; 363(9405): 263–270. [PubMed: 14751698]
- SUPPORT Study Group of the Eunice Kennedy Shriver NICHD Neonatal Research Network. Target ranges of oxygen saturation in extremely preterm infants. New England Journal of Medicine. 2010; 362(21):1959–1969. [PubMed: 20472937]
- Vist GE, Hagen CB, Devereaux PJ, Bryant D, Kristoffersen T, Oxman AD. Systematic review to determine whether participation in a trial influences outcome. British Medical Journal. 2005; 330(7501):1175–1182. [PubMed: 15905256]
- Wendler D. Are physicians obligated always to act in the patient's best interests? Journal of Medical Ethics. 2010; 36(2):66–70. [PubMed: 20133397]
- Wilfond B, Magnus D, Antommaria AH, et al. The OHRP and SUPPORT. New England Journal of Medicine. 2013; 368(25):e36. [PubMed: 23738513]