"Targeted" Consent for Pragmatic Clinical Trials

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Research on interventions within the standard of care has enormous potential, yet it also raises several ethical and regulatory challenges. Perhaps the most important is determining what consent process is needed for these "pragmatic" clinical trials. Some argue that pragmatic clinical trials need to obtain in-depth research consent. This approach ensures that patients are informed, but may introduce substantial selection bias and disruption of clinical care. Others argue that trials limited to interventions within the standard of care do not need to obtain research consent at all. While this approach avoids the problems with in-depth consent, it results in patients not knowing whether they are in research. The present manuscript proposes a way to avoid both sets of concerns. It argues that consent for research needs to supplement appropriate consent for standard care only to the extent that the research differs from standard care. Hence, pragmatic trials designed to mirror clinical care can obtain consent with only minimal additions to consent for standard care. This conclusion suggests that it may be possible for many pragmatic trials to obtain consent that is ethically appropriate, satisfies research regulations, and does not introduce substantial selection bias or clinical disruption.

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Research on interventions within the standard of care has the potential to substantially improve patients' health and well-being. To realize this potential, investigators and review committees must determine what type of consent is needed for "pragmatic" clinical trials.

Some argue that all clinical trials need to obtain in-depth research consent.[1] While this approach allows patients to decide whether to enroll in pragmatic trials, it may introduce substantial selection bias and disruption to clinical care.[2] Others argue that pragmatic clinical trials which pose no added risks do not need to obtain research consent at all.[3] This approach avoids the problems with in-depth consent, but leaves patients uncertain as to whether they are in research.

The present paper argues that these concerns can be avoided by supplementing appropriate clinical consent with "targeted" consent, which discloses the material differences between the trial and standard care. Under targeted consent, pragmatic trials that are similar to standard care need only include minimal additions to consent for standard care. This conclusion suggests that it may be possible for many pragmatic trials to obtain consent that is ethically appropriate, satisfies the research regulations, and does not introduce substantial selection bias or clinical disruption.

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TARGETED CONSENT FOR PRAGMATIC TRIALS

Consider a clinician who prescribes chlorthalidone or hydrochlorothiazide for her hypertension patients.[4] When prescribing either medication, the clinician standardly explains that treatment is likely to improve the patient's hypertension, and describes the most common side effects. She then asks whether the patient has any questions.

Now imagine that the clinician's practice joins a pragmatic trial that randomizes patients to chlorthalidone or hydrochlorothiazide.[3] The study enrolls only patients for whom chlorthalidone and hydrochlorothiazide are indicated and uses standard doses. Moreover, dose adjustments are permitted if needed. What does the clinician need to add to her standard disclosure to obtain consent for this trial?

Targeted consent directs investigators to supplement consent for standard care with information on the material differences between the study and standard care. The most prominent difference between research and care is that enrollment in research involves patients helping investigators to evaluate the treatments under study. The clinician should disclose this fact so that her patients can decide for themselves whether to enroll. She also should disclose any added research risks.[5] This disclosure poses the challenge of determining what additional information she must disclose in order to satisfy the research regulations.

CAN THE CONSENT REQUIREMENTS BE WAIVED OR ALTERED?

US regulations mandate that investigators disclose up to 14 aspects of a study. Given the possible burdens involved with disclosing all this information, some commentators argue that investigators conducting pragmatic trials should seek a waiver/alteration of applicable consent regulations and use an abbreviated consent process.[6]

Waivers and alterations of the U.S. Food and Drug Administration (FDA) consent requirements are permitted only under very limited circumstances.[7] Hence, most pragmatic trials subject to FDA regulations will not qualify for a waiver or alteration.

The U.S. Department of Health and Human Services (HHS) consent requirements may be waived or altered when four conditions are satisfied.[8] Because investigators typically interact with subjects, many pragmatic trials will not satisfy the third condition, which mandates that it is not "practicable" to obtain consent. Similarly, many pragmatic trials may not satisfy the first condition, which requires that the research pose only minimal risk. Trials qualify as minimal risk when the risks "anticipated in the research" do not exceed the risks ordinarily encountered in daily life or during routine examination [http://www.hhs.gov/ohrp/newsroom/rfc/comstdofcare.html]. U.S. regulations do not clarify which risks qualify as "anticipated in the research." However, draft guidance maintains that the risks of interventions being evaluated are risks of the research when 1) subjects may receive an intervention that is different from the standard of care, and 2) the intervention that they receive may pose different risks compared to standard care [http://www.hhs.gov/ohrp/newsroom/rfc/comstdofcare.html].

Most randomized pragmatic trials satisfy these two conditions. Hence, if review committees assume that the risks of the research qualify as risks anticipated in the research, very few randomized pragmatic trials may be categorized as minimal risk.[9] This analysis suggests that, under U.S. regulations, investigators face a dilemma. Many pragmatic trials likely do not qualify for a waiver or alteration of the consent requirements, yet disclosing all of the mandated information seems to pose substantial burdens. Does targeted consent offer investigators a way to satisfy the regulations without introducing these burdens?

THE ELEMENTS OF INFORMED CONSENT

U.S. regulations mandate the disclosure of eight items related to a study (Table 1). Under targeted consent, investigators should explain that enrollment involves helping to evaluate the treatments under study, and should disclose any added research risks. This disclosure helps to satisfy requirements #1 and #2. The clinician could also explain that chlorthalidone and hydrochlorothiazide are standard treatments (#4) and that participation is voluntary (#8).

The consent form could disclose any measures to protect confidentiality (#5) and provide the researchers contact information (#7). Because this study is limited to standard interventions, there are no research benefits to disclose (#3), nor is there a need to describe whether compensation or treatment would be provided for research injuries (#6).

The U.S. regulations also mandate disclosure of six additional items, as appropriate (Table 1). Arguably, none of the six needs to be disclosed in studies limited to interventions within standard care. Nonetheless, investigators might choose to include in the consent form the fact that any new findings will be explained and to list the approximate number of subjects. This analysis suggests that targeted consent for pragmatic trials can satisfy U.S. regulations by supplementing the standard clinical disclosure with a brief verbal disclosure and a short consent form that subjects sign (text box).

Text Box: Targeted Consent for a Pragmatic Trial

Possible Verbal Disclosure
"We would like to invite you to participate in a study of two treatments for hypertension to see whether one is better. We believe this is an important study. However, whether you participate is up to you. If you decide to participate, you will receive either chlorthalidone or hydrochlorothiazide, both standard treatments for hypertension. You might experience some fatigue or nausea from the medication. Do you have any questions, or is there anything else you would like to know about the study?"
Written Consent Form
The consent form should repeat the verbal disclosure information, and should include a description of the following: 1) procedures and duration, 2) instructions on taking the medication, 3) availability of both treatments from a doctor outside the research setting, 4) confidentiality measures, 5) contact information, 6) statement that the patient will not be penalized for declining to enroll or deciding to stop participation

POTENTIAL OBJECTIONS

Randomization and Protection

Many commentators argue that investigators should disclose that subjects' treatment will be selected randomly. However, studies indicate that when the existing data do not suggest that one intervention is better, randomization does not increase risks,[10] suggesting that for the purpose of protecting subjects, pragmatic trials do not need to disclose randomization. Granting this conclusion, one might argue that randomization should be disclosed in order to ensure that patients are afforded an appropriate degree of respect.

Randomization and Respect

Treatment selection for clinical trials typically is not random in the strict sense of assigning treatments based purely on chance. Instead, trials rely on various methods, such as stratification and block design, in an effort to ensure that the treatment groups are relevantly similar. Of course, these approaches are random in the sense that they do not assign treatments based on evidence regarding which treatment is better for a particular individual. However, when the existing evidence does not provide a reason to prefer one treatment over another, treatment assignment in the clinical setting is similarly not based on evidence regarding which treatment is better for a particular individual.

One might respond that potential subjects may still want to know that their treatment is being selected by a random process rather than being chosen by their doctor. Moreover, individuals who enroll in randomized trials may be assigned to a medication that differs from the medication they would have received in standard care. Hence, it might be argued that

Table 1. Elements of Informed Consent in Pragmatic Trials

Element	Requirement	Research Additions
1. Research	Statement that study involves research, explanation of purpose, duration, procedures, including any experimental	Comparing two standard treatments to see whether one is better for hypertension
2. Risks	Reasonably foreseeable risks	None (assuming no added research risks)
3. Benefits	Any reasonably expected benefits to the subject	None
4. Alternatives	Appropriate alternatives that might be advantageous to the subject	Both medications available in clinical care
5. Confidentiality	Extent to which confidentiality will be maintained	Consent form describes confidentiality measures
6. Compensation	If more than minimal risk, whether any compensation or treatment for injury	Not applicable (assuming no added research risks)
7. Contact	Whom to contact	Consent form includes researcher contact information
8. Voluntary	Statement that participation is voluntary, and participation may be discontinued at any time without penalty	Enrollment is voluntary. Consent form explains that subjects can decline and can stop participating without penalty
Additional Items When Appropriate		
1. Unforeseen risks	Treatment may pose currently unforeseeable risks	Not needed for standard care interventions
2. Termination	Circumstances under which participation may be terminated by investigator	Not needed when standard care is an option
3. Costs	Any additional costs to subject	Typically not applicable
4. Withdrawal	Consequences of decision to withdraw and procedures for termination	Not needed when standard care is an option
5. New findings	Statement that new findings will be provided to the subject	Describe in consent form
6. Subjects	Approximate number of subjects in study	Describe in consent form

potential subjects need to understand the differences in risks associated with the available treatments so they can decide whether to enroll in the study or to seek a specific treatment in the clinical setting.

When the risks of the available treatments differ in ways that most individuals consider important, these differences should be disclosed. For example, if one potential treatment poses a risk of hair loss but the other options do not, this should be explained. However, this information is important to disclose whether patients are considering a randomized trial or standard care. It does not represent information that investigators need to add to clinical disclosure.

Finally, even when the possible differences in risks between the study and standard of care are not material to most individuals, some potential subjects may regard these differences as important. Hence, to ensure appropriate respect for all potential subjects, it might seem that investigators should disclose the potential differences in risks.

THE COSTS OF EXTENSIVE DISCLOSURE

It seems plausible to assume that, in order to respect subjects, investigators should disclose all of the aspects of a study that one or more subjects may consider important. The problem with this approach is that there are many aspects of research that one or more subjects may consider important. Some may want to know what the company does with its profits. Others may want to know whether the ethics of the study were reviewed and whether the reviewers had any concerns.

A recent study found that stakeholders identified at least 50 items as important to disclose to research subjects.[11] These data underscore the fact that disclosing every aspect of a study that one or more potential subjects might regard as important would result in all potential subjects being burdened with a considerable amount of information simply because it is of interest to others. This does not seem like a way to respect individual subjects.

Extensive disclosure can also have negative effects. First, the amount of information we expect to be disclosed depends on the importance of a decision. Hence, describing many aspects of a study may confuse potential subjects into thinking that the research differs substantially from standard care, and that they face a critical decision. Second, disclosure of extensive information can lead to worse decisions as a result of individuals defaulting to the status quo[12] or choosing distinctive rather than better options.[13] Third, extensive disclosure can be associated with lower satisfaction[14] and increased anxiety.[15]

This analysis suggests that the best way to respect individual subjects is not to disclose to all potential subjects the information that any single potential subject might consider important. Rather, investigators should explain that enrollment involves helping to assess the treatments under study, disclose any added risks, disclose any information that is important for most subjects, and then discuss with the individual any questions or concerns that they may have.

SUMMARY

Pragmatic clinical trials that do not differ significantly from standard of care can obtain consent without in-depth research disclosure. This is good news ethically and scientifically. It suggests that it may be possible for many pragmatic trials to obtain ethically appropriate consent, satisfy research regulations, and

still not introduce substantial selection bias or clinical disruption. Future research will be needed to determine how best to combine consent for research with consent for clinical care, and to assess the impact of targeted consent on research studies and on patients.

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