Ethical Review and Oversight Issues in Research Involving Standard of Care Interventions: Workshop in Brief

ISBN
978-0-309-36796-7

10 pages
8.5 x 11
2015

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WORKSHOP IN BRIEF JANUARY 2015

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Ethical Review and Oversight Issues in Research Involving Standard of Care Interventions—Workshop in Brief

Common clinical practices might lack a robust evidence base if there have not been empirical, interventional research studies to compare an array of available routine or standard treatment options. Clinical trials that study these "standard of care" interventions examine and compare treatments that fall within the range of what is considered usual clinical practice. The goal is to gather evidence that can be used when selecting a particular intervention.

The Federal Policy for the Protection of Human Research Subjects, known as the Common Rule, governs the ethical oversight of human participation in research, including requirements for informed consent and procedures for research ethics review bodies (i.e., Institutional Review Boards [IRBs]). Under the Common Rule, IRBs are responsible for overseeing clinical trials to ensure that the safety, well-being, and rights of trial participants are protected. In addition, the IRB also oversees the process of obtaining informed consent so that participants understand the risks and potential benefits of the trial before deciding whether to enroll.

Recently, questions have arisen about certain key aspects of regulation and oversight of standard of care trials, including in particular the determination and communication of "reasonably foreseeable risks" associated with participating in a trial comparing standard of care interventions. On October 24, 2014, the Office for Human Research Protections (OHRP), which is the federal office responsible for the protection of the rights, welfare, and well-being of subjects involved in research conducted or supported by the U.S. Department of Health and Human Services (HHS), released and invited comment on a draft guidance document entitled Draft Guidance on Disclosing Reasonably Foreseeable Risks in Research Evaluating Standards of Care ("Draft Guidance").[1]

On December 2–3, 2014, the Institute of Medicine's (IOM's) Board on Health Sciences Policy held a workshop to facilitate dialogue among stakeholders about the ethical issues surrounding study design and informed consent for regulated research studies involving standard of care interventions. The workshop, requested by the National Institutes of Health (NIH), was held while the period for public comment on the Draft Guidance was open, and thus provided an opportunity for stakeholders to describe and exchange their views on the issues covered by the Draft Guidance. This brief summary of the workshop provides highlights from the presentations and discussions. Statements, recommendations, and opinions expressed are those of individual presenters and participants and are not necessarily endorsed or verified by the IOM, and they should not be construed as reflecting any group consensus. The workshop was webcast live, and the slide presentations and videos are archived on the IOM website: http://www.iom.edu/Activities/Research/StandardofCare.aspx.

[1] U.S. Department of Health and Human Services, Draft Guidance on Disclosing Reasonably Foreseeable Risk in Research Evaluating Standards of Care. Available at: http://www.hhs.gov/ohrp/newsroom/rfc/comstdofcare.html (accessed January 12, 2015). In a presentation to the Secretary's Advisory Committee for Human Research Protections (SACHRP) on October 29, 2014, Jerry Menikoff, Director of the Office for Human Research Protections (OHRP), described the Draft Guidance. Menikoff's presentation is archived online, and the video was shown to workshop attendees at the beginning of the workshop, immediately after the workshop chair's opening remarks. U.S. Department of Health and Human Services. Secretary's Advisory Committee on Human Research Protections (SACHRP) (videocast, Wednesday, October 29, 2004). Available at: http://videocast.nih.gov/summary.asp?Live=14938&start=16936&duration=6755&bhcp=1 (accessed January 12, 2015).

BOX 1
Statement of Task

Clinical practices that are commonly used in medical settings can often lack a robust evidence base when there is an absence of empirical interventional studies to compare options for treatment that are viewed as within the bounds of routine, or standard, clinical practice ("standard of care" interventions). An ad hoc committee will plan and conduct a two-day public workshop to explore questions related to ethics and review of human subjects protections in research trials studying standard of care interventions.

Presentations and discussions will be designed to

- Consider how risks associated with receiving standard of care interventions from a health care provider might or might not be distinguished from risks associated with participating in research that compares two standard of care interventions for a condition.
- Discuss criteria for identification of reasonably foreseeable risks associated with research studying standard of care interventions.
  - Highlight approaches for: (a) identifying what constitutes evidence and (b) ascertaining whether the degree or extent of identified evidence informs the determination of reasonably foreseeable risk.
- Discuss issues pertaining to randomization of participants in research studying standard of care interventions, including whether and under what circumstances the act of randomization could be considered a risk to research participants.
- Explore the above outlined issues, as well as gaps and areas of uncertainty in the guidance available to the research community, with specific attention to the following:
  - How researchers evaluate and characterize the above issues in designing research protocols comparing standard of care interventions.
  - How Institutional Review Boards (IRBs) assess and exercise oversight of research studying standard of care interventions.
  - How concepts relating to participation in studies involving standard of care interventions, including potential risks associated with receiving standard of care interventions and with research participation itself, are communicated with research participants.

Overview of Workshop Topics

To address the Statement of Task (see Box 1), the workshop included presentations and discussions designed to explore: (a) the definition of standard of care and its application in clinical practice settings; (b) differences associated with receiving standard of care interventions in a clinical practice versus a research setting and implications for regulation of standard of care research; (c) whether and under what circumstances the act of randomization could be considered a risk to research participants; (d) the defining and identifying of reasonably foreseeable risks of research; and (e) communication of risks and potential benefits with prospective research participants.

Defining "Standard of Care"

In her opening remarks, Workshop Chair R. Alta Charo, University of Wisconsin–Madison, observed that some definitions or concepts of "standard of care" might imply that there is a single standard of care that all clinicians should follow for each condition, whereas others suggest that there could be a range of different approaches to treatment that are each accepted by medical experts as a proper treatment for a certain type of disease and widely used by health care professionals. During the workshop, individual speakers and participants offered their perspectives on defining "standard of care":

The Draft Guidance defines "standard of care" as "medically recognized standards of care. Medically recognized standards of care are treatments or procedures that have been accepted by medical experts as appropriate treatments or procedures for a given type of disease or condition and are commonly used by health care professionals. The medical recognition of standards of care is typically represented by publication in a peer-reviewed journal or some form of recognition by a professional medical society. The evidentiary bases for these recognized standards of care vary."

- Jeremy Sugarman, The Johns Hopkins University, noted that there is a difference between the terminology "standard of care," which he defined as the range of acceptable practice, and "standards of care," which he defined as standards for delivery of care. Charles Weijer, Western University in London, Canada, proposed defining "standard therapy" as "treatment accepted by at least a respectable minority of expert practitioners."
- There was discussion about the extent to which differences in standard of care or usual care practice are attributable to evidence supporting those differences or to other factors, such as physician habit, described by Harold Sox, Patient-Centered Outcomes Research Institute (PCORI). Relatedly, some workshop participants employed the terminology "usual care," such as Donald Brunnquell, Children's Hospitals and Clinics of Minnesota. Brunnquell suggested that this terminology is better reflective of the reality that there are many differences in what care is delivered across institutions and regions. Other workshop participants suggested additional alternative terminology: Sox referred to "comparative effectiveness research," and Benjamin Wilfond, Seattle Children's Hospital, and David Magnus, Stanford University, employed the term "research on medical practice."
- Throughout the workshop, several participants, including Vanessa Northington Gamble, George Washington University, and Ann Bonham, Association of American Medical Colleges, cautioned that not all patients receive the highest or the same standard of care when they present at their health care provider, and these differences could be attributable to socioeconomic or cultural factors, such as race.
- Leonard Glantz, Boston University School of Public Health and Boston University School of Law, argued that employing distinct terminology for "standard of care" research is not useful, because, he said, the relevant moral distinction is whether the activity is research or care delivered in the context of clinical practice.
- Michael Carome, Public Citizen, cautioned that when research on standard of care or usual care interventions is conducted, IRBs should require robust evidence supporting the researchers' claim that the interventions being studied are, in fact, usual care.

Standard of Care Interventions—The Usual Practice Experience

Sox provided remarks about receiving "standard of care" treatment, including whether and to what extent there is a "cryptic randomness" embedded in this experience. He noted that from a patient's perspective, what care is received generally appears to be "random." He further observed that evidence of disparities in treatment patterns suggest that care can be biased toward an individual physician's preferences or routines and not necessarily based on the individual patient's characteristics or specific needs.

Several workshop participants provided their individual perspectives on the meaning of Sox's observations. Greg Simon, Group Health Research Institute, characterized clinical treatment in the "state of nature" as being more haphazard than systematic and as being possibly influenced by the provider's habits or prejudices, or by other cultural or economic factors. Cindy Geoghegan, Patient & Partners LLC, noted that factors other than individualized physician attention, especially payer reimbursement policies, can determine or greatly influence what care is received. Susan Ellenberg, Perelman School of Medicine at the University of Pennsylvania, added that when evidence is murky, and when usual care decisions are influenced by habit or routine, being randomized into a standard of care treatment arm could actually represent an improvement for the patient from receiving care that is affected by bias not relating to that individual's prognosis.

Differentiating Clinical Practice and Research and Implications for Regulation

Weijer presented a two-step theoretical framework called component analysis, which he described as a systematic and comprehensive approach to the ethical analysis of research benefits and harms. The first step, which he noted is not often emphasized, is to separate standard therapy from research interventions. If the interventions are

considered standard therapy, they are managed within the context of the physician–patient relationship and are not subject to regulation as research. Under the second step, any research interventions are separated according to whether they are therapeutic procedures or nontherapeutic procedures. Weijer noted that under component analysis, therapeutic procedures are subject to a different regulatory analysis: clinical equipoise must exist, the procedure must be consistent with "competent care," and the risks must be reasonable in relation to potential benefits to subjects. The regulatory standard is different for nontherapeutic procedures, he said, in which risks must be minimized consistent with sound scientific design and reasonable in relation to knowledge to be gained.

Andy Bertolatus, Veterans Administration Medical Center, Iowa City (University of Iowa), offered observations on how risks of research might be distinguished from risks of clinical practice. He identified a variety of ways in which a trial comparing standard of care interventions could differ from receiving the same interventions in usual clinical practice, such as: (1) when continuous variables are being measured, the risks associated with each arm could possibly not be the same as the actual average intervention delivered in standard clinical practice; (2) when clinical investigators or health care professionals delivering an intervention that they are required to execute under the protocol are not as familiar with that assigned intervention; (3) when "add-ons," such as genetic testing, are introduced that could change risk; and (4) when the loss of patient choice of intervention, due to the need to adhere to a research protocol, exposes the participant to a side effect profile that would not have been what the participant would have chosen as a patient outside of a trial. Bertolatus also commented that in a study comparing standard of care interventions, each participant faces an increased spectrum of risk exposure by virtue of being exposed to the possibility of experiencing the risks of treatment of both study arms. Simon observed that although this increased spectrum of risk exposure is likely to have an effect on an individual participant's outcomes, it does not necessarily alter the overall average expectation of risk of all individuals participating in the trial.

Glantz argued that the fact that these studies compare standard of care interventions is not relevant for determining how the research ought to be regulated, commenting, "We do not regulate research because it is riskier than standard of care." Rather, he said, research is regulated because investigators have a dual loyalty—both to the patient and to the research protocol to support development of new knowledge. In contrast, Glantz noted, the patient's well-being and best interest is the sole focus of the physician in a clinical care context. Some participants countered this perspective, such as John Lantos, University of Missouri at Kansas City and Children's Mercy Hospital Bioethics Center, who cautioned that this dichotomy is "the basis for our current bizarre system in which we know that informed consent for clinical care is terrible." He also suggested, citing theorists such as Otto Guttentag, Henry Beecher, and Jay Katz, that the concept of regulation of clinical investigators to protect research participants from investigators' "dual loyalty" is not relevant when the goal of the research is therapeutic and is performed with a purpose to treat and intention to benefit the patient.

Determining and Communicating Risks of Randomization

Ellenberg discussed as a foundational matter the ethical basis for randomization of research participants into different arms of a study. She defined "equipoise" as a state in which a physician has no preference for either treatment under investigation and elaborated that "clinical equipoise" is a condition in which individual physicians might have preferences but there are differing views throughout the clinical community about which is the preferred treatment. The "uncertainty principle," in which both the physician and the patient are uncertain as to which treatment might be more beneficial, forms another proposed ethical basis for randomization, she said. Ellenberg also commented that the theories and goals of randomization in trials studying standard of care interventions are not distinct from randomization in any other kind of clinical trial; although, she observed, standard of care trials are likely to have many sources of heterogeneity, making treatment effects more difficult to detect.

Miriam Kuppermann, University of California, San Francisco (UCSF), presented observations about research participants' difficulties in understanding the concept of randomization and discussed ways to better communicate the concept. In her presentation and the ensuing discussion, the following factors were discussed as impeding or affecting a participants' understanding: (1) lower reading or health literacy levels; (2) lower participant attention or "emotional" engagement in the consent process (particularly due to long consent forms) (noted by

Steve Hyman, Harvard University and the Broad Institute of Harvard and MIT); (3) "cognitive dissonance"—described by Kuppermann as a state in which "even though they know they are being randomized, there is still a feeling that somehow . . . the doctor is going to think about what's best for them"; and (4) cultural factors (noted by Gamble).

The session objectives included exploration of whether and under what circumstances the act of randomization could be considered a risk to research participants. Nancy King, Wake Forest University, argued that randomization alters risks to research participants, though it does not always increase risk. She offered the following as potential risks of randomization: (1) risk of harm or discomfort from receiving an intervention that the participant would not have been assigned off-study; (2) inconvenience and failure of preference satisfaction; (3) protocol rigidity; and (4) therapeutic misconception. Lewis Leavitt, University of Wisconsin–Madison, stated that the fact that care is not individualized under a research protocol constitutes a fifth risk attributable to randomization. Wilfond responded that other than risk of harm, in his view the other issues identified by King and Leavitt are important to discuss with prospective research participants as "things that might happen" as a result of trial participation but are not "risks" of randomization. He noted that the fact that randomization is performed "matters to patients" and ought to be communicated well, but, he said, should not be described as in itself a risk of harm. Simon offered a perspective that "randomization influences the treatment that people might receive. The effect on risk is mediated through that change in treatment. . . . The constraints on treatment choice are study-specific" and, he said, not necessarily created by the act of randomization.

Defining and Disclosing Reasonably Forseeable Risks

Defining Reasonably Forseeable Risks

The Common Rule requires disclosure, as part of the informed consent process, of "any reasonably foreseeable risks or discomforts to the subject" (45 CFR 46.116(a)(2)). The OHRP Draft Guidance states that "if evaluating a particular risk of research associated with a standard of care is a purpose of the research, then in general OHRP considers that particular risk to be "reasonably foreseeable."[2] In a video presentation shown to workshop participants, Jerry Menikoff, Director of OHRP, stated that this provision of the guidance derives from the concept that, "if a study involves possibly exposing a person to different non-minimal risks from those to which they would otherwise be exposed—risks that have already been identified . . . they should be told about these risks, and allowed to decide if they want to be exposed to them."

Sugarman categorized potential risks, defined as chance of harm, faced by participants in research studying standard of care interventions as: (1) the baseline risks of the underlying disease or condition; (2) the baseline risks or potential benefits of the standard of care interventions being studied; and (3) the incremental risks of research. Carl D'Angio, University of Rochester, suggested categorizing risks as known risks, possible risks, risks of uncertain likelihood, and unexpected risks. Rebecca Dresser, Washington University in St. Louis, argued that "prospective subjects ought to hear about the risks presented by the two arms even though they were standard of care." Wilfond advocated distinguishing known risks of harm from uncertain risks that are under study in the trial, which he said should not be considered and disclosed as "reasonably foreseeable." Sugarman added that the determination about what risks are reasonably foreseeable must be fixed prospectively; harms determined during or after the trial are no longer "risks" but are known harmful outcomes.

Workshop participants discussed approaches and criteria for evaluating whether a risk is reasonably foreseeable. It was noted by Glantz, Robert Califf, Duke Translational Medicine Institute, and others that the term "reasonably foreseeable" is vague. Several individual participants suggested defining reasonably foreseeable risk

[2] The Draft Guidance defines "purposes of research" as "the aims or objectives that determine the design of the research study and provide the scientific and ethical justification for carrying it out. The evaluation of a risk is considered a purpose of the research when a research study is designed and conducted in order to ascertain the existence, extent or nature of a particular harm. If a study is designed to discover the degree to which that particular harm will or will not occur, the possibility of that harm occurring is clearly foreseen by those responsible for the design and conduct of the study."

according to criteria such as frequency (or likelihood), magnitude, and nature/relationship. Jon Tyson, University of Texas Health Science Center at Houston, and Bonham noted that there is a need to evaluate volume and credibility of evidence. For example, Tyson suggested including consideration of whether the risk is biologically plausible with studies finding at least a marginal association with the outcome.

Several participants commented on whether a purpose of the study ought to be considered a risk of the research as specified in the Draft Guidance. Tyson commented that a defined primary outcome is not necessarily a foreseeable risk of the standard of care intervention (e.g., death could be defined as a primary outcome in the protocol for purposes of fidelity to the intention to treat principle, particularly when there is a high expected baseline rate of death). It was further noted by several participants that, to the extent measured harmful outcomes must be considered "risks" of a study, the measured beneficial outcomes ought to be considered potential benefits of a study.

Disclosing Reasonably Foreseeable Risks to Prospective Participants

Glantz remarked that in his view it is a merely "procedural" issue of at which point in the informed consent discussion the risks and benefits of the standard of care interventions are discussed (whether as research risks or otherwise). Simon suggested that it matters whether these risks are attributed to research versus disclosed outside of the research informed consent process, arguing that disclosure of uncertain risks as risks of research could deter participant enrollment. Consistent with this, others were concerned about "over disclosure" of uncertain risks of standard of care interventions rendering informed consent misleading, distracting, or meaningless.

King emphasized that the fact that research participants are facing treatments that could be different from what they or their physician might have chosen if off-study needs to be discussed with participants. She called for an informed consent process that includes discussion about what treatments are in common use at the participant's site of care, whether on-study or off-. She noted that imposing this communication expectation on researchers raises the standard for discussion about informed consent to treatment in regular clinical care. Keith Fargo, Alzheimer's Association, reinforced this suggestion when he noted that it is not reasonable to take the position that because we are not good at communicating about risk in standard clinical practice, we do not need to be good at communicating that same risk with patients in the context of a research study, adding that "you do have to be better at explaining risk of research than you have to be at explaining risk of clinical practice."

Engaging and Communicating with Research Participants

The workshop objectives included exploration of how concepts relating to research participation are communicated with research participants. Workshop discussions included individual speakers' perspectives on how consent forms and the current informed consent process could be improved and suggested approaches to the informed consent process for a trial studying standard of care interventions.

Improving Consent Forms and Processes

Kuppermann presented principles and techniques for communicating the concept of "randomization" to prospective research participants. The World Health Organization provides that the meaning of "randomization" should be explained to participants through relatable concepts, such as tossing a coin. Other organizations, such as the National Cancer Institute and UCSF, state that the term "randomization" should be defined with reference to the more-understandable terminology of "assignment by chance" or "50/50 chance." In an informal survey of colleagues performing randomized trials, however, Kuppermann found that consent forms inconsistently applied these principles. Moreover, Kuppermann cited several studies finding that prospective research participants often do not understand the concept of randomization, even when it is carefully explained. Difficulties understanding these concepts are higher in lower socioeconomic status, lower educational attainment, and lower literacy populations, she noted.

Several individual workshop participants observed that research consent forms are too long and impede rather than facilitate understanding. Glantz remarked that this concern is not unique to research comparing standard of care interventions. Some participants, such as Lantos and Califf, argued that a requirement to disclose the risks of the underlying standard of care interventions as risks of research in the research informed consent form for a standard of care trial would exacerbate problems communicating and understanding or place insurmountable resource burdens on research. Others, including Dresser, King, and Leavitt, emphasized that research participants should be told all of the relevant information about the underlying treatment interventions and that researchers should not rely on the clinical treatment discussion to provide that information. Gamble and Ruth Macklin, Albert Einstein College of Medicine, added that some underserved populations might not receive clinical care outside of the research setting, and thus the research informed consent process might be their only opportunity to receive information about the standard of care interventions.

Models and Approaches to Discussing Risks and Obtaining Informed Consent

Lantos offered a model for a "five-point" conversation with prospective research participants:

1. explain the patient's disease, its natural history, and the patient's prognosis;
2. describe the patient's treatment options;
3. discuss "why doctors disagree" or do not know which option is better, using the following descriptive framework: (a) the two most common risks; (b) the one most serious risk; (c) the two most common benefits; and (d) the one most important benefit;
4. give the patient a choice between entering the trial or not entering the trial and thus to choose among the options;
5. collect outcome data on all patients, whether enrolled and randomized or not.

Lantos suggested that this process could be undertaken in a 5- to 10-minute conversation and that the five elements could be summarized in a short written form that could be stapled to the top of the standard informed consent form. Several participants cited a recent "integrated consent" model proposed by Scott Kim and Franklin Miller[3] that would include, during the routine clinical interaction, discussion of the patient's treatment options; risks and benefits of both options; discussion of the process of random selection; and documentation of the discussion and patient's decision whether or not to enroll in the trial.

Individual workshop participants also made suggestions relating to providing the context for the trial during the informed consent discussion, including

- Consideration of the participant's cultural "language" and interpretation of the study (Gamble)
- Discussion of the potential or anticipated benefits of the intervention or of trial participation (Geoghegan)
- Techniques to ensure connection and understanding with populations and individuals that are less likely to understand or to know what questions to ask to obtain full understanding (Leavitt)

Some workshop participants offered suggestions for new models for informed consent that could apply to research involving standard of care interventions, including (1) peer-to-peer models (Geoghegan and Bonham); (2) multimedia decision aids (Kuppermann and Wilfond/Magnus); and (3) recording the informed consent conversation (Glantz).

Engaging Research Participants in Risk Determinations

Fargo commented that "I have heard people sometimes talk about 'consenting patients' as if consenting is something that you do to a potential participant rather than a potential participant knowledgeably giving their

[3] Kim, S. Y. H., and F. G. Miller. 2014. Informed consent for pragmatic trials—the integrated consent model. *New England Journal of Medicine* 370(8):769-772.

consent or their permission to be part of a study." Sharon Terry, Genetic Alliance, added that participants "need to be engaged and not consented." Califf and Bonham remarked that fuller engagement of patients about the uncertainty associated with the interventions being studied could foster greater understanding and ultimately bolster trust in the clinical research process. Several other workshop participants added that the full engagement and contributions of research participants are important not only during the consent process but also in the design and regulatory oversight of trials. For example, a commenter speaking from the perspective of a patient argued that the patient voice ought to be included in the design of each individual clinical trial to ensure that "the patients at risk decide what is a risk and what they are willing to do" rather than to have that determination made for them through generalized definitions about risk.

Empirical Studies of Participant Perspectives on Informed Consent in Standard of Care Trials

Four research centers have received supplemental awards from the NIH to conduct empirical ethics research to learn about the perspectives of researchers, research participants and patients, and others participating in or overseeing research. Investigators presented their respective projects' aims and, in some cases, preliminary or initial qualitative findings. These individual speakers highlighted the following preliminary observations stemming from their research:

Kevin Weinfurt, Duke University School of Medicine:

- Participants have difficulty understanding studies in which patients are randomized to different FDA-approved treatments because they assume the research is akin to trials of new therapeutics. These difficulties in understanding can be partially addressed through educational presentations and discussion.
- The reported needs and interests of participants differ depending on the type of standard of care intervention (e.g., individual randomization of a pharmacotherapy versus a cluster randomized medical center operations intervention).
- Participants reported that they do not want greater disclosure in informed consent to artificially increase their perception of risk associated with the research ("more [disclosure] is not always better").
- Researchers are finding that participants express many different needs and interests, and these needs and interests sometimes conflict in such a way that tradeoffs may need to be made (e.g., a participant recognized that notifying the public about a trial—one participant interest—would undermine the study methodology—another interest).

Wilfond and Magnus:

- Participants generally support research to determine which common practices and treatments are best and prefer written informed consent for participation in that research, but if written informed consent is too difficult to obtain, most participants support the continued conduct of research through less demanding notification mechanisms (such as discussion and oral consent or broad notification) for both medical record review and randomized designs.
- In contrast, IRBs generally distinguish medical record review from randomization studies (and require much less notification or consent in the case of medical record review), even though prospective research participants reported relatively little difference in their notification preferences for these two types of studies. In fact, preliminary data from this study indicate that a larger proportion of IRB respondents than patient respondents prefer that randomization trials include more stringent informed consent processes.
- The concept of and discussion about risks associated with participating in a study were less significant than the concepts of trust and their relationship with their doctor.

Scott Halpern, Perelman School of Medicine of the University of Pennsylvania:

- Patients and health care providers appear to be at least as willing (and perhaps more so) to relinquish treatment autonomy in the context of a research study as they are in the context of clinical care (e.g., through imposition of new clinical practice guidelines).
- In considering research studies testing interventions within the standard of care, potential participants do not generally raise concerns about research risks or about privacy loss. Instead, they may cite concerns regarding the nature of information exchange about the study, whether there will be less-individualized care in a study, or how the intervention would affect their daily lives (in this case, with altering time spent on dialysis). These concerns are cited for both research studies and clinical initiatives that protocolize care.

Sheila Fireman, Harvard Pilgrim Health Care Institute, provided an overview of the ABATE infection collaboratory project led by Susan Huang of the University of California Irvine, for which preliminary data are not yet available. This project aims to identify whether a common ethical framework exists for certain types of low-risk comparative effectiveness and health care operations studies. The project involves conducting three surveys using research and quality improvement scenarios to assess attitudes and beliefs about informed consent requirements and risk assessment for minimal risk interventions in three key interest groups: IRB chairs, leaders of health care quality improvement programs, and patients.

Comments on the Draft Guidance

The workshop was not a formal venue for providing comments on the Draft Guidance to HHS, and workshop participants were directed to the HHS/OHRP website to provide their individual comments. However, to facilitate concrete discussion and exchange of ideas, workshop participants were invited to offer their perspectives and suggestions about the Draft Guidance as it relates to the topics under discussion at the workshop. The following specific comments about the Draft Guidance were offered by individual speakers:

- The Draft Guidance would benefit from additional clarity, particularly with respect to definitions of key terms such as "standard of care" and "reasonably foreseeable." (Marjorie Speers, Speers Research Strategies, Sugarman, and other commenters)
- The Draft Guidance could be improved by including more specific guidance to IRBs, such as a framework to help guide IRBs' review of standard of care research (Brunnquell, Bonham, Speers). Some commenters expressed concern that unclear guidance could lead to inconsistent or overly conservative interpretations by IRBs. (Bonham, Califf, Bray Patrick-Lake [Duke Translational Medicine Institute])
- It is difficult for one guidance document to cover the full range of standard of care research. It was suggested, for example, that there might be a good rationale for different consent requirements depending on the type or approach of the research, including, for example, the degree and quality of differences between the interventions being studied. (Sugarman) Sugarman added that an HHS Secretarial waiver could be employed to conduct demonstration projects to learn more about what research participants understand and prefer for informed consent or notification, particularly for research projects that are currently difficult to conduct because a minimal risk determination cannot be obtained and thus individual informed consent cannot be waived.

There was also some discussion at the workshop about whether a standard-of-care-specific guidance document is needed. Glantz suggested that the relevant regulatory standards (such as "reasonably foreseeable risk") apply to all research and not specifically standard of care research. There was also significant discussion at the workshop about the length of consent forms and IRB determinations of minimal risk, which also are issues that are not specific to standard of care research. Sugarman suggested that the guidance document may not be able to "solve" these broader issues and that they could be more effectively addressed through the Notice of Public Rulemaking process currently under way to revise the Common Rule.

Cross-Cutting Discussion Points

In the closing session of the workshop, session moderators Simon, Speers, and Celia Fisher, Fordham University, offered their individual observations about the cross-cutting issues that had been highlighted over the course of the workshop.

- **Benefit.** Speers and Fisher both observed that a number of workshop participants had called for additional consideration of the concept of benefit in standard of care trials, including benefits of participating in the research and benefits of the interventions.
- **Participant Engagement and "Evidence-Based Informed Consent."** Speers and Fisher each commented that workshop discussions included focus on the benefit of including and understanding the needs and interests of patients in developing research protocols and informed consent processes. Several workshop participants presented preliminary findings from empirical studies designed to elicit participant preferences, and other workshop participants called for more research, demonstration projects, and other mechanisms to develop processes that are based on actual participant preferences for informed consent.
- **"One Size Does Not Fit All" and Desire for Definitional and Procedural Clarity.** Speers and several others commented that because there are many different types of standard of care studies, "it might not be possible to come up with only one set of criteria for reviewing those studies or one set of criteria for the consent process." For example, King noted that the ethical analysis for standard of care trials is "design-dependent," depending on the interventions being studied and considerations such as the extent to which those interventions have been scientifically validated versus being simply customary practices. Fisher observed that the Draft Guidance could benefit from definitional clarity, patient and participant input, and clearer articulation of the kind of review processes that IRBs will be expected to follow to implement the Draft Guidance.

PLANNING COMMITTEE FOR A WORKSHOP ON ETHICAL REVIEW AND OVERSIGHT ISSUES IN RESEARCH INVOLVING STANDARD OF CARE INTERVENTIONS*
R. Alta Charo (Chair), University of Wisconsin–Madison; **Celia Fisher,** Fordham University; **Steve Hyman,** Broad Institute of Harvard and MIT; **Clay Johnston,** Dell Medical School at University of Texas, Austin; **Greg Simon,** Group Health Research Institute and University of Washington; and **Marjorie Speers,** Speers Research Strategies.

* IOM planning committees are solely responsible for organizing the workshop, identifying topics, and choosing speakers. The responsibility for the published Workshop in Brief rests with the institution.

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DISCLAIMER: This workshop in brief has been prepared by **Christopher DeFeo, Emily Busta,** and **Anne Claiborne,** rapporteurs, as a factual summary of what occurred at the meeting. The statements made are those of the authors or individual meeting participants and do not necessarily represent the views of all meeting participants, the planning committee, or the National Academies.

REVIEWERS: To ensure that it meets institutional standards for quality and objectivity, this workshop in brief was reviewed by **Charles MacKay,** Medstar Health Research Institute; and **Nancy Roach,** Fight Colorectal Cancer**. Chelsea Frakes,** Institute of Medicine, served as review coordinator.

SPONSORS: This workshop was supported by a contract between the National Academy of Sciences and the Department of Health and Human Services (HHSN26300053 [Under Base #HHSN263201200074I]).

For additional information regarding the workshop, visit http://www.iom.edu/standardofcareWIB.