

Meeting New Challenges in Informed Consent in Clinical Research

An Exploratory Workshop

**Sponsored by the Office for Human Research
Protections (OHRP), Department of Health and
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Meeting New Challenges in Informed Consent in Clinical Research: OHRP Exploratory Workshop: September 7, 2018

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Welcome and Introduction

Dr. Lau, Director of the Division of Education and Development (DED) at the U.S. Department of Health and Human Services (HHS) Office for Human Research Protections (OHRP), welcomed everyone to the inaugural Exploratory Workshop, a new initiative intended to increase OHRP's outreach to the research community.

The Director of OHRP, Dr. Menikoff, also welcomed those in attendance. He stressed the importance of the informed consent process as a central protection for human subjects. Important changes have been made in the revised Common Rule to ensure that participants receive the information they need to make meaningful decisions about whether to participate in research, and the research community is working toward successful implementation of the new Rule.

OHRP wishes to support collegial intellectual exchange on issues related to human subjects protection. The workshop will begin with a discussion of ethical perspectives on informed consent, then move into presentations that address the empirical evidence about effective communication of complex information and ways to support comprehension. Finally, presenters will discuss practical applications and consider the example of delivery room research. On behalf of OHRP, the Director thanked all speakers and moderators for their support in making this exchange of views possible.

Session A: Laying the Groundwork for Meaningful Informed Consent

- *Moderator:* David H. Strauss, MD; Austin Riggs Center

Dr. Strauss observed that the regulated community has spent decades complaining about lengthy and overly complex informed consent documents and now has a rare opportunity to address these concerns. He appreciated OHRP's role in sparking discussion of effective informed consent through changes in the Common Rule. Many in the field feel that informed consent has been hijacked by actors other than investigators and subjects. It is appropriate to take this workshop as an opportunity to return to the foundations of human subjects protection and think carefully about the ethical priorities relevant to the informed consent process.

The Ethical Foundations of the Disclosure Requirement

- Danielle Bromwich, PhD; University of Massachusetts
- Joseph Millum, PhD, MSc; NIH Clinical Center and Fogarty International Center

Goals of the Informed Consent Process

Dr. Bromwich noted that informed consent is an ethical requirement for most medical research involving human participants. The consent process typically involves providing potential participants or their surrogates with information about the study—including its purpose, procedures, and possible risks and benefits—and documenting their agreement through a signed consent form. Studies of participants enrolled in medical research, however, show highly variable and frequently poor understanding of key informed consent elements. Large numbers of participants cannot correctly identify key facts about the study in which they are participating. If this is the case, was their consent valid? From an ethical standpoint, what do subjects need to understand?

Dr. Bromwich suggested that the informed consent process should be designed to accomplish two goals:

- To obtain valid consent (an ethical *requirement*); and
- To facilitate good decision-making (an ethical *aspiration*).

The first goal involves obtaining valid consent to the procedures that a study includes, an ethical requirement that is potentially violated when the person responsible for disclosing information to potential participants exercises illegitimate control over participants' decision-making. To avoid this, researchers should disclose information that participants would expect to be told, and in a manner that gives participants a reasonable opportunity to understand what is being said. Valid consent as an ethical *requirement* includes ensuring respect for the autonomy rights for all competent adults (for example, the right to bodily integrity). Granting consent is the exercise of an autonomy right and may permit the investigator to perform an action that would otherwise violate these rights and be a serious moral wrong. An example is allowing a researcher to perform an invasive procedure such as a blood draw.

The second goal involves facilitating good decision-making by potential participants. This goal is ethically preferable, though not required. Dr. Bromwich held that while facilitating good decision-making is a laudable goal of the informed consent process, it can't be a requirement; competent adults maintain their right to make life decisions, however well or poorly they choose to do so. Although studies that show poor understanding by research participants are troubling, they do not necessarily show that participants failed to give valid consent.

Dr. Bromwich also cautioned that providing excessive information can be problematic. For example, if the research is designed to compare the effectiveness of existing interventions and practices, an extensive consent process may burden researchers unnecessarily and slow recruitment.

When is consent invalid? The speaker noted that our autonomy rights are violated if another person exercises illegitimate control over our decision to give or refuse consent through coercion, deception, or certain forms of manipulation. Failure to disclose information that the participant would expect to be told and has reason to believe is relevant can invalidate consent to research. No matter what the nature of the research, a researcher ought to disclose all those facts about the research that

- She knows,
- She has reason to believe would be relevant to a potential participant's decision about whether to give or refuse consent to study participation, and
- The potential participant would expect to be told.

Illegitimate control is also exercised when information is not disclosed in an understandable way. An extreme example would be explaining risks in English to a prospective subject who only speaks Spanish. Some scientific jargon may be similar to a foreign language in that it may obscure critical information.

Requirements for Valid Consent

Dr. Millum further explored the issue of whether participants can give valid consent to participate in medical research even if they do not understand the study's risks or purpose. Clearly, he stressed, participants need to understand the facts necessary to distinguish the act they are consenting to from some other act. However, he held, it is possible to consent without knowing why the research is being conducted. He gave the analogy that it is possible to give valid consent to lend someone your car without knowing exactly why they need to borrow it. Also, the researcher may not know all the risks the study may entail in advance.

In order to give valid consent to medical research participation, participants must understand:

- That they are being asked for consent,
- How to exercise their right to give or refuse consent (e.g., by signing their name), and
- What they are being asked to consent to (e.g., this physician can insert a needle).

Obtaining valid consent is an ethical *requirement*. Meeting this requirement involves disclosing a lot of information about the study to potential participants in a manner that gives them a fair opportunity to understand it, but it does not require that all that information is also understood.

Dr. Millum held, however, that good decision-making is an ethical *aspiration* rather than a goal that must be achieved in order for consent to be valid. He noted that the value of autonomy lies in permitting competent adults to live lives in accordance with their own interests, values, and preferences. Autonomy rights also include the right to make poor decisions (though this does not apply when adults are making decisions for children). It is therefore possible for a competent participant to understand enough to exercise his or her autonomy rights and give valid consent to study participation but still not understand enough to make a good decision by his or her own lights.

In summary, he stressed, the ethical requirement to obtain valid informed consent should get priority over the aspiration to facilitate good decision making, and the value of facilitating good decision making may be weighed against other valuable goals of the research. If the consent process gave prospective subjects a fair opportunity to understand key information, the consent may be considered valid, even if participants have a variable understanding of these facts.

The Reasonable Person Standard and Research Disclosure

- Rebecca Dresser, JD; Washington University in St. Louis

Ms. Dresser cited new requirements in the revised Common Rule that require understanding of the concept of a “reasonable person.” These include:

§ __.116 (a)(4): “The prospective subject or the legally authorized representative must be provided with the information that a *reasonable person* would want to have in order to make an informed decision about whether to participate”

§ __.116 (c)(9): Broad consent disclosure must include “a general description of the types of research that may be conducted with the identifiable private information or identifiable biospecimens. This description must include sufficient information such that a *reasonable person* would expect that the broad consent would permit the types of research conducted.”

Arguably, the concept has been implicit in longstanding provisions of the Common Rule, which required disclosure of “*reasonably* foreseeable risks or discomfort” and “any benefits to the subject that may *reasonably* be expected.” Also, IRBs must determine that study risks to subjects are “*reasonable* in relation to anticipated benefits.” Noting that she has served on IRBs for many years, the speaker argued that IRB members routinely invoke the reasonable person standard implicitly when they debate consent forms. However, this can result in intuitive decisions that produce variations across committees. Greater consistency is needed.

The concept of the “reasonable person” has its origins in law related to torts and criminal negligence. When people engage in harmful conduct, were they negligent? Did the behavior deviate from that of a reasonable person? Such issues may be decided by a jury of peers living lives similar to that of the defendant. In contrast, decisions about whether doctors’ disclosures to patients are adequate have typically been made by referencing professional standards. Some judges have challenged this approach, declaring that the reasonable professional standard is not sufficiently respectful of patient autonomy. Rather than disclosing what a reasonable medical professional would disclose (the *professional standard*), these judges hold that doctors should disclose what patients reasonably need and want to know (the

reasonable patient standard). The [Belmont Report](#) (1979), similarly, endorsed a “reasonable volunteer” standard for disclosure, and the revised Common Rule follows suit.

In her observations of IRBs (Stark, 2012), Laura Stark notes that in decision making IRB members “imagined the people who featured in their own lives as stand-ins for research participants.” In discussions of proposed study consent forms, members described how people they knew, such as relatives, friends, and students, could interpret the information. However, the author points out, IRBs are primarily made up of professionals and experts whose perceptions are not necessarily in line with those of the subjects. There may be differences in background, education, and experiences between experts and study populations. Experts can overlook or downplay information that prospective subjects would regard as relevant to their choices.

As the research field seeks to put the reasonable person standard into practice, Ms. Dresser suggested, researchers and IRBs should learn more about what ordinary people actually want to know about studies. She called for empirical studies of people who have experience deciding about and participating in research. People who have experience as research subjects are especially good informants and are the true peers of prospective subjects. Ms. Dresser recommended that experienced subjects be involved in study planning, IRB review, and educational activities. Eventually, it may be possible to develop “common law” that provides standards for reasonable disclosures for different types of studies. The payoff for the field may well be better prepared subjects who are less likely to drop out and more likely to volunteer again.

Empirical Standards for Informed Consent

- Baruch Fischhoff, PhD; Carnegie Mellon University

The New Common Rule requires that “informed consent begin with a concise and focused presentation of the key information that is most likely to assist a prospective subject or legally authorized representative in understanding the reasons why one might or might not want to participate in the research.” Dr. Fischhoff suggested that, in general, communication is adequate when:

- It contains the information material to effective decision-making,
- Subjects can access that information, and
- Subjects can understand that information.

The analytical challenge is to determine which facts matter to decision makers. There are four approaches to meeting this challenge: IRB consensus, professional consensus, value of information analysis, and prospective patient analysis. The speaker reviewed each of these and commented on its strengths and weaknesses.

IRB Consensus

The speaker noted that the IRB process is deliberative and consensual; its members are somewhat diverse and are generalists. These traits confer benefits. However, it is a challenge for IRBs to have adequate diversity, understand the details of specific proposals, and identify the most critical information.

Professional Consensus

Dr. Fischhoff projected a two-column extract from a professionally produced document describing the risks and benefits of a particular drug, noting that this type of document is frequently the result of a professional consensus process. Benefits include the fact that such documents are technically informed and standardized. They often aspire to being patient-centered and are at least semi-transparent. However,

there is limited patient involvement, communication is only semi-transparent, case-specific communication is lacking, and they are rarely, if ever, tested for usability.

Efforts are underway to improve communication, such as the Drug Facts Box (Schwartz & Woloshin, 2013), which presents key information related to a particular drug in a format that makes it easier to find and understand. The FDA has also been working toward a clearly articulated framework for presenting benefits and risks (Fischhoff, 2017). In addition, FDA's Center for Drug Evaluation and Research (CDER) has initiated a series of reports called "The Voice of the Patient," designed to inform FDA about industry's and patients' critical concerns. Each report is developed through an iterative process with diverse stakeholders.

Value of Information Analysis

A third approach is value-of-information analysis, which formalizes a "materiality standard" to determine what risks are most likely to influence subjects' decision to participate (in other words, which are most "material" to their decision). Risk estimates for patient-relevant outcomes are consulted to make this determination (Merz, Fischhoff, & Mazur, 1993). Researchers determine the percent of hypothetical patients who would decline to participate if informed of each risk and use this information to guide what is emphasized in the informed consent process.

Potential benefits of this approach are that it is transparent, analytically rigorous, and data driven. However, its limitations include that it is non-participatory, requires utility judgments, and is technically demanding. Also, not every IRB can do this type of analysis.

Prospective Patient Analysis

A fourth approach to selecting key information, in fulfilling the revised Common Rule requirement, asks prospective patients what information would be most likely to assist them in deciding whether to join a clinical trial. For example, Krishnamurti and Argo (2016) asked potential participants to review a consent document online and select information critical to their decision making. A follow-up study, conducted in person, found similar responses to the full document and one abbreviated according to these preferences. The advantages of such strategies are that they are transparent, participatory, data driven, and inexpensive. However, they also have potential limitations, if the process does not ensure that participants understand the material and represent the prospective participant population.

A general need, Dr. Fischhoff concluded, is for economies of scope. The field needs standard processes for identifying critical information, evaluating draft consent forms efficiently, and sharing recurring elements to benefit various types of trials. Over time, it may be possible to accomplish informed consent more quickly and less expensively without sacrificing quality.

Panel Discussion for Session A

Dr. Strauss commented that the panel discussion offered rich, diverse offerings and perspectives at the conceptual level. Speakers explored ethical parameters related to disclosure and comprehension that frame our understanding for consent. Presenters made a compelling case that the field has not sufficiently reached out to experienced research participants to engage them in discussions about what participants need to know and understand. Dr. Fischhoff offered an elegant framework for how to think about making judgements about consent forms: how they should be crafted, who should be involved, and how researchers might determine what elements are the most and least important.

Valid and Invalid Consent

Dr. Strauss invited Dr. Millum to explain his view that the consent process was valid in the Phase 1 clinical trial at the NIH referenced during the presentation despite the fact that 29 percent of subjects did not understand that the test product they were being exposed to was in fact an experimental agent. He also invited Dr. Millum to comment on how a consent process can be considered valid when so many subjects incorrectly believed the experimental agent had been proven to be the best treatment for them.

Dr. Millum said that the findings in this case were concerning but did not mean the research was done without consent, even though it was troubling that subjects did not understand something so important. Ms. Dresser expressed reservations regarding this analysis, noting that much of the recent thinking on informed consent holds that it is not valid if it is not informed. Law on medical decision-making holds that “simple” decision-making is insufficient; the choice must also be informed. Though people may not understand everything about a trial, and they do have the right to make foolish choices, they still need to know what they are being foolish about before they choose. Dr. Millum countered that they need to know some of the things they are being foolish about, but they do not need to know and understand everything about all the possible impacts participation might have on their lives. In fact, he held that this is fortunate for the research enterprise, which might otherwise be impossible.

Dr. Millum asked Ms. Dresser whether it was true that from a legal perspective the emphasis is on what is disclosed to someone giving consent, not what the person understood, given that it is hard to “get a handle” on what was actually understood. Ms. Dresser responded that there have been interesting cases in which the focus is on understanding because the subjects involved have questionable capacity to decide. There have also been cases in which it is important to show that a person actually understood something critical, such as the fact that if he or she does not have a limb amputated, the result is death. If the person did not understand this, their consent was not valid.

Dr. Goldkind agreed with Ms. Dresser but observed that wishful thinking plays a part in subject understanding. For example, the literature shows clearly that although the process of randomization is explained, subjects often persist in believing that the investigator will make the choice of treatment that is best for them. They may still be able to explain randomization despite holding this belief. Unfortunately, wishful thinking is part of the human condition.

What Must Subjects Understand?

Dr. Strauss broadened the discussion, asking: “What is our obligation as investigators to ensure understanding and to correct misunderstanding?” Dr. Grady suggested that “key facts” may be the information people need in order to appreciate to what they are consenting. She was not sure what those key facts are. Dr. Millum suggested that another way to get at “key facts” is by analyzing the rights the person has waived. For example, the person needs to know that the investigator is going to draw blood, violating their usual right to autonomy. However, a person who persists in wishful thinking and still does not appreciate what randomization means could still give valid consent. The decision might still be an excellent decision for the person.

Dr. Strauss suggested it was necessary to separate the concept of a “good decision” from “good decision-making.” Subjects should be involved in a good decision-making process. This involves understanding the facts and manipulating them some way to arrive at a conclusion. People will manipulate and use the facts differently. However, he was not sure he agreed that someone who does not grasp the concept of randomization can give “informed” consent to such a study.

Dr. Bromwich made a distinction between what is understandable and understanding. She agreed that the disclosure process should pay a good deal of attention to ensuring that what is presented is understandable. People may grasp the concept of randomization in an abstract way but not fully understand it. However, she held that it is not necessary to fully grasp all of it in order for consent to be valid.

Ms. Dresser noted that when research is conducted in a clinical setting, there are usually no clues that tell the patient that anything different from clinical care is occurring. The person may be sick or distracted. The opportunity to teach them successfully about their options is limited, and it is not surprising that many of them do not understand. To understand how people are making decisions in this situation, it is essential to talk to more participants to understand their experiences and perspectives. It is important to talk to those who declined to take part as well as those who agreed in order to appreciate their thought processes.

Dr. Fischhoff also stressed the need to decode subjects' decision-making, noting that most members of the research community are unable to understand their subjects: "By the time we are here, we are so far removed from their situation we have no intuitive feeling for it." He noted that there are people like himself and Dr. Fagerlin who have acquired toolkits that will help them educate prospective subjects more effectively. He is interested in mental models of how the world works and how these models influence decision-making. It would be interesting to study the mental models people carry regarding research and medical treatment. It is of importance, in the context of research, that many prospective subjects have "no statistical intuition whatsoever."

Dr. Schreiner reflected on a personal observation as an anesthesiologist – that "the more complex or dangerous the surgery, the less patients wanted to know about the anesthetic." He noted that there was no way to successfully communicate all the risks and benefits, but the patients knew they wanted the surgery and they were clear in their communication of that decision. Further, he described other patients with rare diseases who had already decided to participate in the study prior to the informed consent process and prior to receiving all the information they might want. When this occurs, such patients have apparently gotten all the information they feel they need, and their decisions should be respected.

Dr. Goldkind asserted that people generally do not understand the difference between clinical research and clinical care. She stressed the need for basic education on how clinical research differs from clinical care. Potential subjects may see informed consent as a formality, like an online disclosure for which one routinely checks "I accept." A cultural orientation to informed consent in the research process is needed. This can be done well in contexts where people are "captive." An example of such a setting is the waiting room of the Department of Motor Vehicles.

Dr. Strauss asked whether the investigator sitting across from a participant needs to determine that the individual actually understands how clinical research is different from clinical care. Dr. Goldkind said emphatically that this is essential, adding that research institutions have a responsibility to take a systematic approach to educating the people who are treated there.

Dr. Finer said that in his experience as clinical investigator, he regularly presents study information to families and parents who are making decisions on behalf of a baby. How much information do they need when giving a proxy consent? How do you determine what they understand? After he presents information, he asks them to explain what he has said, and if they cannot do so, he does not enroll them in the research. He wondered if he has done the wrong thing by not enrolling them, since he had explained what they needed to know.

Dr. Millum responded that if patients look at the investigator blankly when asked to repeat what they have been told, it is good evidence the information was not disclosed in a way that allowed them to understand it. However, in some situations, understanding certain information is extremely important; in others, it is less consequential. The disclosure process will be different for specific studies. Dr. Simon agreed, noting that it is especially important that the subject grasp critical details when the procedure introduces risks that are irreversible or when the subject will be unconscious during the procedure and have no ability to interrupt it.

Dr. Strauss commented that a major shortcoming in the consent process has been an approach that offers only a unidirectional delivery of information. More contemporary thinking encompasses shared decision-making, in which there is a give and take between the investigator or doctor and the individual, who is free to ask questions. A model of consent is incomplete if the process is seen as over once the information in the consent process is conveyed. Instead, the information presented should be modified based on what the presenter learns during the process of informed consent.

Ms. Dresser noted that the National Commission referenced a *subjective standard* in which individuals are told what they as individuals need to know. Many feel this standard is too high for doctors and researchers, but it is still important to find out if there is information that is especially important to that individual (for example, a possible loss of manual dexterity to someone whose ability to make a living depends on it). Quizzes and questions provide a helpful opportunity for people to raise their concerns. People also may benefit from prompts that are integrated in the presentation.

Dr. Grady said there seemed to be agreement that people need to understand something about the research to give valid consent, but there is no clear consensus on exactly what they need to understand. In one study, researchers were concerned that subjects did not seem to understand they were involved in a study, but in fact it turned out they did understand that data was being collected about them but it simply wasn't that important to them. In contrast, she is aware of instances in which people have agreed to experimental use of Deep Brain Stimulation but did not understand that this requires boring holes in the skull. In one example, understanding was not important; in the other, it was very important. Dr. Grady concluded that researchers need to take a nuanced approach to understanding but at the same time identify things that are important to convey, no matter what type of research is occurring.

Dr. Strauss added that decisions about what is disclosed and how it is framed are determined by those investigators who, of course, have a vested interest in the outcome – that is, increased subject enrollment.

Dr. Bromwich said appropriate disclosure should be influenced by what is known to be relevant to the individual. Autonomy rights are important in identifying key facts. The fact that a hole will be bored in the brain clearly violates autonomy rights, and the person must understand this will happen if he or she agrees to be a subject. However, some risks are unknowable, and that may be part of the reason that the research is being done. She held that the person does not necessarily need to know *why* the research is being done if they do understand clearly *what* will be done. Dr. Grady responded, however: “If you don't understand the purpose, you do not really understand to what you are consenting.”

Dr. Strauss stressed another aspect of understanding – the importance of subjects grasping something about the “universe of possibilities” related to care in the context of research and how research differs from care. If they are taking a medication that has only been tested in five people, they need to understand that there may be things the researchers don't know about the medication that might have serious medical consequences. Dr. Schreiner also said it was important to understand the purpose of the research, though

the person may not grasp all the technical aspects and be able to recite all the goals. They do need to understand what a reasonable person would expect to know about what they are agreeing to do.

Session B: Effectively Presenting Information to Facilitate High-Quality Decision-Making

- *Moderator:* Christine Grady, RN, PhD, FAAN; NIH Clinical Center

Dr. Grady observed that while in theory it is clear that investigators should disclose “relevant” information in the informed consent process, there is disagreement about what is relevant. The focus of this session is on ways of presenting information that promote or detract from effective decision-making. While culture and context must be considered in determining what is relevant to subjects, it also matters how the information is presented.

Presenting Information for Effective Communication

- Lisa M. Schwartz, MD, MS; Dartmouth Institute for Health Policy and Clinical Practice, Dartmouth Medical School
- Steven Woloshin, MD, MS; Dartmouth Institute for Health Policy and Clinical Practice, Dartmouth Medical School

Presenters noted that it is now widely recognized that informed consent documents are too long, hard to read, and hard to understand. It is also known that applying health literacy principles can improve subjects’ comprehension and that it is possible to use substantially shorter forms without decreasing either comprehension or trust. However, it is difficult to compare the effectiveness of strategies across trials to determine their relative effectiveness because of heterogeneous populations and diverse outcome measures.

What is “Key Information”?

The Revised Common Rule now mandates that key information appear at the start of the consent form to help people determine whether or not they want to participate in the study. The presenters reviewed a sample protocol previously provided to the Secretary’s Advisory Committee on Human Research Protections (SACHRP) and created the following narrative driven by question and answer:

What is the science behind this study?

The new idea is to start chemotherapy at the same time as hormone-blocking instead of just when the cancer progresses.

Why it might help? A small trial found that starting chemotherapy with hormone-blocking slowed down the time until progression (PSA increased), yet did not prolong life.

Why it might not help? Some researchers worry that starting them both together may make chemotherapy less effective.

The purpose of this study is to see if starting a chemotherapy (a different drug - docetaxel) at the same time as hormone-blocking helps men live longer than starting hormone-blocking alone. Docetaxel has been known to prolong life when given at the time of progression.

Bottom line: **No one knows the answer – that’s why the trial is being done.**

What are the tradeoffs for you?

Why would you not want to be in the study?

If you or your doctor has a strong feeling about starting chemotherapy now or later, you might not want to take part. Your doctor can start hormone blocking with chemotherapy now or later even if you are not in the study.

Other reasons for not taking part are:

- Having important life events in the next 6 months and you don't want to be tired from chemotherapy
- Being much older or have other serious medical problems and are more concerned with quality of life right now

Why would you want to be in the study?

Starting hormone blocking alone means it's likely that your cancer will progress over the next few years, at which point you will need chemotherapy. The time until progression depends on how much the cancer has already spread: usually about 1 year with a lot of spread and 2-3 years with less spread.

Docetaxel chemotherapy has side effects, including some that are very bothersome or even life-threatening. It's also inconvenient: travel time, tests, and the infusion every 3 weeks.

Starting hormone-blocking and chemotherapy means giving up some quality time now – about 5-6 months for chemotherapy and recovery.

If starting chemotherapy right away helps, it may be worth it: the cancer would take longer to progress and you would live longer. But it might not help – or make quality of life worse because of rare long-lasting side effects.

If you and your doctor would be okay with either treatment, you might want to be in the trial.

The narrative attempts to present the science behind the study and the tradeoffs for the prospective subject. The consent document should continue to further explain the study, including randomization (a simple flow chart is recommended for the latter). It might also add inclusion criteria and details about treatment. It should be explicit about the burdens related to testing and follow-up and explain contingencies (such as the cancer returning).

In summary, the speakers suggested that key information should address:

- *What is the science behind the study?* (Mention prior work that justifies the study, acknowledge concerns, and highlight the fact that the answer to the study question is unknown.)
- *What are the tradeoffs for you?* (Summarize the reasons a patient might want – or not want – to participate.)
- *What will happen?* Include eligibility criteria, randomization (consider metaphors), burden of testing and treatment, and outcome measures.
- Prioritize side effects to answer the questions, *how bad and how often?* Organize by seriousness, provide measures of severity, and quantify likelihood.

Increasing – and Decreasing - Understanding

A recent trial has shed some light on approaches to explaining randomization (Krieger et al., 2017), finding that plain language and a neutral metaphor (in this case, determining a baby's gender) increased score on a comprehension test compared to a control statement which read "cancer patients are offered the opportunity to receive treatment as part of a randomized clinical study". The most successful language read:

It is helpful for some patients to think about randomization as being like the sex of a baby. Just as a pregnant woman has an equal chance of giving birth to a male or female baby, a patient has an equal chance of being in any of the groups being compared in the clinical study.

However, the differences in comprehension were small.

When possible, prospective study subjects should be told the likelihood of side effects of drugs being tested. Often, the likelihood of side effects is presented only using verbal labels. Studies in both subjects and physicians have shown that the understanding of verbal labels is highly variable (e.g., patients asked to quantify the meaning of the word "likely" gave responses ranging from 20% to 100%). Nevertheless, the National Cancer Institute (NCI) now suggests using verbal labels (i.e., common, occasional, and rare) to describe side effects. The speakers believe that numbers are important – and should be presented when available as is the case for approved drugs. To quantify treatment effects, Woloshin and Schwartz (2011) have found that percentages (e.g., 6%) are the easiest to understand, with the frequency format (e.g., “60 out of 1000”) a close second. Speakers strongly recommended that possible risks be sorted not only by frequency but by seriousness. As a model for the use of lay language to describe side effects, they commended NCI's web resource, [“Side Effects of Cancer Treatment.”](#)

Dr. Schwarz's and Dr. Woloshin's suggestions for how to present side effect data are based on a body of work they have conducted in developing and testing "Drug Facts Boxes." Drug Facts Boxes present data on the benefits and harms of prescription drugs in a consistent, structured format inspired by the FDA's Nutrition Facts Box. In a national randomized trial, the new Drug Facts Box was shown to increase the ability of subjects to choose the best drug for the same condition (68 percent vs. 31 percent in the control group) (Schwartz & Woloshin, 2016).

The speakers also highlighted the need to address prevalent misconceptions that can undermine informed consent, for example, the idea that newer drugs are always better than older ones (Woloshin & Schwartz, 2011). They expressed concern over FDA's “breakthrough drug” designation because the term "breakthrough" may be confusing. In ordinary language, the term means an important advance. But in FDA's usage, it applies to drugs that have shown some early promise but are still in early stages of determining their effectiveness. Prospective subjects may respond with enthusiasm to the term “breakthrough” and not understand that there is minimal evidence of the drug's efficacy. Hwang et al. (2018) have concluded that there is “no evidence that these drugs provide improvements in safety or novelty; nor was there a statistically significant efficacy advantage when compared with non-breakthrough-designated drugs.”

Another example of potentially confusing communication with prospective subjects that is becoming increasingly common is misleading volunteer recruitment advertising. Presenters played a video produced by a well-known research institute that shows a volunteer explaining that he chose to participate in a trial because he “wanted the cutting edge” and wanted to “help bring about cancer treatment someday used by everyone.” It would not be clear to a prospective subject that the new drugs being tested are usually not better than standard care and the positive results experienced by the volunteer in the video may not be

common. Speakers stressed the importance of ensuring that subjects do not have unrealistic expectations that undermine the legitimacy of the consent process.

The Role of Decision Aids in Assessing Understanding and Integration of Information

- Angela Fagerlin, PhD; University of Utah

Dr. Fagerlin said that most studies have found that patients want involvement in decision-making. For example, a national study of 2,765 patients found that 96 percent of them wanted their physicians to offer them choices (Levinson et al., 2005). A more recent study of invasive medical procedures found that 80 percent wanted to share in decision-making (Mazur and Hickam, 1997a). However, many of them feel uncomfortable disagreeing with a physician's recommendation (even if they are relatively privileged white men) and worry about being labeled a "difficult patient" if they do (Adams et al. 2012). Dr. Fagerlin noted that a taped conversation with a provider often reveals very little conversation coming from the patient.

Decision aids are intended to amplify the patient's part of the conversation. A decision aid is a tool that is intended to:

1. Provide accurate, balanced information
2. Clarify patients' values, and
3. Improve shared decision-making skills.

Decision aids are developed with patient participation. In 2005, using a Delphi Process with 122 participants, [the International Patient Decision Aids Standards](#) collaboration published criteria for the development and evaluation of decision aids. Resources include a checklist for decision aid content, development, and evaluation. An effective patient decision aid should:

- Provide information about options in sufficient detail
- Present probabilities of outcomes in an unbiased and understandable way
- Include methods for clarifying and expressing the patient's values
- Include structured guidance for deliberation and communication
- Present information in a balanced manner
- Originate in a systematic development process that incorporates users
- Cite up-to-date evidence
- Include conflict of interest (COI) disclosures
- Use plain language, and
- Provide navigation tools if the tool is on the web.

Decision aids can help improve the quality of the decision by helping patients understand their options and how their values and concerns affect their decision. Properly used, they improve the match between the option chosen and the features that matter most to the individual. They can increase participants' knowledge, the accuracy of risk perceptions, and the congruency between values and the choice of care. They can, in general, improve patient-provider communication, and people have been shown to feel better about the conversation (Stacey et al. 2017). The tools can also decrease decisional conflict, the patient's feeling of being uninformed, indecision about personal values, and the proportion of people who were passive in decision-making and who were undecided. They add little time to appointments (a median of 2.6 minutes) and do not add costs (Stacey et al. 2017). However, they rarely change treatment or research participation preferences, and physician recommendations may still trump the patient's own preferences (Scherr, Fagerlin et al. 2017).

In studies with disadvantaged patients (those with lower socioeconomic status and underrepresented minorities) there is some evidence that shared decision-making may increase their knowledge by enhancing:

- Informed choice
- Participation in decision-making
- Decision self-efficacy, and
- Preference for collaborative decision-making.

Meta-analysis of these findings revealed no differences between white and non-white users (Nathan et al 2016).

Dr. Fagerlin stressed, in closing, that patients want to be informed about their choices, and many want to be involved in decisions about their care. Decision aids can be an effective method to communicate information, clarify values, and help patients be involved in their decisions. However, much more needs to be done to give patients a voice in their medical care.

Participant-Centered Design for Informed Consent

- John Wilbanks; Sage Bionetworks
- Megan Doerr, MS, CGC; Sage Bionetworks

Informed Consent on the Internet: The Apple Research Kit

Mr. Wilbanks explained that grant support through the Agency for Healthcare Research and Quality (AHRQ) enabled him to participate in the [Electronic Data Methods Forum](#) and for Sage Bionetworks to explore the challenge of improving informed consent. A series of interviews revealed that institutions might not like their lengthy informed consent documents but still felt they “worked” at their institution. However, there was interest in finding new ways to communicate the content of the documents more effectively.

While an electronic approach to making informed consent more engaging seemed promising, Mr. Wilbanks and the team at Sage Bionetworks were also aware of problems associated with the digital format. Literature indicates people read differently when reading pixels rather than print, actually reading only 1 out of 3 words – though they may believe they read the entire document. The biggest lie on Internet, a recent study found, is “I have read and understood the terms of service” (Obar & Oeldorf-Hirsch 2018). The use of a smartphone or other digital device to communicate crucial informed consent data would need to take this into account.

Sage Bionetworks collaborated with Apple to develop [ResearchKit](#), an open source iOS platform for human subject research application development. As part of this development work, Sage Bionetworks created a model eConsent process, a form of study narrative that precedes the long form consent document. Sage designed a framework for eConsent screens to hold readers’ attention, slow reading speed, and increase processing time to support prospective participants’ informedness and comprehension. The screen framework includes a relevant picture, a very short text “headline,” and slightly longer text sub-headline, with a focus on preserving screen white space. There is also a “learn more” button, allowing the prospective participant to dive deeper into the content presented on any given screen. The team at Sage Bionetworks also included a short assessment as part of the eConsent– either formative or summative – that reinforces (formative) or assesses comprehension of (summative) key concepts.

Mr. Wilbanks added that the process developed for Apple can be duplicated on paper and is now being used by dozens of researchers.

Examples of Internet-Based Tools and Research

Ms. Doerr cited NIH's Precision Medicine Initiative (Collins & Varmus 2015) as an example of an opportunity and a challenge in communicating with participants who are navigating informed consent independently, and often remotely. Recruitment targets for this massive cohort of participants – over one million – in its [All of Us research program](#) are based on 2040 US Census projections, with purposeful oversampling of populations traditionally underrepresented in biomedical research. Ms. Doerr highlighted that one of three adults in the US read at a basic or below basic level. Therefore, the consent process for *All of Us* had to meet the needs of adults with low literacy. The team at Sage Bionetworks collaborated with four Federally Qualified Health Centers on a qualitative assessment of the presentation preferences and informational needs of with people of very low literacy (6th grade reading level or below) who were considering enrolling in the study, including underrepresented populations (paper in press). Participants had questions in several areas:

- How to participate (where is the research taking place, is transportation provided, is there a cost, who can participate)?
- How does it work?
- Why is this part of the research? (For example, why do you want my blood and what are you going to do with it?)
- What are you not telling me?
- Privacy concerns, and
- Results (For example, will I have access to my test results?)

The study team found many of the words that might be used in a typical informed consent document were unfamiliar to those of low literacy (for example, data breach, withdraw, biobank, and database). She noted that illustrations and/or animations can be helpful in “cueing” word meaning in some such cases.

Sage Bionetworks is currently experimenting with allowing prospective participants choosing their own pathway through the information presented within the eConsent given that people are most ready to learn when they seek information directly. This is an adaptation of work done at Kaiser Permanente (that itself was based on Sage Bionetworks' open-source participant centered consent toolkit).

Additionally, participants in other Sage Bionetwork-lead app-mediated research studies have made various suggestions for improvements or additions to the informed consent process (Doerr et al. 2017). These have included building in incentives (goals associated with rewards) and making tasks as game-like as possible, although these suggestions require serious contemplation of associated ELSI issues before their application in a research context.

Finally, she noted that Sage Bionetworks had attempted to solve the difficulty of people not reading and understanding privacy policies and terms of service through readability assessment and pruning legalistic content. She further noted that such documents should be integrated into electronic consent processes and overseeing IRBs should review them.

Panel Discussion for Session B

Dr. Grady observed that the presentations offered a variety of approaches and issues, encompassing strategies for presenting words and numbers, the use of decision aids, and effective use of technology. She invited panelists to comment on the use of plain language, low literacy presentations, and how best to

select the most effective and familiar words for each audience. She noticed that words like “cloud” may be familiar, yet not well understood. How do we think about finding unbiased words that various audiences can understand?

Understanding What Matters Most

Ms. Doerr said it is important to think about what is most critical for people to understand. There is a “careful dance” around this. For example, critical information about the Cloud is that the “Cloud” may not be safe, and the emotional resonance of the word “cloud” can help get across the idea that information may be vulnerable there. Readers may understand a word literally, it may be a “signal” that still conveys a concept, or the subject may not understand it at all but it doesn’t really matter. It is also important to recognize how illustrations can help clarify the meaning of words without actually defining them. For example, it is possible to watch cartoons in a foreign language and begin to understand what words mean by reading the context. Dr. Schreiner gave the example of Randall Monroe’s book, *Thing Explainer: Complicated Stuff in Simple Words*, which is able to explain complex processes through illustrations.

Dr. Bromwich asked Dr. Fagerlin to what extent one-sided conversations persist despite the use of decision aids. Do they really change what is communicated or the likelihood of the subject simply saying yes? Dr. Fagerlin noted that the process works best when patients are prepared to participate in the process by patient decision aids. These are read prior to the consent process so prospective subjects are more prepared to ask questions. Researchers have also designed “encounter tools” and “option pages” for providers to help break up their “spiels” and encourage them to ask the patient questions. It is difficult to get providers to actually use them, however. She stressed the importance of asking questions based on the patient’s values and concerns rather than basing the presentation solely on medical knowledge.

Dr. Grady invited discussion on the implications of the finding, especially in cancer studies, that trust in one’s physician is a primary reason many people are willing to participate in research. Ms. Doerr said that research in Federally Qualified Health Centers shows that many people conclude that if the doctor presents research as an option, it must be a good idea. Ms. Dresser said that this is a good reason for personal doctors not to be the ones who inform patients of research trials available to them. She speculated that people with low literacy may be considered especially vulnerable to the doctor’s perspective because of lack of ability to explore other sources of information. Ms. Doerr observed, however, that some people with low literacy are well able to research their options despite a low reading level. Many of them make creative use of adaptive technology to have documents read to them or ask friends to read documents for them, while others have few sources of help. Dr. Fagerlin noted that it is perfectly appropriate for doctors to make recommendations so long as they are aware of the patients’ concerns as well as medical knowledge.

Dr. Strauss expressed discouragement at the fact that Apple presumably had the tools and skills to facilitate high quality decision-making but still developed a version of Terms and Conditions that is 109 pages long. He wondered how the field can overcome the inertia around shortening the informed consent form. Ms. Doerr noted that service and privacy policies are traditionally written by lawyers, who are driven by concerns about liability. In contrast, she and Mr. Wilbanks were fortunate to participate in the *All of Us* project, a participant-centered initiative in which town halls were used to garner a variety of perspectives on what should be included in this kind of policy. The core values that came out of those consultations at the inception of the program drive the study. While there have been some tense moments and heated conversations, the shared value placed on transparency as a result of this process helped the team move through the revision process toward more focused and understandable documents.

Mr. Wilbanks noted that the original Request for Applications (RFAs) for *All of Us* envisioned a grantee acting as a coordinating center. NIH made the decision to instead act as the coordinating center themselves. The IRB for the study is not associated with an institution, and it includes patient representatives and ethicists. Ms. Doerr agreed it was helpful to have a single IRB independent of the program itself. However, Mr. Wilbanks noted, this study is unique and not widely replicable. A single IRB could also become a “race to the bottom” rather than a way to improve.

Conveying Privacy Risks

Dr. Simon returned to the discussion thread exploring what information is critical for subjects to understand and what is not. There is apparent agreement that if the subject did not understand blood will be drawn, then the consent was not informed. What about the risk of reidentification? What do researchers do in complicated areas like this? It is unlikely that people who have not mastered calculus can really grasp the level of risk posed by reidentification. How does the researcher signal “we have your back on this” in an honest way that does not mislead subjects? The recruitment video by a well-known cancer center shown earlier got some public shaming for its misleading signals. It gave the impression that the study is “all for you, the subject” when it is not. Signaling is powerful and can be used for good or ill. What would an authentic and appropriate signal about privacy protections look like?

Ms. Doerr observed that people are becoming increasingly aware of privacy risks in the digital world through scandals and news. Digital presentations can allow prospective participants to reflect on risk statements and determine which would make them join or not join a proposed study. This information can be reflected back to them to help them make a decision that works for them. Mr. Wilbanks added that teaching about risks and benefits can provoke reactions at a deep level, from the “lizard brain,” to see what really matters to the prospective participants. “If you knew an insurance company could ask for the results of your genetic test, would it make you more or less comfortable requesting the results?” If the person says he or she would be more uncomfortable, you can ask: “Are you sure you want to proceed?”

Mr. Wilbanks added that when he presented the informed consent model used in the *All of Us* project at a conference, one response was that he was “building a Cadillac” that would not work in the real world. He said he does not have a good response to this concern. He would like to test the hypothesis that when recruitment is done in a more ethical and respectful way, more people will be motivated to participate and more will be enrolled over time.

Working Toward Readability

Dr. Schreiner offered his perspective as an IRB chair. A major impediment to simplifying consent forms in his experience is that the NIH lead site for multi-site studies often sends a consent form to the investigator and refuses to allow changes. He would like to see OHRP insist that the investigator still has a responsibility to ensure informed consent documents are understandable and can push back when given a lengthy document containing many unnecessary elements. This is a “huge battle.” He added the observation that NIH’s certificate of confidentiality is written at a level over grade 20. Dr. Grady pointed out, however, that it is not possible to do a solid multi-site study if each investigator is doing his or own informed consent. Dr. Schreiner said the possibility of pushing back is an advantage of the single IRB model. Dr. Fagerlin observed that research suggests that the less information is presented, the more likely the reader is to absorb it.

Understanding Public Perceptions

Dr. Goldkind proposed that there are two communities from which the research community should seek information. The first is the general public. She recommended a “deeper dive” into public perceptions about research and privacy issues, coupled with education. People voluntarily submit cheek swabs that

reveal private information and allow genetic findings to be put on public websites – yet they are hesitant about providing clinical data to a database that allows researchers to improve public health. Why is this the case? The second community that can contribute to more effective consent processes is volunteers. What would be a red flag for them when they review medical documents and give them pause about the risk of participating? What is the doctor’s role in providing information? She held that physicians are derelict in their obligations when they fail to put alternatives in a medical context and have a real dialogue with subjects.

Mr. Wilbanks noted that it would be possible to put videos in waiting rooms that teach people about research. He observed that people do struggle with privacy risks outside the study context, especially in regard to credit card fraud. The constant cycle of scandal and outrage increases awareness of vulnerability, and people do not understand how much safer their private information is in a research context as compared to on social media such as Facebook.

Ms. Dresser stressed the importance of following up with subjects after 5 or 10 years. People who dropped out could be asked what they needed to know that wasn’t clear; what surprised them? The relationship with subjects in a long-term study should be like a marriage in which it is necessary to renew vows periodically – and in which future events are often unpredictable.

Session C: Pragmatic Clinical Trials (PCT) – Challenges and Innovations in Getting Informed Consent

- *Moderator:* Gregory E. Simon, MD, MPH; Kaiser Permanente Washington Health Research Institute

Dr. Simon observed that the meaning of the term pragmatic trials has become obscured with overuse. In general, it refers to trials in which the research apparatus is intermingled with the provision of health services and the interventions are widely available. Comparisons may be loosely controlled.

Practical Issues with Pragmatic Trials: Challenges with Informed Consent and Lessons Learned from the VA Point-of-Care Program

- Sarah Leatherman, PhD, MA; US Department of Veterans Affairs
- Ryan Ferguson, ScD, MPH; US Department of Veterans Affairs

Dr. Leatherman explained that within the US Department of Veterans Affairs (VA), Point of Care Research (POC) is used to perform comparative effectiveness research on well-understood interventions and is embedded in clinical care. The electronic medical record (EMR) shows the workflow for the trial and provides the research interface with the physician. Data collection and follow-up are also accomplished through the EMR. The speaker defined POC research within the VA as follows:

- A clinical trial with a substantial portion of its operations conducted by clinical staff in the course of providing patient/subject’s routine clinical care and where the choice of treatment is between two equivalent operations.

Exploring POC Research in the VA

Dr. Leatherman reported that VA did a pilot study to lay the groundwork for the POC program. The study sought to demonstrate the feasibility of the program, which would be used to address substantive clinical

issues, closing the implementation gap to make the most effective treatments available as soon as possible. The program did not require any modification to interventions as they exist in the VA system.

The pilot demonstrated the feasibility of the approach. Both physicians and patients accepted the program, as shown by the consent to participate and follow-up conversations and focus groups. Use of the EMRs proved to be a hot topic, but the IRB agreed that some work could be done using EMRs. No substantive modifications to the consent process were required.

The [Diuretic Comparison Project \(DCP\)](#) sought to implement POC research using these methods in a much larger study. VA's goals were to:

- Implement POC methodology nationally
- Streamline consent, and
- Limit both physician engagement and the research burden.

Patients were identified at a central location and contacted by researchers to avoid physician influence. Informed consent was solicited by telephone. All trial operations were completed by the coordinating center. Provider consent, randomization, data collection, and follow up were all done through the EMR system. Providers were also considered participants and asked to consent to the research.

Lessons learned through the study focused on patient and site engagement. Researchers learned, in regard to patient engagement:

- Although the study sought to remove the burden of interacting with the patient about the study from the provider, the patient still wanted the provider to okay their participation.
- Doing the informed consent process by telephone did not make it less time consuming, since several calls were often required to make contact.
- No amount of pragmatism can overcome the need for the human touch. People want to know someone is looking over their care in an individualized way. Even if they are eager and willing to participate in research, they still want that connection with someone.

Lessons were also learned about site engagement.

- Simplifying participation turned out to also simplify nonparticipation. The study turned out to be easy to ignore. It was important to have someone local who is engaged and can help foster participation.
- It is possible to change the approach to getting informed consent, but it introduces new challenges and barriers.

Challenges in Establishing a Consent Model for PCTs

Dr. Ferguson explained that PCTs seek to accomplish the following goal:

- To facilitate learning within the healthcare system while still being able to obtain informed consent that is ethically sound and consistent with regulations.

Dr. Ferguson observed that one of largest challenges in informed consent within the PCT context is the differing clinical and research perceptions of what informed consent means. Clinicians do not routinely share the details of everything they will do. For example, a surgeon doing a surgical repair of a hernia would not explain to the patient whether he is doing an overhanded or underhanded procedure, but in research this would have to be disclosed. Each group is somewhat intolerant of the other: the clinical model is driven by workflow and necessity, while the research model is driven by regulation and risk.

Researchers tend to see clinical consent as too loose, inadequate, and even borderline unethical. The relationship between consent to research and consent to care is not straightforward.

Participants in VA focus groups showed only a moderate concern with data security but little tolerance for the 17-page consent form. They encouraged the use of infographics to convey key ideas. They were not enthusiastic about embedding research in clinical care because it implied the physician didn't know what he or she was doing: "My doctor told me I need to be on a blood pressure pill, and now you're telling me they don't know which pill I should be on?"

Challenges also arise around the appropriateness of clinical providers obtaining consent. In addition, it is not clear how risks should be articulated when two different drugs or procedures are both in common use. How should the research intervention be described? In the context of comparative effectiveness research, how different is non-randomized usual care from the research?

Dr. Ferguson presented two VA case studies to illustrate the implementation of PCTs within the VA. The Stenosis Outcomes in Lumbar Instrumentation and Decompression (SOLID) Trial involved either the use of laminectomy alone or laminectomy with fusion to treat low back pain. The trial used in-person consent prior to randomization to surgical arm, but surgeons and patients both found it untenable that the surgeon actually doesn't know what he or she will be doing to the patient. Field personnel (nursing staff) were used for the informed consent process. The approach was driven by issues related to risk perception, the autonomy of the surgeon, and the need to engage patients with an in-person conversation prior to an invasive procedure.

The VA's End-Stage Renal Disease (ESRD) Trial involved the use of high vs. low dialyzable beta blockers for patients receiving dialysis. General consent was prior to treatment, followed by an abridged disclosure model. As patients received access for dialysis, they were approached about participating in the research. The discussion of beta blockers became a bridge leading to an interactive consent process.

Dr. Ferguson said his experience with PCTs has convinced him that a paradigm shift is needed in regard to the consent process in clinical research. He observed:

- Cultural barriers and perception of risk (to the institution and to the patient) can prevent a meaningful consent that respects participants and honors their autonomy. It is not respectful to prospective subjects to overload them with information they don't need.
- Clinical learning and clinical trials are becoming the standard of care in some specialties of medicine (e.g., oncology). What does an appropriate consent process look like when this is the case (for example, for childhood lymphoma)?
- Patients should be engaged in planning trials and all the way through the trials. This includes having conversations about what information is most relevant to them.

Naked and Afraid: Protecting Research Subjects from Overly Excited Pragmatic Investigators

- George Annas, JD, MPH; Boston University School of Public Health

Calling most consent forms "giant and irrelevant," Mr. Annas hoped for a one-page form that would ensure that when a patient says he or she willingly agreed to participate in a trial, it is actually true. But consent is much more than a form: it is a process of joint decision-making.

The speaker described many hospitalized patients as “naked and afraid”; they are sick, don’t understand what is happening, and will do whatever the people in white coats ask of them to get well. In general, the difference between research and treatment is invisible to most patients.

As enshrined in medical vs. legal practice, the concept of “standard of care” is essentially the same. From a medical perspective, the doctor follows “custom,” a practice standard set by the actions of the medical profession. Both medicine and law define the standard of care as what a reasonably prudent physician would do under the same or similar circumstances. If the standard of care is broad and includes different alternative treatments (e.g., very high or low doses of a drug), these are alternatives that the patient has a right to know about. That is because of the legal doctrine of informed consent, a doctrine which is defined by courts in legal opinions, not by physician practices. For example, if all physicians act in a certain way, that way becomes the standard of care — set by physician conduct.

Informed consent is different, in that its content is set by law in regulations and judicial opinions. Specifically, patients (and subjects) have a legal right to know the risks, benefits, and alternatives available whether or not what is being proposed by the physician is a research trial, a therapeutic intervention, or a standard of care trial. In every case, regardless of physician practice (even uniform failure to obtain consent) the consent rules are set by law and regulations, and physicians cannot change them even by universal disregard of them. Both physicians and researchers have a fiduciary duty to honor patients’ autonomy and dignity and to present alternatives and risks, especially risks of death or serious bodily injury. The standard for consent, both for treatment and research, is set by law, and is virtually identical.

PCTs can seem to blur the line between treatment and research, and carry a significant risk of fostering the “therapeutic illusion” (on the researcher’s part) in which research is viewed as treatment, the researcher is the physician, and the subject is the researcher’s patient. When the standard of care is so wide that it can be seen as including two or more different treatments, the patient-subject must be informed of the alternatives and their risks and benefits. That is because the hypothesis is that they are different, and the subject has a right to know of the different treatments (and their risks and benefits). If a random device is selected to determine which will be used, the subject has a right to consent (or not) to randomization. In such trials, IRBs should not rubber stamp protocols but ensure that the consent process reflects clinical reality, as well as fostering dignity, autonomy, privacy, and fairness. It also needs to be made clear to the subject that he or she has the right to withdraw from the experiment at any time. (If the participant does not know he or she is involved in research rather than simply receiving treatment, this is not possible.) The basic job of the IRB is to implement the principles of [The Nuremberg Code](#), which includes ensuring that consent to the trial, including a pragmatic trial, is “voluntary, competent, informed, and understanding.”

Panel Discussion for Session C

The Treating Physician and Informed Consent in PCTs

Dr. Simon said the session had explored issues related to consent when research that occurs in practice settings, highlighting the role of the treating physician. Presenters stressed that patients want to know their doctor is on board with whatever research is proposed. What is the appropriate role of the treating physician in this type of research, given the potential for coercion?

Mr. Annas said he did not believe the physician should ever be involved in recruitment – “you can’t say no to your doctor” – but should be involved in informed consent. Dr. Ferguson agreed. He said the physician needed to be involved in the decision to participate in research.

Dr. Simon observed that people want to know that their doctor will do what is best for them. It should nevertheless be possible for the doctor to admit what is unknown about treatment at the present time. The fact that there is a choice where there is no clear preference should not be taken as a sign the doctor doesn't know how to treat the patient. Dr. Leatherman said VA's experience has been that providers are willing to admit that either of the two options presented might work.

Dr. Schreiner said that someone experienced in the procedures should get the patient's informed consent. This person should be able to explain the difference in possible side effects in a medically accurate way. Dr. Simon held that the treating surgeon is the person most qualified to give this explanation. However, Dr. Goldkind was not sure the treating surgeon was always the person best able to explain key concepts in plain language. A patient advocate might be helpful. An advocate can also find ways to bolster the process so that patients feel more able to ask questions. The default should not be that the investigator and treating physician are the same person.

Dr. Fagerlin suggested that the presentation of research options and the procedure itself should be different. She agreed with Dr. Goldkind that surgeons are not always the best explainers. "Informed" and "consent" steps might be separated. The treating provider could provide information, introduce the researcher as a colleague, and walk out of the room while the researcher presents the consent process.

Other Challenges in Comparative Effectiveness Research

Panelists highlighted several challenges in comparative effectiveness research. Dr. Schreiner observed that if one option may prevent death more effectively than another, risks are more than minimal and his IRB would not waive consent. Also, if someone is randomized to treatment he or she would not have gotten outside the research process and does badly, that is attributable to the research.

Dr. Finer offered an example for discussion. He noted that Hydrochlorothiazide and Chlortalidone are both diuretics; Chlortalidone may be preferable, but Hydrochlorothiazide has a 98 percent share of the market. Could these two be compared in a comparative research study? Is it possible that Chlortalidone seems preferable only for lack of sufficient studies?

Mr. Annas observed that it was difficult to dictate anything that happens in the physician-patient relationship; the physician should never be placed in a role in which either the physician or patient cannot choose to do what they think is best. Dr. Simon wondered, given these complexities, "How will we ever get the evidence to change the practice to something that may be superior?"

Dr. Millum asked whether the two types of surgery described in the VA SOLID trial are performed by different people. Dr. Ferguson explained that after patients enter the study and are randomized to one arm or the other, the surgeon will proceed with the informed consent for the surgery. Dr. Millum speculated that it might be terrifying to go through the research consent process and hear about the risks of each of the options to which you might be randomized, then have to hear the physician talk through all of them again. Dr. Ferguson responded that there are no short cuts that would respect both the patient's autonomy and that of the surgeon. It is a valid concern and field testing will be needed.

Panelists discussed the relative merits of various approaches to the consent process in this type of research. Dr. Schreiner commented that a waiver of documentation would allow the patient to consent to the research over the phone, but this is unacceptable from a regulatory standpoint if the research has more than a minimal risk. Dr. Ferguson observed that doing the process by phone somewhat reduces the amount of information to be presented, as compared with a 17-page form, but not by much.

Dr. Simon noted that in *All of Us*, the participant gives consent at each stage only to whatever they are about to do. He wondered, “Is that better or is that slowly heating the frog?” Dr. Annas called this approach both fair and courageous, since every time the investigator talks to the subject the person has a chance to say, “I’m done.” Dr. Ferguson agreed that this makes information more digestible and will facilitate ongoing discussion. Dr. Strauss said this type of model works well with a single patient population and multiple researchers who can create an overarching plan. However, Dr. Simon noted that choosing a particular type of surgery cannot be undone; in this type of decision there is not a series of choices, but one.

Ms. Dresser had the impression that some people envision a more minimalist consent process and observed that none of the panelists were talking about that. Dr. Simon said that the term “learning health system” is often used to describe two processes: use of routinely collected records information for research and systematically altering treatment (sometimes through randomization) for purposes of research. For the former purpose (use of records data), a general notification with an “opt out” procedure may be adequate. When treatment is altered for a reason other than a patient’s welfare, then investigators must consider what additional information must be provided and how a patient may decline that alteration. There may be a series of consent modules with a café of different options associated with each. In this context, the decision to allow research may be accomplished through a brief, simple survey.

Session D: Delivery Room Research and the Challenges for Informed Consent

- *Moderator:* Sara F. Goldkind, MD, MA; Goldkind Consulting, L.L.C.

Dr. Goldkind introduced the session, which provided perspectives from an investigator and an IRB chair who had conducted clinical research on newborns or reviewed clinical research enrolling newborns or pregnant women in the delivery room. She noted that there is a dearth of information on treatment choices for neonatal care, and many products have little data behind them to support safety and effectiveness for these populations. The situation is complex because an investigational intervention may need to be used in an emergent or urgent manner truncating the time available for informed consent/parental permission. Further, the situation is made more complex by the fact that newborns, pregnant women, and women in the process of giving birth (who may be on drugs that impair their decision-making) are vulnerable populations. How can consent be conducted responsibly in such a setting?

IRB Chair’s Perspective: Are There Special Considerations for Informed Consent in Delivery Room Research?

- Mark Schreiner, MD; The Children’s Hospital of Philadelphia

Dr. Schreiner highlighted three issues that an IRB must consider when reviewing proposed delivery room research:

- Can the need for emergency treatment be anticipated?
- Are the research interventions no more than minimal risk?
- Does the research qualify for an [Exception from Informed Consent \(EFIC\)](#) if FDA regulated, or, if not, a [waiver of informed consent](#)?

If the need for emergency treatment is predictable, then informed consent is required. If not, and if the research is no more than minimal risk, the research may qualify for a waiver. If the research is greater

than minimal risk, it may qualify for exemption from informed consent under the FDA's regulations or OHRP's waiver.

Is it Really Impossible to get Informed Consent?

When is a Waiver of Consent appropriate in a neonatal clinical trial? Dr. Schreiner proposed the following hypothetical research question: *For non-vigorous infants born with meconium-stained amniotic fluid (MSAF), is it preferable to intubate and suction before ventilating an infant or to stimulate the infant and encourage breathing without suctioning?*

The hypothetical investigator writes, "It would be impossible to get informed consent for this study because we usually do not know whether amniotic fluid is meconium stained until delivery. We propose to defer informed consent."

Three sets of commentators were asked to respond to this scenario (Schreiner et al. 2014). The first agreed with the investigator, in part, that it would not be possible to obtain informed consent. A variety of rationales were cited:

- Antenatal consent would bias the research; less educated parents would be underrepresented due to lesser likelihood of seeking antenatal care
- Consent is not practicable
- Seeking consent would be harmful – by inducing anxiety
- If the IRB determines the risk to be greater than minimal, research qualifies under EFIC.

The second set of commentators held that *"because random assignment to intubation or no intubation probably carries equal risk to the patient, we believe study enrollment carries no more than minimal risk compared with standard care."* They held that valid consent was not possible due to the need for emergency care.

The speaker questioned the conclusions of both groups. Dr. Schreiner's analysis is as follows:

- Risks are greater than minimal. *The risks and benefits of the two treatment arms differ in important ways and those differences are the fundamental motivation for conducting the trial.*
- Risks and benefits of the two interventions are not equivalent. Someone with a strong preference for one treatment option ought not to participate in randomized study where they could be assigned their less preferred treatment.
- There is no such thing as "deferral of consent" as requested by the investigator. Either the parents' consent is secured before their infant's research participation begins or a waiver is required.

Subsequent to publication of this hypothetical case and commentary (Schreiner et al. 2014) an actual clinical research study was conducted and documented in the literature (Chettri et al. 2015). The study randomized non-vigorous term babies born through MSAF to either endotracheal suction or no-suction groups. The investigators demonstrated that, contrary to the assertions of some of the commentators, informed consent was entirely practicable. Consent was obtained from 1115 of 1271 infants born with meconium-stained amniotic fluid and for 122 of 127 non-vigorous infants who were the intended target population.

Waiver of Informed Consent in Certain Emergency Research

In 1996, OHRP established a [waiver for informed consent requirements in certain emergency research](#), provided certain conditions are met. The waiver may be applicable with subjects who "are in need of

emergency therapy...and for whom, because of the subjects' medical condition and the unavailability of legally authorized representatives (LAR) of the subject, no legally effective informed consent can be obtained." While the preamble specifies that the LAR had to be unavailable, in the body of the guidance, the concept of a "therapeutic window" was introduced. The therapeutic window is the timeframe in which it would be feasible to obtain consent before treatment had to commence. In addition, if an LAR is not immediately available on site, guidance further requires that the investigator try to contact a family member who is not an LAR if it is feasible within the therapeutic window, to allow the family member to opt out from participation. A family member was defined as including any of the following "legally competent persons: spouses; parents; children (including adopted children); brothers, sisters, and spouses of brothers and sisters; and any individual related by blood or affinity...."

Also, the speaker noted that the exemption applies only when there is no reasonable way to identify prospectively the individuals likely to become eligible for participation in the research. Dr. Schreiner noted that when the Children's Hospital of Philadelphia (CHOP) IRB has issued a waiver under EFIC, it still requires that the investigator obtain consent whenever it is feasible to do so and have a plan for conducting the consent process.

Dr. Schreiner offered the following guidance for investigators who are evaluating standard of care interventions in emergency room settings:

- When assessing risks, apply 2014 OHRP's draft guidance on [*Disclosing Reasonably Foreseeable Risks in Research Evaluating Standards of Care*](#).
- Develop a strong case for why consent isn't practicable based on evidence, rather than unsupported assertions.
- If the research intervention is no more than minimal and consent is not practicable, request a waiver of consent under 45 CFR 46.116(d).
- When EFIC applies (emergency research with greater than minimal risk), in addition to satisfying the commonly understood components of the EFIC requirements, it is important to also develop plans for:
 - Consent (in the rare situations, if any, when it would prove practicable to obtain consent), and
 - Provide an opportunity for parent(s) or other family members to opt-out (if practicable within the therapeutic window).

Delivery Room Research-Challenges and Opportunities

- Neil Finer, MD; Sharp Mary Birch Hospital for Women and Newborns

Dr. Finer explained several features of delivery room research that make it a challenging environment for human subject research:

- There are always at least two patients to consider (the mother and the newborn, or newborns).
- This is a high stress time for parents, especially if mother is in preterm labor or there is a concern about the baby necessitating delivery.
- The time frame can be very compressed (for example, the need for urgent delivery).
- The mother may be receiving treatment and/or not be in stable condition. Some institutions do not want the mother to be approached for consent.
- It is not an ideal time to discuss consent!
- For a given trial question, some mothers may be approachable while others are not.

It is sometimes possible to discuss such studies prior to hospital admission, or after admission and before delivery – ideally before the mother is having additional treatments or very active labor. Also, fortunately, not all delivery room research is emergency research.

Four options exist for informed consent related to delivery room research:

- Antenatal, pre-delivery consent;
- Antenatal Information, post-natal waiver of consent;
- Antenatal Information, waiver of consent; and
- Exception from Informed Consent for Emergency Research.

Case Study: Consent in the SUPPORT TRIAL

Dr. Finer reviewed several findings related to the challenges of getting parental consent for the SUPPORT trial, in which infants were randomly assigned to continuous positive airway pressure or intubation and surfactant in order to compare target ranges of oxygen saturation (Rich, Auten et al. 2010). He noted that:

- Many women and fathers had to be approached in advance whose infant did not ultimately qualify for the trial (five were consented for every one enrolled). This increased parental anxiety, as well as time and staffing requirements.
- The most at-risk pregnancies were excluded because of the inability to obtain individual informed consent in emergencies and other situations (for example, the mother was in labor or receiving medication).
- Most mothers who were approached for the study were more likely to be non-Hispanic white, older, have a high school education, have private medical insurance, and have at least one visit for prenatal care.
- Mothers who were not in the study received significantly less antenatal steroids, which could affect the outcomes.

A later study of outcomes found that differences in outcomes for enrolled and non-enrolled infants were actually related to the characteristics of the pregnancy before enrollment, and were NOT a Trial Effect, i.e., not due to differences in procedure/approaches being tested (Rich, Finer et al. 2012).

The Hi-Lo Trial

Dr. Finer discussed challenges of conducting research to determine the best approaches to reducing mortality in seriously underweight preterm newborns. Would a low or high fraction on inspired oxygen (FiO₂) be most likely to resuscitate the infant safely? The Hi-Lo Prem Trial, a proposed randomized trial to answer this question, remains unapproved. The coalition of researchers that wish to sponsor the study wanted a crossover cluster in which institutions were doing both practices, an adequate power to look at outcome of death, and a waiver of consent.

Guidance critical to the study was issued by OHRP in 2014: “Draft Guidance on Disclosing Reasonably Foreseeable Risks in Research Evaluating Standards of Care.” According to this draft guidance, identified risks associated with a standard of care that are being evaluated as a purpose of research should be considered reasonably foreseeable. The guidance notes that “adequate knowledge about the effectiveness and risks of standards of care and how these standards compare to each other is sometimes lacking.” In the case of the HI-Lo trial, investigators were concerned that – based on the best available evidence that existed at the time and to the present – the risks with the *current* recommended standard of care could be greater than the risks for the proposed use of a higher initial oxygen level.

Researchers met with OHRP in 2016, and OHRP expressed concern that the initial use of higher oxygen levels than recommended was risky enough to require parental consent. (A waiver can only be granted for minimal risk research.) OHRP initially suggested that the Emergency Consent pathway be explored, but this would require antenatal consent for all women who could be approached. OHRP then consulted with FDA, which recommended that the study be done as an FDA trial using an emergency waiver. The investigators felt that the proposed design was not feasible if it required antenatal consent when possible, and the study was abandoned in the USA. Dr. Finer noted that FDA trials are neither simple nor inexpensive. The study has yet to be initiated and is currently being considered in other countries.

Recommendations for Delivery Room Consent

Given the complexities of delivery room consent, Dr. Finer strongly recommended that research institutions establish mechanisms that allow parents to provide their perspective on proposed studies. At Sharp Mary Birch Hospital for Women and Newborns, a Parents Committee reviews all perinatal research projects. They evaluate the studies for risk, alter wording, and make design suggestions. One parent represents the committee to the IRB when the protocol is discussed. A parent is also invited to sit on the study steering committee.

Dr. Finer recommended that researchers:

- Use the Emergency Research Pathway where appropriate,
- Have a community committee of parents review the project and provide community assent if they agree,
- Consider both mothers and babies as possible subjects, and
- Consent all approachable families antenatally.

Panel Discussion for Session D

The panel discussion focused on the informed consent issues central to the proposed Hi-Lo Prem Trial as explained by Dr. Finer.

Dr. Goldkind asked Dr. Finer what feedback researchers had received from the Parents Committee regarding the trial. Dr. Finer said the committee took a strong leadership role and developed a document that would be distributed to parents who came to the hospital. They were very concerned about exactly what would be said in the delivery room setting, knowing that the baby is typically delivered and resuscitated in the same room – often with the father and mother both present and, understandably, deeply stressed and concerned. Some parents wanted the father to be present, but Dr. Finer was concerned that the father would collapse if there were not someone assigned to sit with him and explain what was going on. Dr. Finer found that parents often perceive things as a big deal that don't seem like a big deal to researchers, and vice versa.

Dr. Goldkind then wondered whether researchers had considered the possibility of consenting all pregnant women antenatally at a particular hospital. Dr. Finer responded that it was considered, but most investigators thought it would be prohibitively difficult to approach and consent the number of parents required, given that most of them would not have babies that qualified for the trial. Some hospitals in the study are very large (one delivers 9000 babies annually) so the prospect of responsibly conducting an informed consent process for all those families was overwhelming. He noted that some cluster randomized trials have been done without consent.

Dr. Schreiner explained that there are several different types of cluster randomized trials. One is the cluster-cluster trial (e.g., institutions or neonatal intensive care units are randomized), in which people

cannot opt out and there is no individual consent. There are also cluster-individual trials in which the intervention is delivered at the level of the individual. The Ottawa document addresses the issue of consent and would require individual consent for the latter type of trial. He noted that Dr. Finer made a strong case for consent not being practicable, however, and his IRB would consider the possibility that it qualifies for the exception from informed consent (EFIC) for emergency research under FDA's regulations at 21 CFR 50.24. Community consultation would be necessary. For this study, a review of complaints related to the CLOVERS (Crystalloid Liberal or Vasopressors Early Resuscitation in Sepsis) trial would be helpful, since failure to include usual care as a study arm was seen as problematic. He also expressed regret that EFIC was not incorporated in the new version of the Common Rule rather than leaving the matter to a memorandum.

Dr. Millum asked whether parents typically have any input into the level of oxygen provided. Dr. Finer said the issue is generally not discussed. Most people would probably prefer to follow existing guidelines that recommend lower oxygen, although some centers may be more liberal in the extent to which they increase this level. If asked, parents typically will say, "whatever you think best." Dr. Millum sought to clarify: since this is the case and practice varies, why there was such concern about the risks posed by the trial? Dr. Finer responded that investigators do not believe that the research was more risky than current care. Investigators believed that the best available information at present suggests that the recommended guideline is riskier than the proposed approach. However, the research on what works best is conflicting and simply does not answer the study question definitively. At this point, the risks of either approach are unknown. That is why the team wanted to do the study. Dr. Simon asked whether the direction of practice patterns led toward or away from a particular option. There may not be equipoise between the two options, given the practice environment. Dr. Goldkind asked if Dr. Simon felt the trial should not be done if this was the case. He responded that if the market share is changing on its own, the trial may not be needed. Dr. Finer noted, however, that in questioning the current guidelines, the Hi-Lo team is admittedly "swimming against the tide."

Dr. Goldkind wondered whether the Hi-Lo Perm Trial needed to be as large as projected in order to interpret the data. A smaller study would simplify the community study, and many centers have experience with EFIC. Dr. Finer said emergency research regulations would require that all approachable women be reached to go through the informed consent process, and this would require an expensive, aggressive approach. A high percentage of women are approachable. The workload required to get consent is problematic; the team did not have the staff/funding to approach people and get consent. Also, Dr. Finer noted, most babies are not delivered as true emergencies and would not be appropriate for the study. A previous small trial using a waiver option failed miserably, partly because many premature babies were born when research staff were not available.

Dr. Goldkind asked how the risks and benefits of the two interventions might be explained to individuals. Dr. Schreiner said it would be important to state that it is not possible to predict which infants will need to be resuscitated. He suggested the EFIC process could still be pursued. It would be possible to use a tiered consent process that began with informed consent, opt out, or a full waiver depending on the condition. Dr. Finer thought this was promising. Dr. Goldkind agreed that a tiered approach was best, but she noted that the question remained of how best to explain the study and its risks to expectant mothers.

Dr. Finer observed that he did not understand why the suggestion was made that the trial be an EFIC trial under the FDA regulations. This implied to him that it would be more complex, given the need for additional monitoring and data collection. Dr. Schreiner suggested using a single IRB with two or three

focus groups to provide feedback, which would simplify compliance with the requirement for community consultation.

An FDA representative present at the workshop suggested that Hi-Lo researchers need not be afraid of EFIC. He explained that the trial was referred to FDA's Center for Drug Evaluation Research because oxygen is considered a drug product. He noted that FDA gets questions like this all the time. He counseled Dr. Finer to work with the review division responsible for oxygen to see if the study might be exempt from Investigational New Drug (IND) regulations or if the study would qualify for EFIC. The fact that antenatal consent is possible, even if it might introduce bias, might mean that the study could not fall under EFIC. This is a complex discussion and was referred to FDA for further clarifications.

Closing Session: Moderators' Panel

Session A: Summary

Dr. Strauss, moderator for "Laying the Groundwork for Meaningful Informed Consent," noted that much of the discussion in this session focused on what constitutes *meaningful* consent in different domains. Dr. Millum and Dr. Bromwich approached the question by stating that the consent process had two distinct goals, one of which must be met and one of which is aspirational. Valid consent *must* disclose relevant information the participant would expect to be told in a manner that would give the participant a reasonable chance to understand it. However, the second goal of the process – to "facilitate good decision-making" – was considered desirable and should be pursued, but was not required from an ethical perspective.

Ms. Dresser described the origins of the reasonable person standard, soon to be embodied in the revised Common Rule, in law and in the medical field. She noted the reasonable volunteer standard described in the *Belmont Report*. She emphasized the need to learn more about what ordinary people want to know and suggested that researchers should be doing a better job of engaging experienced subjects in discussions of what is relevant to disclose.

Dr. Fischhoff explored various approaches to deciding what is relevant to decision making. The determination might be made by IRBs, by professionals, through evaluation and measurement, or by patient preference. He challenged the field to explore how the research community thinks about what is relevant and what its obligations are to subjects. How should investigators be involved in making sure subjects actually understand the implications of giving their consent?

Session B: Summary

Dr. Grady, moderator for "Effectively Presenting Information to Facilitate High-Quality Decision-Making," focused on how best to present information related to informed consent. She recalled that Dr. Schwartz and Dr. Woloshin focused on implications for presenting information based on scientific findings, including those related to the use of simple language, graphics, and neutral metaphors, to help people think through decisions. Dr. Fagerlin explained how decision aids are being used in clinical care contexts to help people become more engaged in decisions than if they were passively receiving data. These clearly should be incorporated in research decision making. She also noted that, surprisingly, what people say is most important to them is not always reflected in their decisions.

Mr. Wilbanks and Ms. Doerr explored how smart phones and other electronic devices can be used effectively to provide information and make the consent process more interactive. They showed a model presentation that combines key graphics with meaningful headings and subheadings to convey a sequence

of information. Information can be broken into pieces to help subjects assimilate information. The *All of Us* trial offers an interesting model for this type of approach. The field is now challenged to see how the findings and models presented can be applied in a variety of trials.

Session C: Summary

Dr. Simon, moderator for “Pragmatic Clinical Trials – Challenges and Innovations in Getting Informed Consent,” recalled that Dr. Leatherman and Dr. Ferguson laid the groundwork for this session by defining the concept of a pragmatic trial as a clinical trial that is embedded in everyday practice and studies treatments that are commonly in use. However, it alters treatment patterns for the purpose of research rather than to benefit the individual. This difference is a bright line that separates the trial from clinical practice. Discussion focused on what is similar and different to other types of clinical trials and the implications for the consent process. The use of automatically created information acquired through clinical practice creates efficiencies, but it can also create confusion about what part of care is actually research and who is responsible for obtaining consent. Presentations also considered the possibility of a consent process that unfolds in stages.

Mr. Annas noted that the role of the treating physician is key, since this type of trial is particularly likely to confuse subjects about how decisions about their care are being made and by whom. He suggested that the physician, who is in the best position to provide guidance to the prospective subject about his or her interests, may need to leave the room as information about the trial is provided. An interesting sidebar discussion focused on the issue of access to normally available treatment and its implications for decision making.

Session D: Summary

Dr. Goldkind, moderator for “Delivery Room Research and the Challenges of Informed Consent,” observed that although Dr. Schreiner and Dr. Finer approached the discussion from different perspectives, their presentations had several commonalities. Both talked about the implications of evidence-based practice as a guide for the informed consent, IRB deliberations, and study design. Both stressed the importance of ensuring that scientific necessity and the ability to meet stated objectives drive the approach to securing informed consent.

Both observed that a traditional approach to informed consent may mean that some prospective subjects cannot be approached. Real challenges exist in conducting appropriate, scientifically based research in settings like the delivery room. However, sometimes investigators and sponsors assume that informed consent cannot be secured when it actually is possible. It is important to consider the scientific data on whether or not consent can be obtained in difficult circumstances.

Open Discussion

In summary, Dr. Strauss observed that the day was enormously informative. Presenters described a number of important ideas and innovations, also clarifying work that needs to be done to meet the challenges facing the field. He suggested that creating a repository of good ideas, tools, and innovative practices would help move it forward. He was not sure of the most appropriate venue for this effort.

Audience member Evelyn Hoagh, a clinical trial specialist with the AIDS Clinical Trials Group, was struck by the fact that a number of studies show that subjects often do not understand either the goal of the study or evidence for the treatment offered. Her work includes writing informed consent documents. She felt this issue was not sufficiently explored. Coming from a background in sociolinguistics, she wanted to believe that subjects’ comprehension really matters and was concerned to hear that the physician’s recommendation seems to trump whatever participants hear about the trial. She queried,

“What is the “fix” for this situation?” She stressed the importance of educating the general population about research, noting that the people that actually consider research are an important subset of this population. Finally, she wondered what percent of subjects opt out of studies of their own volition, speculating that this may be a distinctive subpopulation.

Dr. Schreiner observed, in response, that there is a huge literature on the effect of simplifying informed consent forms, and we do know which elements make the biggest difference. However, the improvement in understanding so far appears to be disappointingly small. New methods may be better. He added that while IRBs think of informed consent as the floor for human subject protection, the study’s sponsor may think of it as the ceiling. He wryly noted that IRBs generally have less trouble with informed consent documentation than with 100-page protocols.

Dr. Strauss commented that in the U.S., the research community does not do a good job in educating the public about the value of clinical research (except in self-promoting messages). If the field were successful in creating a sense of the value of the research enterprise, it would promote informed consent in a broader way and researchers could worry a little less about subjects’ understanding of specific protocols.

Dr. Strauss also observed that good research ethics, like good research, costs money. Improvement will require time, effort, and resources. This is what prevents Dr. Finer from using the optimal informed consent process for the proposed Hi-Lo study. Dr. Finer confirmed this perception, stating that he cannot staff his study the way he’d like to. It would be helpful to give thought to how improvements in informed consent could be funded.

Dr. Grady said that, to date, there is no agreement on what people really need to know to give consent. Data show that subjects have a variable range of understanding of what they are doing. Special attention should be given to the things that are most important for them to understand – for example, that they have the right to say no. Insisting on their ability to recite risks or describe them in detail may be asking too much. For now, the data is flawed. We need to know more about what is really necessary to communicate. Perhaps, she suggested, the focus on understanding is misplaced. It might be more useful to understand subjects’ motivation for participating in research and why they care about it.

Highlighting the expressed concern that a subject might make a poor decision, an audience member asked what would be considered a bad decision on the part of a subject. Dr. Bromwich said a bad decision would be one in which the subject’s choice is against his or her own interests, given the subject’s values. This is not a bad decision from the researcher’s point of view. Dr. Simon said a helpful example is a recently married man interested in having children who selects the surgery option for prostate cancer that would have the greatest risk of rendering him impotent.

Dr. Millum observed that while it may be true that changing the consent form does not radically change comprehension, some changes in the consent *process* have been shown to improve understanding substantially – for example, interaction, the opportunity to ask questions, and adding a quiz. He also emphasized the importance of distinguishing between studies in which there is certain information that it is critical subjects understand and those in which understanding is less crucial, such as those with little risk.

References

- Adams JR, Elwyn G, Légaré F, & Frosch DL. (2012). Communicating with physicians about medical decisions: A reluctance to disagree. *Arch Intern Med*, 172(15), 1184–1186.
- Arora NK & McHorney CA (2000). Patient preferences for medical decision making: Who really wants to participate? *Medical Care*, 38, 335– 341.
- Braddock CH, Edwards KA, Hasenberg NM, Laidley TL, & Levinson W (1999). Informed decision making in outpatient practice: Time to get back to the basics. *JAMA*, 24, 2313-2320.
- Bromwich, D. & Millum, J. (2015). Disclosure and consent to medical research participation. *Journal of Moral Philosophy*, 12 (2), 195-219.
- Bromwich, D. & Millum, J. (2017). Informed Consent to HIV cure research. *Journal of Medical Ethics*, 43 (2), 108-113.
- Chettri S, Adhisivam B, & Bhat BV (2015). Endotracheal suction for nonvigorous neonates born through meconium stained amniotic fluid: A randomized controlled trial. *J Pediatr*, 166, 1208-13.
- Collins, FS & Varmus, H. (2015). Perspective: A new initiative on precision medicine. *New England Journal of Medicine*, 372,793-795.
- Doerr M, Truong A, Bot BM, Wilbanks J, Suver C, & Mangravite LM. (2017). Formative evaluation of participant experience with mobile eConsent in the app-mediated Parkinson mPower Study: A mixed methods study. *JMIR Mhealth Uhealth*, 5(2), E14.
- Dresser, Rebecca (2016). *Silent Partners: Human Subjects and Research Ethics*. Oxford University Press.
- Durand M-A, Carpenter L, Dolan H, Bravo P, Mann M, Bunn F, et al. (2014) Do interventions designed to support shared decision-making reduce health inequalities? A systematic review and meta-analysis. *PLoS ONE* 9(4): e94670.
- Fischhoff, B. (2017). Breaking ground for psychological science: The U.S. Food and Drug Administration. *American Psychologist*, 72(2), 118-125.
- Fischhoff, B., Brewer, N.T., Downs, J.S. (2011). *Communicating Risks and Benefits: An Evidence-Based User's Guide*. US Department of Health and Human Services, Food and Drug Administration Risk Communication Advisory Committee and consultants. Available on line at: <https://www.fda.gov/AboutFDA/ReportsManualsForms/Reports/ucm268078.htm>
- Holmes-Rovner M, Montgomery JS, Rovner DR, Scherer LD, Whitfield J, Kahn VC, Merkle EC, Ubel PA, & Fagerlin A. (2015). Informed decision making: Assessment of the quality of physician communication about prostate cancer diagnosis and treatment. *Med Decision Making*, 35(8), 999-1009.
- Hwang, TJ et al. (2018). Efficacy, safety, and regulatory approval of Food and Drug Administration–designated breakthrough and non-breakthrough cancer medicines. *Journal of Clinical Oncology*, 36 (18), 1805-1812.

- Krieger, JL, Neil, JM, Strekalova, YA, Sarge, MA. (2017). Linguistic strategies for improving informed consent in clinical trials among low health literacy patients. *JNCI: Journal of the National Cancer Institute*, 109 (3). Available on line at: <https://doi.org/10.1093/jnci/djw233>
- Krishnamurti, T., Argo, N. (2016). A patient-centered approach to informed consent: results from a survey and randomized trial. *Medical Decision Making*, 36, 726-740).
- Krishnamurti T, Woloshin S, Schwartz LM, Fischhoff B. (2015). A randomized trial testing US Food and Drug Administration “breakthrough” language. *JAMA Intern Med*, 175(11), 1856-1858.
- Levinson W, Kao A, Kuby A & Thisted RA (2005). Not all patients want to participate in decision-making: a national study of public preferences. *Journal of General Internal Medicine*, 20, 531–535
- Mazur, DJ & Hickam, DH (1997a). Patients’ preferences for risk disclosure and role in decision-making for invasive medical procedures. *Journal of General Internal Medicine*, 12, 114-117.
- Mazur, DJ & Hickam, DH (1997b). The influence of physician explanations on patient preferences about future health-care states. *Medical Decision Making*, 17 (1), 56-60.
- Merz, J., Fischhoff, B., Mazur, D.J., & Fischbeck, P.S. (1993). Decision-analytic approach to developing standards of disclosure for medical informed consent. *Journal of Toxics and Liability*, 15(1), 191-215.
- Millum, J. and Bromwich, D. (2018). Understanding, communication, and consent. *Ergo* 5, 45-68.
- Nathan AG, Marshall IM, Cooper JM, Huang ES (2016). Use of decision aids with minority patients: a systematic review. *J Gen Intern Med*, 31, 591.
- National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. (1979). *Belmont Report*. Washington, D.C.: U.S. Department of Health & Human Services. Available on line at: <https://www.hhs.gov/ohrp/regulations-and-policy/belmont-report/index.html>
- Obar, JA & Oeldorf-Hirsch, A. (2018). The biggest lie on the Internet: Ignoring the privacy policies and terms of service policies of social networking services. TPRC 44: The 44th Research Conference on Communication, Information, and Internet Policy, 2016. Available at SSRN: <https://ssrn.com/abstract=2757465> or <http://dx.doi.org/10.2139/ssrn.2757465>
- Politi M et al. (2016). Decision aids can support cancer clinical trials decisions: results of a randomized trial. *The Oncologist*, 21, 1461-1470.
- Rich WD, Auten KJ, et al. (2010). Antenatal consent in the SUPPORT trial: challenges, costs, and representative enrollment. *Pediatrics*, 126(1), e215–221.
- Rich WD, Finer NN, Gantz MG, et al. (2012). Enrollment of extremely low birth weight infants in a clinical research study may not be representative. *Pediatrics*, 129(3), 480–484.
- Scherr KA, Fagerlin A, Hofer T (2016). Physician recommendations trump patient preferences in prostate cancer treatment decisions. *Medical Decision Making*, 37(1), 56–69.
- Schreiner MS et al. (2014). When is Waiver of Consent appropriate in a neonatal clinical trial? *Pediatrics*, 134, 1006-1012.

Schwartz, L., & Woloshin, S. (2013). The Drug Facts Box: Improving the communication of prescription drug information. *PNAS*, *110*, 14069-14074.

Stacey D, Légaré F, Lewis K, Barry MJ, Bennett CL, Eden KB, Holmes-Rovner M, Llewellyn-Thomas H, Lyddiatt A, Thomson R, Trevena L. (2017). Decision aids for people facing health treatment or screening decisions. *Cochrane Database of Systematic Reviews*, Issue 4.

Stark, L. (2012). *Behind Closed Doors: IRBs and the Making of Ethical Research*. Chicago: University of Chicago Press.

Ubel PA., Scherr KA, & Fagerlin A. (2018). Autonomy: What's shared decision-making have to do with it? *The American Journal of Bioethics*, *18*, W11-W12.

U.S. Food and Drug Administration (various). The Voice of the Patient: A Series of Reports from the FDA's Patient-Focused Drug Development Initiative. Center for Drug Evaluation and Research (CDER), FDA.

Woloshin S, Schwartz LM. (2011). Communicating data about the benefits and harms of treatment: A randomized trial. *Ann Intern Med*, *155*, 18, 87-96.

Online Resources

The following online resources are recommended by various speakers:

Design issues in eConsent: <http://journals.sagepub.com/doi/abs/10.1177/1073110518766025>

eConsent white paper: https://papers.ssrn.com/sol3/papers.cfm?abstract_id=2769129

Electronic Data Methods Forum: <https://www.academyhealth.org/EDMForumStory>

Informed consent flow for ResearchKit:

<http://researchkit.org/docs/docs/InformedConsent/InformedConsent.html>

International Patient Decision Aids Standards: <http://ipdas.ohri.ca/>

mPower study (iPhone): <https://parkinsonmpower.org/>

My BP Lab study (Android): <https://mybplab.com/>

Open source code for mPower: <https://github.com/Sage-Bionetworks/mPower>

Side effects of cancer treatment: <https://www.cancer.gov/about-cancer/treatment/side-effects>