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Target Article

Reframing Consent for Clinical Research: A Function-Based Approach

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Although informed consent is important in clinical research, questions persist regarding when it is necessary, what it requires, and how it should be obtained. The standard view in research ethics is that the function of informed consent is to respect individual autonomy. However, consent processes are multidimensional and serve other ethical functions as well. These functions deserve particular attention when barriers to consent exist. We argue that consent serves seven ethically important and conceptually distinct functions. The first four functions pertain principally to individual participants: (1) providing transparency; (2) allowing control and authorization; (3) promoting concordance with participants' values; and (4) protecting and promoting welfare interests. Three other functions are systemic or policy focused: (5) promoting trust; (6) satisfying regulatory requirements; and (7) promoting integrity in research. Reframing consent around these functions can guide approaches to consent that are context sensitive and that maximize achievable goals.

Keywords: informed consent, research ethics

Informed consent is the most widely recognized and endorsed ethical norm for clinical research. Yet questions persist regarding when it is necessary, what it requires, and how it should be obtained. For example, recent debate over whether consent is needed for research on standard medical practices points to fundamental questions regarding its purpose and goals (Truog et al. 1999; Kim and Miller 2014; Platt et al. 2014; McKinney et al. 2015). Similarly, it is widely agreed that adults with decisional impairments and adolescents should be involved—consistent with their capacity—in decisions about whether they are enrolled in research (U.S. Department of Health and Human Services 2009a; Wendler 2006). Yet it remains unclear what justifies this requirement and how it should be implemented.

The standard view in bioethics and clinical research grounds the requirement to obtain informed consent in respect for individual autonomy (National Commission for the Protection of Research Risks 1979; Faden and Beauchamp 1986; Beauchamp and Childress 2001; Grady 2015). Specifically, the function of the informed consent process is to allow individuals to decide, based on their own preferences and values, whether they want to enroll in a particular study. While this analysis is consistent with

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traditional understanding of autonomy, it omits several other distinct and often underrecognized functions that consent promotes. For example, while information disclosure facilitates consent's autonomy-respecting function, it also promotes transparency, integrity, and trustworthiness. These functions each have independent ethical value.

Standard research consent processes typically realize many different functions, serving many different goals. However, there are important reasons to distinguish among and clarify these functions. First, the extent to which each function can and should be realized in a given case is a matter of degree. Distinguishing these functions puts investigators and review committees in a position to develop context-sensitive approaches to consent for specific studies. Tailoring the consent process to emphasize specific functions can be especially important when some functions are more important than others to the study in question. For example, if multiple other measures are in place to ensure transparency, the role of the consent processes in providing transparency may be less critical. More importantly, there are situations in which it is not possible to implement an in-depth consent process that realizes all of the functions. In these situations, distinguishing the functions of consent can allow investigators and review committees to develop and implement a consent process that realizes achievable functions and to design additional mechanisms to advance other consent-related functions that cannot be realized by consent.

The term "consent" is typically limited to in-depth, written consent that allows individuals time to consult with others and to make a decision. However, for present purposes, we use the term broadly to refer to processes across the entire spectrum of involvement, from simply informing an individual that an activity involves research, to providing a brief description of the study and allowing individuals to opt out, to obtaining in-depth written consent.

We argue that consent processes can serve one or more of four participant-centered ethical functions: (1) providing transparency; (2) allowing control and authorization; (3) promoting concordance with participants' values; and (4) protecting participants' welfare interests. In addition, we describe three systemic or procedural functions that are more policy focused: (5) promoting trust; (6) satisfying regulatory requirements; and (7) promoting the integrity of research and researchers. These functions derive from both conceptual reflection and empirical scholarship and are widely recognized to be ethically important concepts in clinical research.

CLARIFYING THE PROBLEM

There are at least three reasons to reframe the way we think about the functions of informed consent for clinical research. First, the assumption that individual autonomy alone can account for the ethical importance of consent ignores the fact that involving individuals in decisions about their research participation is a multidimensional process that serves a number of important emotional, professional, and societal functions with various ethical underpinnings (Capron 1974, Eyal 2012, Wertheimer 2014). While an expansive interpretation of respect for persons (not just for autonomy) may accommodate and undergird functions not related to autonomy, it may not capture them all (Dickert 2009). Moreover, broad interpretations of this principle may not provide sufficiently specific guidance to inform research consent in practice.

Second, there are situations in which regulations appropriately permit waivers of standard in-depth consent. In these situations, an emphasis on respect for autonomy alone may lead to the belief that there is no reason to involve potential subjects in the process of deciding whether they are enrolled. However, attention to multiple functions of consent may reveal meaningful ways to involve potential subjects in deciding whether they are enrolled. Patients having a heart attack, for example, may be asked to participate in a randomized trial while being prepared for emergent catheterization. Although heart attack patients generally express a desire to be involved in enrollment decisions, it is difficult in that setting to imagine making a fully informed and autonomous enrollment decision about whether to enroll (Gammelgaard, Rossel, and Mortensen 2004; Dickert et al. 2015; Dickert and Miller 2015). In fact, limitations in understanding of research participation appear to be more common than many accounts recognize. The concept of randomization, for example, can sometimes be difficult for potential participants to comprehend (Snowdon, Garcia, and Elbourne 1997; Kodish et al. 2004; Mandava et al. 2012). And the fields of decision science and behavioral economics continue to highlight ways in which subtle variations in language and decision structure substantially affect participants' understanding and the choices they make (Featherstone and Donovan 1998; Featherstone and Donovan 2002; Wendler 2009; Weinfurt et al. 2012). Understanding the key functions of consent is essential in order to design processes that advance achievable goals in cases where it is not possible to achieve all of them. In contrast, invoking a global concept of autonomy can lead to all-or-none decisions about consent.

Third, existing regulations and guidelines tend to promote a one-size-fits-all approach to consent. The Common Rule, for example, articulates a list of essential elements that must be disclosed prior to obtaining consent for all clinical trials. Proposals to omit even one item may be approved only when the study qualifies for a waiver or alteration of consent (U.S. Department of Health and Human Services 2009b; Kim and Miller 2016). Yet the same elements may not be important for every study. For example, there may be studies for which it is ethically necessary to obtain consent due to medical risks, even though it is not ethically meaningful to disclose "the extent, if any, to which confidentiality of records identifying the subject will be maintained" (U.S. Department of Health and Human Services 2009b). This may be the case in studies where the entire research team is local and confidentiality risks are essentially absent. A more fine-grained, function-

based approach may similarly help in operationalizing international guidance documents such as the Council for International Organizations of Medical Sciences (CIOMS) guidelines and the Declaration of Helsinki (World Medical 2013; Council for International Organizations of Medical Sciences 2016).

FUNCTIONS OF CONSENT

Providing Transparency

Perhaps the simplest function that consent processes serve is to make individuals aware that research is taking place and to explain the nature of the study in question. Describing a study to potential participants is often a precursor to obtaining their agreement to enroll. But transparency can have ethical value independent of any decision. It helps participants to appreciate what they are involved in, avoids or minimizes deceit, and conveys a message that they are respected as persons. It also can reduce the stress of uncertainty and may play an important role in educating individuals about research.

Transparency can be achieved to different degrees and through numerous mechanisms, only some of which involve an individualized consent process. System-wide announcements about a study being conducted within a health system have been proposed as one alternative mechanism for providing transparency when individual consent is not sought (Faden, Beauchamp, and Kass 2014). Similarly, the importance of transparency is context dependent, and both the extent and timing of disclosure matter. For example, while disclosure is generally viewed as beneficial, it is possible that providing very detailed study information at initial enrollment may be distressing or overwhelming; it may even generate a harmful "nocebo" effect (Cohen 2014).

Allowing Control and Authorization

If providing transparency is the simplest function that consent processes serve, enabling individuals to make participation decisions themselves is the most obvious. At the most basic level, obtaining consent respects individual liberty. It allows participants, rather than investigators or others, to decide whether to enroll or to continue to participate in a study. This is important, given that research participation is not generally considered obligatory and can involve risks to participants that are not justified by individual benefit.

The threshold for granting individuals control over their research participation is often exceedingly low. In this respect, a consent process can allow control even in situations where individuals are substantially nonautonomous. For example, we typically accept an individual's decision to decline participation in a research study without requiring her to provide any reasons or to demonstrate either decision-making capacity or understanding of the study. Similarly, the ethical importance of control is one of the main reasons researchers seek assent from adults with cognitive impairment. This also supports providing an opportunity for acutely ill patients to refuse being enrolled in research in emergency settings, even for studies that have been approved under the exception from informed consent (EFIC) mechanism (Dickert et al. 2016). Finally, considerations of liberty provide a reason to consider obtaining consent even when a study poses no added risks and there is no reason to think enrollment might conflict with the individual's values.

To enroll individuals in research that intrudes on bodily integrity or privacy, it is often not sufficient simply to give individuals control over whether enrollment occurs; authorization of enrollment by that individual becomes important. Authorization requires voluntary agreement from a competent individual who has been sufficiently informed, or has had a fair opportunity to be informed, about the study (Faden and Beauchamp 1986; Miller and Wertheimer 2011). Ethically valid authorization has significant justificatory force in making it ethically acceptable for an investigator to enroll a particular individual in a study (Miller and Wertheimer 2010). Merely allowing individuals to control whether enrollment occurs does not have the same potential to alter the permissibility of enrollment.

An example of the progression along the spectrum from control to authorization is the process of assent with pediatric participants. Assent allows young children to control whether they are enrolled in research, but they cannot authorize enrollment. As children become older and more cognitively developed, their capacity for real authorization grows, and eventually parental permission may serve a primarily legal rather than ethical function.

Promoting Concordance With Participants' Values

Consent processes can enhance the extent to which individuals' decisions whether to enroll and continue to participate in research reflect "who they are" and what they care about. In other words, consent can facilitate authentic decisions that reflect their values (Brudney 2009). Promoting concordance with participants' values in research aligns with a general emphasis on respecting individual values and shared decision making in clinical medicine and has particular importance in situations where individuals face very different options within a research protocol. For example, one arm of a study may involve an invasive surgical treatment with a potential for high rate of cure but an appreciable risk of mortality. The other arm may be a medical therapy with few side effects but a potentially lower rate of cure. The consent process for this type of trial can help individuals to assess whether both options, as well as being involved in the study, are consistent with what they care about. Similarly, in research with stored tissues, consent can be used to allow participants to make decisions that minimize the chances that their tissues are not used in ways that conflict with their values. Various forms of consent, for example, have been proposed to avoid recurrence

of situations such as the Havasupai Indian tribe case (Mello and Wolf 2010).

Obtaining consent is not the only way to ensure coherence with individuals' values. Some individuals with advanced dementia, for example, may retain key values (or previously espoused values that have not obviously changed) despite losing the ability to make fully competent contemporaneous decisions. Processes designed to identify and incorporate those values, such as conversations with family or research advance directives, may advance the extent to which enrollment decisions cohere with them in circumstances in which the individual cannot achieve this alone (Jaworska 1999; Kim and Karlawish 2003; Brudney 2009).

Protecting and Promoting Welfare Interests

Investigators and institutional review boards (IRBs) are charged with protecting individuals from research risks. This is largely done through ensuring that the research design minimizes risks and does not unnecessarily involve participants forgoing otherwise expected clinical benefits. However, as a buffer against error and abuse and because individuals often have special insight into what constitutes benefits and harms for them, consent provides an individualized supplement to IRBs' and investigators' roles in promoting the welfare interests of potential participants as a group. Specifically, engaging individuals in enrollment decisions can reveal unanticipated ways in which participation may affect them. Telling a potential participant that an interview study will involve questions about past drug use or abuse, for example, may allow that person to recognize that participation may be traumatic or risky for him. Similarly, disclosing a list of potential contraindications or exclusion criteria may enable a potential participant to recognize that enrollment would be particularly risky for her. Note that in both of these cases, the function of consent is not merely to allow the individual to weigh or evaluate unique risks but rather to ensure that these risks are included in the weighing process.

The four functions of the consent process just described are focused on the interaction between a participant and an investigator. Any given instance of a consent process may engage each of these four functions to a greater or lesser extent. However, consent processes, when instituted and practiced as a matter of policy or within a system, serve three further important functions.

Promotion of Public Trust

Analyses that focus on the rights and well-being of current research participants can underestimate the social value of consent processes or norms. Clinical research, after all, is designed to generate knowledge that contributes to the public good, is often funded by public resources, and is becoming increasingly integrated into many health care delivery systems. Assuring the public that individual participants are involved in enrollment decisions can help to maintain trust in the research enterprise, especially given what appear to be widespread expectations and preferences for informed consent even in low-risk studies (Kass et al. 1996; Eyal 2014; Cho et al. 2015; Nayak et al. 2015). The involvement of individuals using appropriate consent processes can also demonstrate trustworthiness of investigators, institutions, and sponsors. Recognition of the role that consent processes play in promoting trust highlights the need for additional steps to achieve this goal when consent is impossible. For example, community engagement activities are required for studies conducted under the exception from informed consent for research in emergency settings. One important function of these processes is to promote and maintain public trust (U.S. Department of Health and Human Services and Food and Drug Administration 2013).

Adherence to Regulatory Requirements

Research regulations are intended to reflect and have their roots in key ethical principles. To this extent, satisfying regulatory requirements may help to ensure that other goals are advanced. Regulations also promote important policy goals, play a key role in legitimating research activities, and provide measures of legal protection to investigators who follow them. The function of meeting regulatory requirements is, in some sense, a more explicitly practical and concrete function than some of the others described. However, it is an important function nonetheless; to the extent that consent is required by laws and regulations, compliance with those laws and regulations is a valuable function of consent processes.

Promoting Professional Integrity of Research and Researchers

A final function of involving participants in enrollment decisions is to promote the integrity of the research enterprise, which includes investigators, institutions, and the public that benefit from the conduct of clinical research (Wertheimer 2014). Clinical research entails investigators and, by implication, their institutions imposing risks and burdens on individual participants. As a result, there is a collective obligation to ensure that this is done correctly and only when appropriate. Consent helps to demarcate activities done for research purposes that represent deviations from standard clinical practice and it provides an opportunity for investigators, regulators, review boards, and potential participants to assess potential reasons why enrollment would be inappropriate. In addition, consent helps to ensure accountability to key stakeholders. It can also force investigators to be honest with themselves and to become the kind of researcher who would seek the consent of enrollees (Eyal 2015). Instituting policies and practices of requiring consent thus helps to demonstrate and promote a culture of respect for participants that helps to maintain integrity.

GENERAL PRACTICAL IMPLICATIONS

The function-based approach has several practical advantages over the standard approach. Most importantly, by unpacking consent into its functional components, we can engage in a more fine-grained analysis of consent needs and processes across the range of real contexts in which research takes place. This is particularly evident when considering processes for involving individuals in research decisions that do not fulfill traditional conceptions of written informed consent. For example, the present framework clarifies why a brief oral consent process that provides only the most basic information and leaves out some traditionally required elements of informed consent (e.g., contact information, confidentiality statements, etc.) may be both necessary and sufficient in the context of a low-risk pragmatic trial. Such a process may provide transparency, allow control, and promote trust. It does not play a substantial role in protecting welfare interests, but this is not necessarily problematic since the risk is already very low. This process also may do little to promote concordance with participants' values, but this also may be acceptable if a study does not engage preference-sensitive decisions. Clarifying what functions such a process can serve provides a reason to require some level of engagement rather than waiving consent altogether. And clarifying what functions such a process will *not* advance can demonstrate a need for alternative methods of advancing those functions in some cases (such as rigorous scientific and IRB review to ensure that research risks are low).

Second, the function-based approach helps us to address and understand a perennial paradox in discussions of informed consent: Often, attempts to "enhance" consent seem to be counterproductive. This is due to the fact that although the seven functions we have proposed can overlap and complement one another, they can also conflict. For example, attempts to promote trust or increase participant understanding through exhaustive disclosure of the details of a study may overwhelm individuals with so much information that their ability to provide meaningful authorization or to advance their preferences or values may be compromised. Such extensive disclosure may also contribute to the perception that trivial risks are more risky than they really are, or even suggest that a study poses significant risks when in fact it does not. The function-based approach helps to identify and clarify these trade-offs, though how they should be balanced remains an area for further study and a challenge for investigators and review boards to address in practice.

A third advantage of the function-based approach is that it facilitates a context-sensitive rather than a one-size-fits-all approach to consent. Just as there is no reason to believe that a unified conceptual theory can account for all valuable functions of informed consent, there is no reason to believe that all functions are equally necessary across all studies. To continue the example of a low-risk pragmatic trial, the need to promote concordance with patients' values and preferences regarding each intervention is likely to be less important when the choice is not preference sensitive. And the emphasis on context sensitivity should help investigators and IRBs to recognize and attend to the fact that a consent strategy that may help potential participants to feel valued and respected in one context may have very different effects in other settings. Providing detailed information to potential participants about an outpatient oncology trial, for example, may be perceived as respectful, whereas similarly extensive disclosures regarding biobanking may be seen as confusing or even disrespectful.

A final broad practical advantage of this approach is its ability to identify challenges and barriers to informed consent and focus empirical scholarship to help identify optimal approaches across various research contexts. For example, studies focused on the impact of different consent strategies on participants' understanding or awareness of study features may help to clarify the best methods for achieving transparency and providing an opportunity for authorization. Similarly, studies evaluating the extent to which participants value transparency in different contexts can help investigators and IRBs to determine both the relative importance of transparency compared to other functions and the level of detail that is needed to sufficiently advance this function. Implicit in both of these examples is the importance of evaluating the emotional impact of various consent strategies. While attending to emotional needs is not a specific function of consent processes, conducting consent in ways that express respect to participants is essential, and empirical scholarship can refine ways to advance key functions while attending to emotional needs of real patients in real clinical contexts.

SPECIFIC APPLICATIONS IN THE PRESENCE OF BARRIERS TO CONSENT

Research in Acute Illness

In research in acute settings such as ST-elevation myocardial infarction (STEMI), it is hard to imagine how a traditional informed consent process that theoretically allows potential participants to make autonomous enrollment decisions might be possible. The recent Unfractionated Heparin Versus Bivalirudin in Primary Percutaneous Coronary Intervention (HEAT-PPCI) trial provides a helpful example. In this trial, patients with active STEMI were randomized to one of two anticoagulant medications within minutes of arrival at the emergency department (Shahzad et al. 2014). Both medications were approved for this indication based on rigorous clinical trial data and considered standard treatments, but anticoagulation carries real bleeding risks and can affect mortality and morbidity in treatment of STEMI. It was unclear at the time of the trial which of these two drugs was superior in safety and efficacy; the motivation for the trial was to assess the impact of the two medications on these outcomes. This question had particular significance given the substantial cost differences between these two drugs. In this clinical setting, a

patient is typically not engaged in the choice about which anticoagulant is used (or even that one will be used at all), and trial investigators believed that patients would not be able to meaningfully understand the risks and benefits and make an informed decision regarding inclusion in the randomized trial. For all of these reasons, in addition to a desire to prevent selection bias in a pragmatic trial, investigators and others argued that the trial should be conducted without prospective consent (Shaw 2014). The trial was thus approved by an IRB under British guidelines allowing for "deferred consent" in the emergency setting.

The HEAT-PPCI investigators' concerns about prospective consent in this context were legitimate, and existing empirical data suggest that decisions about research participation in the context of acute myocardial infarction (MI) are rarely well-informed (Ågard, Hermerén, and Herlitz 2001; Agard, Herlitz, and Hermeren 2004; Gammelgaard, Rossel, and Mortensen 2004; Dickert et al. 2015). However, recognition that informed consent has a number of important functions suggests that engaging patients in enrollment decisions in this context could still be ethically meaningful (Dickert and Miller 2015). First, briefly describing the existence of the study at the time of enrollment promotes transparency by informing patients what the activity involves. Second, even the simplest opt-out process could give patients control by providing an opportunity to refuse. Third, the choice to involve patients in whether they are enrolled in the study may bolster public trust. Fourth, it may promote the integrity of researchers and the institution by providing accountability and by demonstrating a lack of presumption on the part of researchers that they know what patients might want in this circumstance.

The function-based approach also clarifies what abbreviated involvement in research decisions would not do in a trial like HEAT-PPCI. Investigators cannot be confident that agreement to be enrolled during STEMI implies that study participation substantially aligns with patients' preferences or values. Similarly, acutely ill patients are not likely to be good stewards of their welfare interests in the context of complex decisions. In these respects, partial involvement does not contribute substantially to justifying risk exposure, and it does not provide ethically valid authorization. However, when independent review determines that a trial poses relatively low incremental risks over standard care for the condition (as in trials such as HEAT-PPCI), these functions may be less critical.

Research on Standard Medical Practices

The function-based approach also contributes importantly to the active debate over the need for consent in the context of trials of standard medical practice embedded within learning health systems (Platt et al. 2014; Sugarman and Califf 2014). Extensive or lengthy consent processes may make such trials impracticable due to a combination of time and resource constraints and due to the fact that primary clinical staff (who may not know the trial well) may be principally responsible for enrollment (Kass, Faden, and Tunis 2012, Faden et al. 2014). In addition, because these trials often involve low risks compared to routine clinical care, investigators and IRBs may seek a waiver of consent, assuming there is little value in engaging patients or surrogates in enrollment decisions. While such waivers may be approvable under current regulations, a substantially abbreviated consent process (as opposed to complete waiver) may nevertheless accomplish key functions (Kim and Miller 2014; McKinney et al. 2015; Kim and Miller 2016). Simply disclosing the conduct of the study to individual participants would presumably advance transparency more than a system-wide announcement or general notification regarding the conduct of those studies (Kim and Miller 2014), and allowing the opportunity to opt out can give patients control. Relying on general notifications and not mentioning the trial during face-to-face interactions may be perceived as disrespectful (unless, of course, a genuine cultural change has taken place in which the patients in the system have adopted a different set of expectations). Finally, a substantially shortened process—in contrast to no direct involvement—may bolster public trust in medicine and research.

As in the acute setting, very short consent processes in standard medical practice trials may not serve to protect welfare interests or promote coherence with individuals' values. These functions, however, are less important in trials that involve qualitatively similar treatments and pose low incremental risks. Quite simply, few, if any, welfare interests or values are at stake when treatment arms are qualitatively similar. If treatment arms do differ importantly, these functions rise in importance, and partial involvement strategies may be inadequate. The function-based approach, however, can help to identify and clarify preference-sensitive decisions—for example, about surgical versus medical treatment or trading a higher morbidity risk for a lower mortality risk—that are inadequately addressed by simplified consent. In these ways, this approach contributes to a finer-grained evaluation of appropriate involvement in pragmatic trials than do proposals that rely almost exclusively on evaluation of the net risks of research.

Dementia Research

Finally, clinical trials in patients with Alzheimer's disease (AD) and other cognitive impairments are situations where simplified consent or assent processes that do not meet traditional standards for informed consent may promote coherence with participants' preferences and values without advancing other functions. Because structural or situational barriers such as time constraints are not typically present in AD research, more sophisticated conversations can take place (often with a surrogate) regarding the patient's values and preferences and the impact of participation on the patient's life (Brudney 2009; Kim 2011). Although patients with dementia may be unable to understand extensive information regarding risks and benefits,

and therefore not in a position to provide authorization, they may retain a sense of their values and preferences and may be able to engage in more general discussions about the goals of research or a particular project. Adopting this approach may allow involvement of the patient by focusing more on overall goals and values.

REGULATORY IMPLICATIONS

The present approach also has important regulatory implications. It helps to clarify, for example, that the role of consent is not entirely contingent on risk and that the extent of the role a potential participant should play in an enrollment decision does not depend simply on whether enrollment poses more than minimal risks. This approach also clarifies that consent is not "all-or-nothing"; it may serve some functions in cases where others are less important.

This framework has important implications regarding the use of using waivers and alterations of consent. Current U.S. regulations under the Department of Health and Human Services, for example, only allow for alteration or waiver of the required elements of informed consent in situations where a study is considered minimal risk, the research is impracticable without the waiver or alteration, and the waiver or alteration does not adversely affect the rights and welfare of subjects. However, they do not distinguish in appropriateness between a waiver and an alteration (Kim and Miller 2016). As illustrated by the preceding cases discussed, the function-based approach helps to highlight real differences between waivers and alterations by clarifying the ethical value of approaches that do not meet traditional standards for informed consent. Similarly, it helps to clarify important functions that consent may serve and that do not in any way depend on risk. This is especially important in the context of active debate about how to evaluate and frame research risks (Magnus and Wilfond 2015; Weiss and Joffe 2015; Chen and Kim 2016). In both respects, the function-based approach has direct implications for ongoing regulatory discussions regarding comparative effectiveness research and pragmatic trials, as well as broad consent for data use and biospecimen research.

A second example of how the function-based approach can identify difficulties in the current regulations is the case of emergency care research. The regulation allowing an exception from informed consent (EFIC) for emergency research was intended to address emergency care research in which patients are incapacitated and lack appropriate surrogates. However, in many emergency contexts, potential participants are conscious and not obviously incapacitated, or they may have surrogates who are available to make decisions on their behalf (Dickert et al. 2016). These situations remain, however, highly stressful and are typically time sensitive. The function-based approach provides strong reasons to consider involvement of these individuals in enrollment decisions despite widespread recognition that their decisions will not meet traditional standards for informed consent. Currently, Food and Drug Administration (FDA) regulations require either informed consent (including all required regulatory elements) or the conduct of the study under EFIC regulations (U.S. Food and Drug Administration 1991; U.S. Food and Drug Administration 2004). Department of Health and Human Services (DHHS) regulations allow more flexibility in the context of minimal risk trials, and FDA incorporation of similar flexibility regarding minimal risk studies could be helpful. However, many trials in the emergency care space are not properly characterized as minimal risk (U.S. Department of Health and Human Services 2009b). More empirical evaluation is needed regarding precisely what processes cohere best with the nature of the study and with participants' views and expectations. The function-based approach, however, clarifies the potential value of "partial involvement" and the need for regulatory adaptations to address these situations (Dickert et al. 2016).

CONCLUSION

The general importance of consent in clinical research is clear, but it remains challenging and incompletely understood. Our goal is to better achieve the purposes of consent by unpacking its multiple functions and providing guidance for how varied involvement of participants in research enrollment can be understood, studied, and optimized across the real range of clinical studies and contexts. Further work is necessary to figure out how best to carry out the function-based approach at a practical and regulatory level, but it offers a promising path forward. This approach provides practical guidance, facilitates contextualization, clarifies what may be valuable about different approaches to consent, and identifies areas for improvement and further study.

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REFERENCES

Agard, A., J. Herlitz, and G. Hermeren. 2004. Obtaining informed consent from patients in the early phase of acute myocardial infarction: Physicians' experiences and attitudes. *Heart* 90 (2):208–10. doi:10.1136/hrt.2003.021501.

Ågard, A., G. Hermerén, and J. Herlitz. 2001. Patients' experiences of intervention trials on the treatment of myocardial infarction: Is it time to adjust the informed consent procedure to the patient's capactiy? *Heart* 86:632–37. doi:10.1136/heart.86.6.632.

Beauchamp, T. L., and J. F. Childress. 2001. *Principles of biomedical ethics*. New York, NY: Oxford University Press.

Brudney, D. 2009. Choosing for another: Beyond autonomy and best interests. *Hastings Center Report* 39 (2):31–37. doi:10.1353/hcr.0.0113.

Capron, A. M. 1974. Informed consent in catastrophic disease research and treatment. *University of Pennsylvania Law Review* 123 (2):340–38. doi:10.2307/3311492.

Chen, S. C., and S. Y. Kim. 2016. A framework for analysis of research risks and benefits to participants in standard of care pragmatic clinical trials. *Clinical Trials* 13 (6):605–11. doi:10.1177/1740774516656945.

Cho, M. K., D. Magnus, M. Constantine, et al. 2015. Attitudes toward risk and informed consent for research on medical practices: A cross-sectional survey. *Annals of Internal Medicine* 162 (10):690–96. doi:10.7326/M15-0166.

Cohen, S. 2014. The nocebo effect of informed consent. *Bioethics* 28 (3):147–54. doi:10.1111/j.1467-8519.2012.01983.x.

Council for International Organizations of Medical Sciences. 2016. *International ethical guidelines for health-related research involving humans*. Geneva, Switzerland: CIOMS.

Dickert, N. 2009. Re-examining respect for human research participants. *Kennedy Institute of Ethics Journal* 19 (4):311–38. doi:10.1353/ken.0.0295.

Dickert, N. W., J. Brown, C. B. Cairns, et al. 2016. Confronting ethical and regulatory challenges of emergency care research with conscious patients. *Annals of Emergency Medicine* 67 (4):538–45. doi:10.1016/j.annemergmed.2015.10.026.

Dickert, N. W., A. E. Fehr, A. Llanos, V. M. Scicluna, and H. Samady. 2015. Patients' views of consent for research enrollment during acute myocardial infarction. *Acute Cardiac Care* 17 (1):1–4. doi:10.3109/17482941.2014.994642.

Dickert, N. W., and F. G. Miller. 2015. Involving patients in enrolment decisions for acute myocardial infarction trials. *British Medical Journal* 351:h3791. doi:10.1136/bmj.h3791.

Eyal, N. 2012. Informed consent. *The Stanford encyclopedia of philosophy*. Available at: http://plato.stanford.edu/archives/fall2012/entries/informed-consent (accessed February 6, 2017).

Eyal, N. 2014. Using informed consent to save trust. *Journal of Medical Ethics* 40 (7):437–44. doi:10.1136/medethics-2012-100490.

Eyal, N. 2015. Informed consent to participation in interventional studies: Second-order in a different sense. *Journal of Law and Biosciences* 2 (1):123–28. doi:10.1093/jlb/lsv001.

Faden, R., and T. L. Beauchamp. 1986. *A history and theory of informed consent*. New York, NY: Oxford University Press.

Faden, R. R., T. L. Beauchamp, and N. E. Kass. 2014. Informed consent, comparative effectiveness, and learning health care. *New England Journal of Medicine* 370 (8):766–68. doi:10.1056/NEJMhle1313674.

Featherstone, K., and J. L. Donovan. 1998. Random allocation or allocation at random? Patients' perspectives of participation in a randomised controlled trial. *British Medical Journal* 317 (7167):1177–80. doi:10.1136/bmj.317.7167.1177.

Featherstone, K., and J. L. Donovan. 2002. "Why don't they just tell me straight, why allocate it?" The struggle to make sense of participating in a randomised controlled trial. *Social Science and Medicine* 55 (5):709–19. doi:10.1016/S0277-9536(01)00197-6.

Gammelgaard, A., P. Rossel, and O. Mortensen, in collaboration with the DANAMI-2 Investigators. 2004. Patients' perceptions of informed consent in acute myocardial infarction research: A Danish study. *Social Science and Medicine* 58:2313–24. doi:10.1016/j.socscimed.2003.08.023.

Grady, C. 2015. Enduring and emerging challenges of informed consent. *New England Journal of Medicine* 372 (22):2172.

Jaworska, A. 1999. Respecting the margins of agency: Alzheimer's patients and the capacity to value. *Philosophy and Public Affairs* 28 (2):105–38. doi:10.1111/j.1088-4963.1999.00105.x.

Kass, N., R. Faden, and S. Tunis. 2012. Addressing low-risk comparative effectiveness research in proposed changes to US federal regulations governing research. *Journal of the American Medical Association* 307 (15):1589–90. doi:10.1001/jama.2012.491.

Kass, N. E., J. Sugarman, R. Faden, and M. Schoch-Spana. 1996. Trust, The fragile foundation of contemporary biomedical research. Hastings Center Report 26 (5):25–29. doi:10.2307/3528467.

Kim, S. Y. 2011. The ethics of informed consent in Alzheimer disease research. *Nature Reviews in Neurology* 7 (7):410–14. doi:10.1038/nrneurol.2011.76.

Kim, S. Y., and F. G. Miller. 2014. Informed consent for pragmatic trials—The integrated consent model. *New England Journal of Medicine* 370 (8):769–72. doi:10.1056/NEJMhle1312508.

Kim, S. Y., and F. G. Miller. 2016. Waivers and alterations to consent in pragmatic clinical trials: Respecting the principle of respect for persons. *IRB: Ethics and Human Research* 38 (1):1–5.

Kim, S. Y. H., and J. H. T. Karlawish. 2003. Ethics and politics of research involving subjects with impaired decision-making abilities. *Neurology* 62:1645–46. doi:10.1212/WNL.61.12.1645.

Kodish, E., M. Eder, R. B. Noll, et al. 2004. Communication of randomization in childhood leukemia trials. *Journal of the American Medical Association* 291 (4):470–75. doi:10.1001/jama.291.4.470.

Magnus, D., and B. S. Wilfond. 2015. Research on medical practices and the ethics of disclosure. *Pediatrics* 135 (2):208–10. doi:10.1542/peds.2014-3578.

Mandava, A., C. Pace, B. Campbell, E. Emanuel, and C. Grady. 2012. The quality of informed consent: Mapping the landscape. A review of empirical data from developing and developed countries. *Journal of Medical Ethics* 38 (6):356–65. doi:10.1136/medethics-2011-100178.

McKinney, R. E., Jr., L. M. Beskow, D. E. Ford, et al. 2015. Use of altered informed consent in pragmatic clinical research. *Clinical Trials* 12 (5):494–502. doi:10.1177/1740774515597688.

Mello, M. M., and L. E. Wolf. 2010. The Havasupai Indian tribe case—Lessons for research involving stored biologic samples. *New England Journal of Medicine* 363 (3):204–7. doi:10.1056/NEJMp1005203.

Miller, F. G., and A. Wertheimer. 2010. Preface to a theory of consent transactions: Beyond valid consent. In *The ethics of consent: Theory and practice*, ed. F. G. Miller and A. Wertheimer, 79–106. New York, NY: Oxford University Press.

Miller, F. G., and A. Wertheimer. 2011. The fair transaction model of informed consent: an alternative to autonomous authorization. *Kennedy Institute of Ethics Journal* 21 (3):201–18. doi:10.1353/ken.2011.0013.

National Commission for the Protection of Research Risks. 1979. *The Belmont report: Ethical principles and guidelines for the protection of human subjects of research*. Washington, DC: Government Printing Office.

Nayak, R. K., D. Wendler, F. G. Miller, and S. Y. Kim. 2015. Pragmatic randomized trials without standard informed consent?: A national survey. *Annals of Internal Medicine* 163 (5):356–64. doi:10.7326/M15-0817.

Platt, R., N. E. Kass, and D. McGraw. 2014. Ethics, regulation, and comparative effectiveness research: Time for a change. *Journal of the American Medical Association* 311 (15):1497–98. doi:10.1001/jama.2014.2144.

Shahzad, A., I. Kemp, C. Mars, et al. 2014. Unfractionated heparin versus bivalirudin in primary percutaneous coronary intervention (HEAT-PPCI): An open-label, single centre, randomised controlled trial. *Lancet* 384 (9957):1849–58. doi:10.1016/S0140-6736(14)60924-7.

Shaw, D. 2014. HEAT-PPCI sheds light on consent in pragmatic trials. *Lancet* 384 (9957):1826–7. doi:10.1016/S0140-6736(14)61040-0.

Snowdon, C., J. Garcia, and D. Elbourne. 1997. Making sense of randomization; Responses of parents of critically ill babies to random allocation of treatment in a clinical trial. *Social Science and Medicine* 45 (9):1337–55. doi:10.1016/S0277-9536(97)00063-4.

Sugarman, J., and R. M. Califf. 2014. Ethics and regulatory complexities for pragmatic clinical trials. *Journal of the American Medical Association* 311 (23): 2381–82. doi:10.1001/jama.2014.4164.

Truog, R. D., W. Robinson, A. Randolph, and A. Morris. 1999. Is informed consent always necessary for randomized, controlled trials? *New England Journal of Medicine* 340 (10):804–7. doi:10.1056/NEJM199903113401013.

U.S. Department of Health and Human Services. 2009a. Title 45 (Code of Federal Regulations), Part 46. Protection of Human Subjects, Subpart D. Available at: https://www.hhs.gov/ohrp/regulations-and-policy/regulations/45-cfr-46/index.html#subpartd (accessed October 24, 2017).

U.S. Department of Health and Human Services. 2009b. Title 45 (Code of Federal Regulations), Part 46. Protection of Human Subjects. Available at: https://www.hhs.gov/ohrp/regulations-and-policy/regulations/45-cfr-46/index.html (accessed October 24, 2017).

U.S. Department of Health and Human Services and Food and Drug Administration. 2013. Guidance for institutional review boards, clinical investigators, and sponsors: Exception from informed consent requirements for emergency research. Retrieved from http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM249673.pdf.

U.S. Food and Drug Administration. 1991. Title 21 (Code of Federal Regulations), Part 50. Protection of Human Subjects. Available at: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=50 (accessed October 24, 2017).

U.S. Food and Drug Administration. 2004. Title 21 (Code of Federal Regulations), Part 50.24 Protection of Human Subjects. Available at: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=50.24 (accessed October 24, 2017).

Weinfurt, K. P., D. M. Seils, L. Lin, et al. 2012. Research participants' high expectations of benefit in early-phase oncology trials: Are we asking the right question? *Journal of Clinical Oncology* 30 (35):4396–400. doi:10.1200/JCO.2011.40.6587.

Weiss, E. M., and S. Joffe. 2015. Promoting informed decision making for comparative effectiveness randomized trials. *JAMA Pediatrics* 169 (9):803–4. doi:10.1001/jamapediatrics.2015.0906.

Wendler, D. 2006. Assent in paediatric research: Theoretical and practical consideration. *Journal of Medical Ethics* 32:229–34. doi:10.1136/jme.2004.011114.

Wendler, D. 2009. Must research participants understand randomization? American Journal of Bioethics 9 (2):3–8. doi:10.1080/15265160802654145.

Wertheimer, A. 2014. (Why) should we require consent to participation in research? *Journal of Law and Biosciences* 1 (2):137–82. doi:10.1093/jlb/lsu008.

World Medical Association. 2013. World Medical Association Declaration of Helsinki: Ethical principles for medical research involving human subjects. *Journal of the American Medical Association* 310 (20):2191–94. doi:10.1001/jama.2013.281053.