Key Information in the New Common Rule: Can It Save Research Consent?

Nancy M. P. King

Key Information

There is something new in the new Common Rule[1]: something called "key information."

Section ___.116(a)(4) states: "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, and an opportunity to discuss that information."[2] Next, section ___.116(a)(5)(i) explains: "Informed consent must 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. This part of the informed consent must be organized and presented in a way that facilitates comprehension."[3]

This new required component of (most) research consent forms has engendered a great deal of discussion and head-scratching among IRB professionals in the two years since it was enshrined in this final form in the final rule. What is it? How are investigators supposed to write it? How are their IRBs supposed to help them? What sort of "concise and focused key information presentation" will comply with this new requirement? And how does it relate to that new player in the final rule, the reasonable person?

Key information is discussed at some length in the preamble to the final rule. Let's see if that discussion helps.

The preamble first acknowledges that some commentators have argued "that consent forms have evolved to protect institutions rather than to provide potential research subjects with the most important pieces of information that a person would need in order to make an informed decision about whether to enroll in a research study. Instead of presenting the information in a way that is most helpful to prospective subjects — such as explaining why someone might want to choose not to enroll — these individuals argued the forms may function more as sales documents or as a means to protect against institutional liability. ... [A] growing body of literature ... suggests informed consent forms have grown too lengthy and

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complex, adversely affecting their ability to effectively convey the information needed for prospective participants to make an informed decision about participating in research."[4]

This discussion clearly recognizes the well-known potential gap between regulatory compliance and ethics; it is, after all, quite possible for a consent form to meet all of the regulatory requirements, at least nominally, and nonetheless be too long, complex, and difficult to wade through to accomplish the goal of making an informed decision possible. Moreover, when the compliance-ethics gap appears, it is quite understandable for IRBs and investigators to concentrate on compliance, which is generally viewed as far easier to demonstrate to regulators than that variable, context-dependent, squishy ethics stuff.

To address these important concerns, the final rule makes "key information" a new regulatory compliance requirement — and then the preamble proceeds to emphasize its flexible and context-specific nature: "We recognize that how this requirement applies will depend on the nature of the specific research study and the information presented in the informed consent and believe that this requirement strikes an appropriate balance between facilitating the comprehension of subjects of key issues and allowing study-specific flexibilities. In general, our expectation is that this initial presentation of the key pieces of information will be relatively short. This section of the consent could, in appropriate circumstances, include a summary of relevant pieces of information that are explained in greater detail later in the consent form. The requirement that key information be presented in a concise and focused way will require an assessment that is specific to a study and its informed consent."[5]

The preamble's discussion of key information continues by placing emphasis on the desirability of study-specific tailoring of the length, form, and content of key information — "This flexibility is responsive to public comments recommending against a rigid approach to enable institutions and individuals to tailor informed consents to the circumstances of particular studies."[6] It alludes to the possibility of future guidance. It then provides a list of items generally expected to be included in key information, and concludes with a pushme-pullyou-worthy compliance-vs.-flexibility maneuver: "As a general matter, a brief description of these five factors would encompass the key information most likely to assist a reasonable person (or legally authorized representative) in understanding the reasons why one might or might not want to participate in research, as required by §__.116(a)(5)(i) and §__.116(a)(4). However, we recognize that this determination is necessarily fact-specific and that IRBs and institutions may require that somewhat different (or additional) information be presented at the beginning of an informed consent to satisfy §__.116(a)(5)(i)."[7]

And what are the five factors that every investigator and IRB will want to be sure they can list concisely at the beginning of each consent form and thus be in compliance? Surprise: They are:

1. the fact that consent is being sought for research and that participation is voluntary;
2. the purposes of the research, the expected duration of the prospective subject's participation, and the procedures to be followed in the research;
3. the reasonably foreseeable risks or discomforts to the prospective subject;
4. the benefits to the prospective subject or to others that may reasonably be expected from the research; and
5. appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the prospective subject.[8]

These five factors match almost perfectly the first four basic elements of informed consent at _6.116(b). It is not surprising, then, that IRBs might be somewhat confused about how the key information presentation is supposed to differ from the rest of the consent form, or what the preamble's acknowledgment that IRBs may require a different key information presentation might mean in practice. The preamble's discussion of what "concise and focused" means as regards consent form length is, similarly, both enlightening and somewhat opaque. It first describes the key information requirement at __.116(a)(5)(i) as simultaneously specific, detailed, and flexible, which is actually a pretty neat trick, and as striking a balance between facilitating subjects' comprehension of key issues and allowing study-specific flexibilities[9] — which is an important balance to consider in practice, to which I'll return later.

Next, however, the preamble sets forth the expectation that "this initial presentation of the key pieces of information will be relatively short" — "a summary of relevant pieces of information that are explained in greater detail later in the consent form."[10] To illustrate that what "concise and focused" means is highly study-specific, the preamble offers the example of a complex oncology trial with a 20- to 25-page consent form, and states that a key information presentation of "no more than a few pages" would be appropriate, whereas 10 pages would not satisfy the "concise and focused" requirement: "[I]nstead of needing to men-

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tion every reasonably foreseeable risk, ... this beginning section of the consent form should identify the most important risks, similar to the information that a doctor might deliver in the clinical context in telling a patient how sick the chemotherapy drugs will make them, but with a particular emphasis on how those risks are changed by participating in the study."[11]

At this point, the regulated community might be forgiven for being a little confused. Nonetheless, some academic medical centers immediately started developing key information models, genuinely searching for that balance between creativity and compliance. This is very much to their credit, but it also reflects the reality that the long path taken by the Common Rule revisions, from ANPRM to final rule, informed and was informed by two complex and ongoing dialogues: one between OHRP and the Common Rule agencies, and the other between OHRP and the regulated community.

An exhaustive examination of the massive body of Federal Register commentary along the pathway to the revised final rule is far beyond the scope of this essay, but it would probably yield insights worthy of someone's dissertation. As regards key information, though, research ethics scholars going back at least to Jay Katz,[12] along with many in the regulated community, have long wanted to offer a short consent summary focused on the information most needed by potential subjects, but compliance concerns intervened. Thus, as a result of the discussion process, everybody knew that something like this was coming, and many stakeholders took — and continue to take — responsibility to help shape the final product.

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The Reasonable Person

Now, at least, we know that research consent forms must be rethought, so that they can begin with "a concise and focused presentation" of "the key information most likely to assist a reasonable person ... in understanding the reasons why one might or might not want to participate in research."[13] This passage from the preamble to the final rule specifically links key information to the reasonable person. But how did the reasonable person get in here?

The reasonable person is not really a new actor. Since the final Common Rule revisions were published, IRB professionals and others have been asking questions like "Who is reasonable? Who gets to decide that?" Those are actually the wrong questions. Instead, the reasonable person standard seems intended to parallel the application of the reasonable person standard to informed consent disclosure and decision-making in the clinical context, albeit fitted into the prospective context of research oversight. The reasonable person in the revised Common Rule is thus not directly related to the reasonable person as actor in ordinary negligence case law; it has a more complex pedigree, following from the reasonable person as decider in informed consent case law.[14]

The reasonable person began as a hypothetical actor in negligence law and was transformed into a hypothetical decision-maker as part of the process of moving the failure to obtain informed consent in clinical medicine from battery to professional negligence. As exemplified in *Canterbury v. Spence*, subsequent case law, and state statutes choosing the reasonable patient standard over the professional standard of disclosure, this shift required the reasonable person to become a split personality, governing both (1) what information should be disclosed as material to the patient's decision whether to agree to what the physician recommended and (2) whether the patient's agreement would have been withheld if undisclosed information had instead been provided.[15] When the reasonable person standard appears in the clinical context, then, it governs both the forward-looking determination of what information is material and thus should be disclosed, and the backward-looking determination of

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whether specific material information should be considered dispositive under the circumstances. Because the research context is entirely forward-looking, the reasonable person standard can apply only to what information counts as material, not also to determining what should be dispositive. But as __.116(a)(5)(i) provides, it also applies to the way material information is presented, in order to enhance the decision-making process of potential subjects in a specific way: toward understanding the reasons each might decide to join a study or not to join it.

Invoking the reasonable person in the research context thus resembles the shift in clinical informed consent law to focus on the decisions made by reasonable patients, rather than to consider only the actions and choices of their physicians. Applying the reasonable person standard to informed consent in research ought therefore to remind IRBs and study teams of an essential aspect of informed decision-making that is fundamentally similar in the clinical and research contexts: The consent form and process in both treatment and research are intended to support and enhance the patient's and the potential subject's decision-making capacity. Thus, reasonableness is not meant to be a fixed or testable characteristic of potential subjects. "Who is reasonable?" is not the most salient inquiry; "What is reasonable?" is far more important.

"Reasonableness" is a deliberate chosen term, distinguishable from "rationality" with its illusion of mathematical objectivity. "Reasonable" acknowledges not only reasoning and context but also the inescapably emotional components of human decision-making. Reasonableness is the central characteristic of the decision-making model that informed consent is meant to bring to fruition; indeed, the key question to ask is "Do this consent form and process help potential subjects understand the reasons on which to base their decisions about participating in this study?" All people faced with decisions about research participation need help to make reasonable sense of the choices they are offered.

The reasonable person standard is therefore a guiding principle about how to frame and conduct a genuine engagement with potential subjects, especially if they are also patients: "Here are the things we think you should think about; here is what's different about being in this research study from being treated for your condition; now let's talk about what's important to you, and what else might help you decide to join this study or not." The reasonable person standard is the new Common Rule's way of turning the form and content of consent toward decision support, in order to enable potential subjects to say either yes or no to participation based on their understanding of the reasons they might want to participate or not. This necessarily shifts the content and form away from both institutional self-protection (with its extensive, exhaustive liability-limiting detail) and research promotion (featuring the subtle manipulations of word choice and emphasis designed to lead potential subjects toward saying yes and away from saying no).

How Key Information and the Reasonable Person Speak to Each Other

I promised to return to the preamble's argument that the concise and focused presentation of key information strikes a balance between facilitating subjects' comprehension of key issues and allowing study-specific flexibility. One of the most important and, arguably, groundbreaking aspects of key information is its focus on the reasons that potential subjects might have for deciding whether to join a study. This study-specific tailoring to what might be important to a given subject population permits and encourages consultation with the relevant population, and with the experienced subjects who, as Rebecca Dresser has eloquently argued, belong on IRBs and study teams and should be involved in human subjects research in a wide range of other ways.[16]

Yet investigators and IRBs must be aware of a potential problem that could flow from this kind of population-specific inquiry: What should happen if members of the relevant study population tell the study team, "You have it all wrong; we don't need to know A, B, or C. There's nothing good out there for our condition, so all we need to know is where to sign!" This response is far from implausible. The study team and the IRB could respond in several ways. They could say "Sorry, you need to hear items 1-5 in the regulations, whether you want to or not." Or they could say "Okay, the regs say that we can be flexible, so let's leave all that out of key information for this study." The first response might be regarded as paternalistic maintenance of the status quo: "We know better than you what you need to know." And the second response both ignores the preferences of some minority percentage of reasonable potential subjects and leaves others vulnerable to the insight of hindsight when they learn about what they thought they didn't need to know.

So I recommend a third way of thinking about this: Key information ought to include information that reasonable people who are potential subjects should want, whatever other information they want.[17] This formulation errs on the side of information inclusion rather than exclusion, but that default is acceptable because it nonetheless requires the IRB and the study team to consider carefully what information reasonable potential subjects should want and do want under

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the relevant circumstances. It does not endorse a comprehensive listing of everything in the preamble's five factors; instead, it mandates a genuine examination of the fit of the five factors to a given study, and then invites an examination of what else potential subjects may want to know under the circumstances. Finally, and perhaps most important, it endorses an ongoing process of mutual education among IRBs, investigators, potential subjects, and experienced subjects about (1) the reasons for including certain information and (2) good ways to explain the importance of included information.

I acknowledge the need to explain why this formulation is at all distinctive. Certainly, it is true that potential subjects want and need to know some things that are not always well addressed in consent forms. The list of such things could be quite long and is necessarily specific to the study and the subject population. But what makes "the information that reasonable potential subjects should want" any different from "We already know that you need to know the Five Factors"? The answer lies in the conundrum of the therapeutic misconception.

The Therapeutic Misconception

Potential subjects of biomedical or behavioral research are in many circumstances at least somewhat likely to confuse research and treatment, either because they are insufficiently aware of the difference or misunderstand the information provided about research participation, or because they are patients who are given — or at least not disabused of — reason to hope that the research intervention is likely to provide them with significant direct benefit. When Paul Appelbaum and colleagues first described the therapeutic misconception — that is, misconstruing research as treatment — they attributed this misunderstanding to all stakeholders, but focused primarily on the therapeutic misconception of research subjects.[18] Historically, in order to minimize the likelihood of the misconception, many IRBs have preferred that consent forms significantly downplay their discussions of potential benefit, limiting them to vague and uninformative statements, such as "You may or may not benefit" or "Personal benefit cannot be guaranteed."[19] This vagueness, however, fails to explain what sort of benefit is at issue in a given study; thus, providing more detail about the nature, magnitude, and likelihood of direct benefit may be far more informative and therefore better able to correct misunderstandings. To give a simple example, "benefit" might mean reduction of symptoms, or it might mean "cure;" only a more detailed description of potential benefit can enable potential subjects to interpret it appropriately. Moreover, clarifying the distinction between research and treatment helps to inform even potential subjects who are convinced that the research is their treatment, by emphasizing uncertainty and explaining the data gathering that is intended to reduce it. In this way, more detailed discussion of potential direct benefit can help both to correct the therapeutic misconception and to minimize the temptation to overestimate direct benefit.[20]

Countering the therapeutic misconception and the overestimation of direct benefit is increasingly difficult, however, for several reasons. First, emerging biotechnologies don't always demonstrate predictable dose-response relationships; thus it is often less than clear how the potential benefits and risks of harm should be described and discussed in first-in-humans and other early-phase research studies. A paucity of good preclinical data — attributable to many factors, including the lack of good animal models — contributes to this uncertainty, and can contribute to inflated expectations about study participation.

Second, changes in translation and study design have increased the likelihood of potential direct benefit in many trials. For example, research with a surgical component (which includes much regenerative medicine research) can be challenging to conduct on subjects who are not patients. Thus, enrolling only patients as subjects in early-phase research increases both the expectation of, and perhaps also the potential for, direct benefit. This development mirrors the challenges already posed by phase I oncology trials to accuracy, clarity, and honesty in the consent form and process.[21]

In addition, gene-based intervention research is increasingly conducted with children and other treatment-naive patients as the first subjects. This is in part because genetic interventions, if effective at all, are more likely to be effective early in the disease course, and effective levels are often easier to achieve in younger, smaller patient-subjects. Both of these factors also increase expectations of direct benefit.[22]

Third, learning health care systems, community-engaged research, quality assessment and improvement activities, and system-based designs like cluster randomization, which bypasses individual decision-making, have all helped to blur the distinction between research and treatment, deemphasize information-sharing and the consent process, and suggest that most (if not all) health-related research interventions are equivalent to "new treatments." Comparative effectiveness research offers one useful example of the difficulty. When two standard or commonly used treatments are compared in a clinical trial, it is tempting to characterize participation in that trial as without added risks of harm beyond what is known

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about both treatments, and thus as meriting little or no disclosure. However, a meaningfully specific consent form and process should at least explain that the treatment to which a patient-subject is randomized in the trial might be different from what the physician or hospital would recommend outside the trial context.[23]

Finally, both science journalism and popular media, increasingly in search of clickbait, are more likely to contribute to the hype about experimental interventions that are being studied than they are to support and promote understanding of the uncertainties that necessarily play a role in medical advances. Social media hype plays a significant role as well; for example, discussion of the Charlie Gard case in media and social media,[24] Change.org petitions for access to expensive and/or unproven interventions,[25] and GoFundMe efforts to raise the large sums of money sought by shady stem cell clinics[26] all support heightened expectations of direct benefit that are often unwarranted.

What makes the research informed consent process, and its memorialization in the consent form, so important that it warrants the addition of key information? Well, for one thing, there is at least some evidence that the consent process follows the consent form. It is unusual for a study team member to tell a potential subject: “We have to say that in the consent form, but you can ignore it, because here’s the truth.” Instead, clear, cogent, and accurate information in the consent form shapes a clear, cogent, and accurate discussion in the consent process.

For all of these reasons, an IRB’s determination that saying less about potential benefit is preferable is not a solution for the problem of the therapeutic misconception. It could of course be argued that the therapeutic misconception is not, in at least some of these new circumstances, a misconception at all. Yet even if the distinction between research and treatment is genuinely blurrier now than it has ever been, it is still true that receiving treatment as part of a research study suggests some potentially important differences in data-gathering and use, and perhaps other relevant design features. That makes for something different from ordinary treatment, and warrants disclosure about those differences, at the very least — even if some of these differences are becoming ubiquitous as learning health care systems grow.

Information and Consent

What makes the research informed consent process, and its memorialization in the consent form, so important that it warrants the addition of key information? Well, for one thing, there is at least some evidence that the consent process follows the consent form.[27] It is unusual for a study team member to tell a potential subject: “We have to say that in the consent form, but you can ignore it, because here’s the truth.” Instead, clear, cogent, and accurate information in the consent form shapes a clear, cogent, and accurate discussion in the consent process. It is worth remembering that informed consent encourages self-scrutiny by the physician-investigator.[28] The mere exercise of putting clear information on paper and saying it out loud — not just mechanically cutting and pasting from the protocol into the consent form template — is an exercise of moral imagination and relationship-creation with research subjects.

Study teams and IRBs could learn even more from research subjects if they routinely asked them to contribute their views of the consent form and process. For instance, a simple exit interview or survey could help investigators learn a great deal about how consent forms are understood and about barriers to and facilitators of a good consent form and process.[29] In fact, some research into assessing patient-subjects’ research experiences has begun, using standardized surveys administered through patient portals.[30] More would be even better. It is possible to envision a standard starting question set, designed for short open-ended responses:

- Did the consent form and process prepare you for being in this clinical trial? Why or why not?
- Did you have other questions? What were they?
- Did you need/ask for more information during the trial? Why or why not?
- What other information could have helped you if you had known it sooner? Why?
- What information didn’t you need? Why not?
- What should have been explained more clearly? In more or less detail?

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- What were the most important things for you about the trial/your experience in the trial? Why?
- What were the least important things for you about the trial/your experience in the trial? Why?
- How would you explain this trial to somebody thinking about joining?

An exit survey like this doesn't directly inform future trials, of course. Still, it seems to me that learning how now-experienced research subjects view the consent form and process after participating could teach study teams a lot about how to approach the consent form and process for the next trial, whatever that trial may be.

SACHRP Key Information Commentary

Even if I have convinced some readers that the inclusion of key information makes sense, it's understandable that IRBs and investigators want guidance about it. So, in December 2017, the Office for Human Research Protections (OHRP) and the Food and Drug Administraiton (FDA) asked the Secretary's Advisory Committee on Human Research Protections (SACHRP) a set of questions, the answers to which could potentially form the basis of a joint guidance on the new key information requirement. The final version of SACHRP's commentary, which includes recommendations, was submitted to the Secretary of the Department of Health and Human Services in November 2018.[31]

The commentary tries hard to address the compliance-vs.-flexibility problem, emphasizing that SACHRP sees "these new consent requirements as providing an opportunity to fundamentally change and improve the consent process and the consent form" while admitting that "the best solutions are not immediately apparent" but that "the new requirements provide the regulatory mandate and the flexibility to test and implement substantial improvements."[32] However, in responding to OHRP's questions about what should be included in key information and how it should be discussed, SACHRP's answers are probably best characterized as "it depends," as they focus more on encouraging the regulated community to be creative, in particular by organizing information differently, than on enumerating specifics.

The commentary emphasizes that the key information summary should be regarded "as an opportunity to orient, guide, and assist potential subjects in the decision-making process,"[33] and argues that it "should lead to new ways of organizing and presenting the required elements of consent, and … to the inclusion of new information … in order to best facilitate informed decision making."[34] It concludes by noting the flexibility inherent in e-consent and similar new models, calling for ongoing empirical research and collaboration, and observing that "the Common Rule agencies and the regulated community have a significant opportunity to make the informed consent process better for research subjects."[35] Thus, the commentary reinforces the message that creativity is welcomed, but this may not satisfy those in search of more specificity and certainty.

Conclusion

Nobody likes uncertainty. What makes the new key information summary requirement unique — its open-ended call to focus consent forms on supporting and promoting informed decision-making based on the reasons a potential subject might or might not choose to enroll in a given study — is precisely what makes some IRBs and investigators nervous about it. Key information is not a checklist; it is meant to be a way of introducing potential subjects to the decision-making process and of providing essential information in a format calculated to facilitate choices that are reasonable under the circumstances. This perspective demands flexibility, but the regulated community, worried about compliance, is more likely to demand certainty. Thus, the key information summary could easily become a battleground between compliance certainty and creative flexibility.

The tension between compliance and ethics that is exemplified by the regulated community's concerns about the key information summary cannot be resolved by the simplistic request that IRBs and PIs be creative, or by the simple promise of flexibility (or even of "enforcement discretion"). Key information actually expects more from IRBs and investigators — it asks them to avoid waiting passively for direction from OHRP and instead to continue critically reflecting on the role that they themselves should play in protecting the rights and interests of research subjects while all contribute to the process of clinical translation. In other words, a key component of the IRB's role and investigators' responsibility is to develop better ways of communicating effectively with potential subjects, to make use of those new communication models, to test their effectiveness in facilitating informed decision-making about research participation, to explain and justify their use to OHRP, and to share them with the regulated community. This is work that already happens throughout the regulated community, and that enriches it greatly when shared broadly and thoughtfully. Yet it still may be viewed by some IRBs and investigators as beyond their pay grade. The

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revisions to the Common Rule ought to change that. Human subjects protection programs should not be governed by a risk management mindset.

But that is far easier to say than to do, as the passive risk management mindset is an overall system issue that cannot be corrected by one small change to the Common Rule, no matter how potentially significant it could become. In this respect, the key information summary operates in concert with patient-centered outcomes research, "citizen science," increased efforts in education and outreach about research with human subjects, and the many ways to involve patients, patient groups, and patient-subjects in all stages of research, from community engagement to design advice to consent form review. Perhaps the most important and most challenging aspect of the new key information requirement is its iterative nature — that is, a model of dialogue, research, review, redo, and repeat is required in order to continually improve the information exchange that is essential to supporting, promoting, and making reasonable decisions about research participation under all the relevant circumstances.

This iterative learning process is a far cry from the one-time drafting and approval of a multipage paper consent form that is plucked directly from the protocol. As Capron notes, regarding informed consent as an isolated moment in the physician-patient or the researcher-subject relationship means that the opportunity has been lost to help patients or patient-subjects "understand their medical care within the context of their life stories and the choices they make."[36] The iterative process that is needed also mirrors the learning cycle by which science proceeds. Importantly, that process is itself only now being recognized as very different from the straight and speedy shot from bench to bedside that is the popular but unrealistic model of research success (a model which, by the way, also contributes to the therapeutic misconception).[37]

The real, complex, sometimes meandering path of genuine learning appears difficult and time consuming. However, it may be surprisingly easy to build on the burgeoning e-consent format to accomplish much of this ambitious new agenda of learning how to support and promote reasoned decision-making in human research. E-consent models can exhibit great flexibility, highly user-friendly design, multimedia formats for conveying information, including links to other content and further learning, and ways to help promote reading and understanding rather than the click-through-to-accept behavior common in smartphone use.[38]

Despite its support among many in the scholarly and regulated communities, this broad and deep approach to key information may not be an easy sell. Nonetheless, the key information summary is as good a try as any at simultaneously improving both knowledge production and science's service to society. Whether key information can begin to make the researcher-subject collaboration more meaningful depends on whether the individuals who become research subjects actually continue to matter as subjects, rather than as objects solely of administrative value. In fact, Capron notes that research informed consent ought to be singularly able to promote this collaboration, since uncertainty is inherent in research and therefore does not threaten the researcher-subject relationship: "Indeed, to genuinely involve a patient in research is to make the resolution of that uncertainty a part of the patient's narrative of his illness and of his life."[39]

And that is why doing more research on what potential subjects want to know, and thinking together more carefully about what they need to know, really matters, and why involving them more deeply in research matters too. But even more than that, self-scrutiny matters, because those who regulate research need to do a better job of acknowledging the ethical duties and responsibilities of clinical investigators, as well as those of IRBs (including their ever-ballooning numbers of midlevel administrative staffers). Even if it offers an imperfect solution, the key information summary may get us closer to acknowledging the problems that have been created by viewing research subjects primarily as data providers.[40] If research informed consent can ever be more than a bare means of minimizing harm — if, as SACHRP reminds us, it is really intended to be about respect for persons[41] — then the key information summary may be a long-needed step toward making mutually respectful researcher-subject relationships truly meaningful in clinical research.

Note

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14. This history is described far more thoroughly and eloquently in A. M. Capron, "Where Did Informed Consent for Research Come From?" *Journal of Law, Medicine & Ethics* 46, no. 1 (2018): 12-29. See also R. Dresser, "The Reasonable Person Standard for Research Disclosure: A Reasonable Addition to the Common Rule," *Journal of Law, Medicine & Ethics* 47, no. 2 (2019): 194-202, for a perspective on the reasonable person standard that is complementary to and more complete than my own.
15. See N. M. P. King, "The Reasonable Patient and the Healer," *Wake Forest Law Review* 50 (2015): 343-361.
16. R. Dresser, *Silent Partners: Human Subjects and Research Ethics* (New York: Oxford University Press 2017). See also S. A. Kraft et al., "Comprehension and Choice Under the Revised Common Rule: Improving Informed Consent by Offering Reasons Why Some Enroll in Research and Others Do Not," *American Journal of Bioethics* 17, no. 7 (2017): 53-55, and J. Sugarman, "Examining Provisions Related to Consent in the Revised Common Rule," *American Journal of Bioethics* 17, no. 7 (2017): 22-26.
17. I've drawn this formulation from M. Powers and R. Faden's discussion of a range of justice theories in *Social Justice: The Moral Foundations of Public Health and Health Policy* (New York: Oxford University Press 2006), e.g., p. 191. The analogy is based on thinking about justice beyond questions of distribution, focusing instead on substantive determinations of what societies owe their members — and, in this context, on what information the research enterprise owes potential subjects as reasonable persons.
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19. N. M. P. King, "Defining and Describing Benefit Appropriately in Clinical Trials," *Journal of Law, Medicine & Ethics* 28, no. 4 (2000): 332-343.
20. N. M. P. King, G. E. Henderson, L. R. Churchill, et al., "Consent Forms and the Therapeutic Misconception: The Example of Gene Transfer Research," *IRB: Ethics and Human Research* 27, no. 1 (2005): 1-8; S. Horng and C. Grady, "Misunderstanding in Clinical Research: Distinguishing Therapeutic Misconception, Therapeutic Misestimation, and Therapeutic Optimism," *IRB: Ethics and Human Research* 25, no. 1 (2003): 11-16. Even though the distinction between research and treatment has always been far more nuanced than the sharp dichotomy that is often posited (see, e.g., T. L. Beauchamp and Y. Saghai, "The Historical Foundations of the Research-Practice Distinction in Bioethics," *Theoretical Medicine and Bioethics* 33, no. 1, (2012): 45-56), the value of distinguishing between research and treatment, based not primarily on risks of harm but on information provision and mutual education, remains vital.
21. S. A. Koyfman, M. S. McCabe, E. Emanuel, and C. Grady, "A Consent Form Template for Phase I Oncology Trials," *IRB: Ethics in Human Research* 31, no. 4 (2009): 1-8.
22. N. M. P. King and O. Cohen-Haguenauer, "En Route to Ethical Recommendations for Gene Transfer Clinical Trials," *Molecular Therapy* 16, no. 3 (2008): 432-438.
23. Knowing what a particular hospital or practice would recommend outside the context of a comparative effectiveness trial is site-specific information that could be very useful to patients who are potential subjects, especially if the points of comparison are described. See, e.g., C. Feudtner, M. Schreiner, and J. D. Lantos, "Risks (and Benefits) in Comparative Effectiveness Research," *New England Journal of Medicine* 369, no. 10 (2013): 892-894. The differences between participating in comparative effectiveness research and receiving treatment outside the research context thus may not be measurable as changes in risks of harm, but they are readily describable nonetheless.
24. "Charlie Gard: The Story of His Parents' Legal Fight," BBC News, July 27, 2017, *available* at <https://www.bbc.com/news/health-40554462> (last visited March 20, 2019); S. Begley, "Trump Tweeted About a Dying Boy. Here's What You Need to Know About His Rare Disease," *STAT News*, July 3, 2017, *available at* <https://www.statnews.com/2017/07/03/trump-tweet-dying-boy/> (last visited March 20, 2019); "Parents of Charlie Gard Raise £1.2m for Pioneering Treatment," *BBC News,* April 2, 2017, *available at* <https://www.bbc.co.uk/news/uk-england-london-39471712> (last visited March 20, 2019).
25. E.g., Petition: "Dear Biogen Company," Change.org, *available at* <https://www.change.org/p/biogen-idec-dear-biogen-company-please-gift-kiana-compassionate-use-of-spinraza-she-deserves-treatment?j=377479&sfmc_sub=416434023&l=32_HTML&u=64606725&mid=7233053&jb=1713&utm_medium=email&utm_source=aa_sign_human&utm_campaign=377479&utm_content=&sfmc_tk=Wz7V9pgtrCGuxMfvFP8fnFSrHVGTui6r0JrDBSXnH8NZsECw8Wo3GdxvEsAzcuiu&j=377479&sfmc_sub=416434023&l=32_HTML&u=64606725&mid=7233053&jb=1713> (Last accessed Jan. 8, 2019). See also, e.g., N. M. P. King and C. E. Bishop, "New Treatments for Serious Conditions: Ethical Implications," *Gene Therapy* 24, no. 9 (2017): 534-538; K. Tay-Teo, A. Ilbawi, and S. R. Hill, "Comparison of Sales Income and Research and Development Costs for FDA-Approved Cancer Drugs Sold by Originator Drug Companies," *JAMA Network Open* 2, no. 1 (2019): e186875, doi:10.1001/jamanetworkopen.2018.6875, at 7/11; C. Klugman, "Cute with a Good Story: How Social Media Selects Experimental Subjects," April 1, 2014, *available at* <http://www.bioethics.net/2014/04/CUTE-WITH-A-GOOD-STORY-SOCIAL-MEDIA-SELECTS-EXPERIMENTAL-SUBJECTS/> (last accessed Jan. 8, 2019).
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27. G. E. Henderson, A. M. Davis, N. M. P. King, et al., "Uncertain Benefit: Investigators' Views and Communications in Early Phase Gene Transfer Trials," *Molecular Therapy* 10, no. 2 (2004): 225-231, at 229.
28. A. M. Capron, "Informed Consent in Catastrophic Disease Research and Treatment," *University of Pennsylvania Law Review* 123, no. 2 (1974): 341-438 at 371-374.

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32. *Id.*
33. *Id.*
34. *Id.*
35. *Id.*
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37. J. Kimmelman, *Gene Transfer and the Ethics of First-in-Human Research: Lost in Translation* (New York, NY: Cambridge University Press, 2009). Recent controversy about the so-called Chinese CRISPR babies has only reinforced the need to change that popular and dangerous view of research progress. See, e.g., two summaries of these claims and responses to it that provide an overview: S. Begley and A. Joseph, "The "CRISPR Shocker: How Genome Editing Scientist He Jiankui Rose from Obscurity to Stun the World," STAT, Dec. 17, 2018, *available at* <https://www.statnews.com/2018/12/17/crispr-shocker-genome-editing-scientist-he-jiankui/> (last accessed December 26, 2018); E. Yong, "The CRISPR Baby Scandal Gets Worse by the Day," *The Atlantic*, Dec. 4, 2018, *available at* <https://www.theatlantic.com/science/archive/2018/12/15-worrying-things-about-crispr-babies-scandal/577234/> (last accessed December 27, 2018).
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