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## Targeted Consent for Research on Standard of Care Interventions in the Emergency Setting

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### Abstract

**Objective**—There has been significant debate over what consent process, if any, should be used for clinical trials that compare two or more interventions within the standard of care. Some claim that all clinical trials should obtain in-depth research consent because they use subjects to obtain data for the benefit of future patients. Others argue that clinical trials which are limited to interventions within the standard of care do not need to obtain research consent at all. Settling this debate is especially challenging in the emergency setting. The potential for significant morbidity and mortality provides a strong reason to obtain research consent for standard-of-care trials in the emergency setting. Yet, the emergency setting also introduces significant barriers to traditional in-depth research consent. The present paper considers to what extent a targeted consent process can resolve these tensions.

**Data Synthesis**—We first identified the ethical goals that are promoted by obtaining consent for standard-of-care research and the barriers to obtaining consent that arise in the emergency setting. We then evaluated whether, despite the barriers, it is possible to develop a targeted consent process that promotes the goals for consent in the context of standard-of-care trials.

**Conclusions**—Targeted consent offers an ethically appropriate way to obtain consent for many standard-of-care trials in the emergency setting. For studies subject to US regulations, and those subject to other regulations that include similar consent requirements, targeted consent's verbal disclosure and written form provide a way to satisfy research regulations without blocking valuable studies. For trials that qualify for a waiver of the consent requirements, targeted consent's verbal disclosure is preferable to waiving consent, provided a slight delay is consistent with appropriate care, and there is a capacitated patient or surrogate available.

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## Keywords

Informed consent; clinical research; pragmatic trials; emergency care

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## Introduction

There is considerable variability within standard medical care. Whether a patient receives one intervention or another often depends, not on objective data, but on anecdotal experience and local practice. In this setting, trials comparing standard-of-care interventions have the potential to significantly improve clinical care by identifying which approaches are associated with better patient outcomes. To give one example, TASTE-MI was a registry based trial that compared two common approaches for ST elevation myocardial infarction (STEMI): thrombus aspiration followed by percutaneous coronary intervention (PCI) versus PCI alone (1). The finding that routine thrombus aspiration before PCI did not reduce 30-day mortality had important implications for the treatment of STEMI.

The need for urgent treatment in the emergency setting often precludes traditional in-depth research consent. With this in mind, the US Food and Drug Administration (FDA) and Department of Health and Human Services (DHHS) allow exceptions from the requirements for informed consent for emergency research studies, provided the studies satisfy a number of other requirements. These include requirements that neither the patient nor the patient's surrogate can give consent, the available treatments are unproven or unsatisfactory, and the research offers participants the potential for clinical benefit (2).

This framework, which makes sense for trials of novel interventions, is not well suited to standard-of-care trials. These trials often evaluate interventions that are widely used and already approved. Moreover, many emergency patients retain the capacity to consent and, in other cases, a surrogate may be available. These studies typically do not qualify for a waiver of the consent requirements under the emergency regulations.

US DHHS (but not FDA) regulations also permit a waiver or alteration of the research consent requirements for studies that satisfy four conditions, including posing no greater than minimal risk (3). Yet, there is considerable debate over whether standard-of-care research can be categorized as minimal risk (4). Even more controversial is the possibility of categorizing standard-of-care research in the emergency setting as minimal risk. Given the clinical outcomes at stake, review committees may be reluctant to categorize these trials as minimal risk. It follows that many standard-of-care trials in the emergency setting will be required, under existing US regulations, to obtain research consent.

This conclusion raises the need for a consent process that is suitable to standard-of-care trials in the emergency setting. In particular, there is need for a consent process that is suitable to the combination of high clinical stakes, urgency of treatment, and stressful circumstances. The present manuscript therefore considers whether it is possible to develop a consent process for standard-of-care trials in the emergency setting which is feasible, ethically appropriate, and satisfies the US regulations, as well as the regulations of other countries that rely on similar consent requirements.

## Discussion

### Types of Standard-of-care Research in Emergency Settings

To identify an appropriate consent process, it is important to recognize that standard-of-care trials in emergency settings represent a wide spectrum. Some standard-of-care trials in emergency settings involve noninvasive diagnostic algorithms. Such studies might compare time intervals for cardiac enzyme monitoring in acute coronary syndrome or lactate levels in septic shock. In these cases, treatment is not directly assigned, but may be affected downstream. Other trials compare two or more commonly used drugs in a similar class, different treatment targets of a standard drug, or varying strategies for protocol-driven delivery of standard care.

Standard-of-care trials sometimes assign patients to different variants of a common procedure or randomize subjects to conservative versus expectant treatment. Finally, some trials compare procedural versus medical interventions. For example, the SHOCK II trial randomized patients with acute myocardial infarction complicated by cardiogenic shock to upfront use of an intra-aortic balloon pump (IABP) versus IABP use only if medical therapy failed (5). These examples highlight the fact that a consent process for standard-of-care trials in the emergency setting will need to be suitable to a wide range of study types.

### Factors Relevant to Consent

The emergency setting introduces a number of complications that a suitable consent process must address (6). These include time constraints, possible cognitive impairment, stressful circumstances, potential differences in risk/benefit profiles, and qualitative differences in undergoing the interventions being tested.

First, some emergency treatments, including initial treatment for severe hemorrhage and cardiac arrest, must be delivered immediately. Assuming potential subjects cannot be identified in advance, these studies offer no opportunity to obtain consent prior to enrollment; they can be conducted only with a waiver of the research consent requirements. Similarly, some emergency care patients are unconscious or otherwise unable to make decisions. And frequently no surrogate is available. These studies also can be conducted only when they qualify for a waiver of the requirement for initial informed consent.

In other cases, the reviewing institutional review board (IRB) or research ethics committee (REC) might find that a short delay prior to the initiation of treatment is consistent with appropriate care (7). In addition, many emergency care patients retain the ability to make decisions, or a surrogate is available. For example, many patients with acute myocardial infarction have sufficient cognitive capacity to participate in enrollment decisions (8). At the same time, the stress involved in emergency care can make it difficult or impossible to obtain in-depth research consent. Moreover, obtaining in-depth research consent can introduce an important selection bias, further underscoring the need for a brief consent process.

Second, standard-of-care trials vary in what is known about the treatments being evaluated, and can vary with respect to whether they pose additional risks compared to standard care.

Frequently, there are few or no data to indicate whether one intervention is better than the other. In other cases, there is evidence which suggests, but does not confirm, that one arm may be superior. Furthermore, while many trials do not include additional procedures, some pose added risks, such as the risks of added research blood draws or extra imaging tests.

Finally, the experience of undergoing the interventions being tested can vary. For example, a study might compare a surgical procedure, with a relatively brief period of operative pain, to medical treatment, with a longer period of moderate discomfort.

### Reasons to Involve Patients in Enrollment Decisions

Some commentators argue that there is no need to obtain research consent when enrollment in a standard-of-care trial does not pose any *additional* risks compared to standard care (9, 10). For example, Troug et. al argue that “the obligation to seek specific consent for research should ... depend on the risk–benefit ratios of the intervention and the alternatives” (11)

The presence of added risks provides a strong reason to obtain research consent. When a study includes additional research procedures, potential participants should be informed and allowed to decide whether to accept the associated risks and burdens. Similarly, when there is evidence that one intervention may be better than the other, IRBs should assess whether the evidence is of sufficient strength that it should be disclosed to potential participants.

While disclosure of risks is an important reason to obtain potential participants' consent, it is not the only reason. Studies that do not pose any added risks still involve participants contributing to the collection of data. Obtaining research consent shows respect for patients by informing them of the study and allowing them to decide whether to contribute to it (12). In addition, when the clinical stakes are high, patients should have a say, to the extent possible, in whether their treatment is provided in a clinical trial. The use of randomization to evaluate very different types of interventions precludes patients from choosing which option they receive. Informed consent discloses these differences and allows patients who have a strong preference to decline randomization, and request their preferred approach (assuming both approaches are available at the site). Finally, obtaining research consent may help to maintain trust in research among patients, surrogates, and the public by providing assurance that investigators are not taking advantage of acutely ill patients.

Existing data suggest that patients endorse obtaining research consent, when possible, even for studies that are limited to indicated treatments. Two surveys found that most patients prefer to give consent for standard-of-care trials in less acute situations (13,14). Even patients who recognize the limitations inherent in obtaining consent in the emergency setting report that they want to have a say in whether they are enrolled in research (15,16). And patients sometimes decline to enroll in acute care trials, suggesting that some patients may not want to participate in emergency care trials. The preferences of these patients are ignored if research consent is waived entirely.

### Targeted Consent

The conclusion that there are reasons to obtain consent for standard-of-care trials, together with the substantial barriers to obtaining in-depth consent in the emergency setting, points to

the need for a brief consent process. Given that many standard-of-care trials in the emergency setting are not candidates for a waiver of the research consent requirements, a brief consent process ideally would be context-sensitive and satisfy the research regulations.

The US FDA and DHHS regulations list eight items as essential to informed consent for clinical research and six additional items that should be disclosed when appropriate to the study in question (Text Box 1). In addition, with a few exceptions, US regulations require potential subjects or their surrogates to indicate their agreement by signing the consent form. Frequently, investigators explain the mandated information using an in-depth consent form and process. This approach can make sense when standard care and research are very different. In contrast, standard-of-care trials and clinical care are similar in many cases. In particular, these trials use standard treatments and typically pose few, if any added risks compared to standard clinical care.

The fact that there are relatively few significant differences between standard-of-care trials and clinical care offers the opportunity to develop a brief, targeted consent process that satisfies the research regulations. A targeted consent process could begin by explaining that the study is comparing different standard interventions to see whether one is better, that the study has the potential to improve treatment for the condition in question, and that participation is voluntary (Text Box 2). When there is reliable evidence that one intervention may be better than another (but not enough evidence to determine practice) this information should be disclosed, along with any additional research risks. If the experience of undergoing the different interventions is very different, this information should be disclosed as well.

To satisfy the US consent regulations (17), this discussion could be accompanied by a consent form which very briefly describes the potential benefits and prominent side effects of the interventions, describes any measures to protect confidentiality, provides the researchers' contact information, explains that the interventions are available in standard care, and explains that the patient may decline to enroll and may stop participating at any time (Text Box 2). Finally, the investigator should solicit any questions or concerns and invite the patient or surrogate to sign the consent form if they are willing to enroll.

This approach can be used for trials that are subject to the US regulations and do not qualify for either an exemption or a waiver or alteration of the research consent requirements. This approach also might be used in countries whose research consent requirements are similar to those in the US, and might be modified for countries whose consent requirements mandate the disclosure of more or less information. A brief oral explanation and a 1 page consent form were used in DANAMI-2 (18), a Danish study of patients with MI. This experience suggests that a brief, targeted consent process might be feasible. Future research should evaluate patients' views on the present approach, the extent to which it results in patients understanding the study in question, and the extent to which it introduces a selection bias.

### **Staged Consent**

While a slight delay to intervention may be sufficient to explain relatively straightforward studies, it likely will not offer sufficient time to explain more complicated studies. For

example, a standard-of-care trial comparing two different therapies for acute stroke may provide initial treatment that could be explained briefly, but also include several follow-up interventions— imaging, data collection, and sample storage— that require more explanation. Similarly, when patients are experiencing significant stress or anxiety, they may not be able to comprehend the entire study before treatment must be initiated.

A staged approach, combined with targeted consent, may offer a way to satisfy the research regulations for these studies (19). On this approach, investigators use targeted consent for the initial treatment phase of the study, while deferring explanation and consent for the follow-up interventions until the patient is stable. At that point, it would be emphasized that participation is voluntary, and the fact that the patient consented to initial enrollment in the trial does not commit them to the follow-up procedures.

The IMPROVE trial randomized critically ill patients with ruptured abdominal aortic aneurysm to endovascular repair versus open surgical repair (20). The patients were asked to provide brief, initial consent prior to enrollment and more in-depth consent later on. Of the 652 patients who were approached, 83% provided brief initial consent and a relative or caretaker provided brief initial consent for another 7%. In contrast, 6.4% of the patients declined enrollment because they preferred no treatment or a specific treatment (21). Similarly, the FEAST trial evaluated three different fluid resuscitation strategies in critically ill children at six hospitals across three African countries. Prior to enrollment, investigators described the trial briefly to the parent or guardian and explained that enrollment was voluntary; further consent was solicited later on (22).

By focusing on the immediate decisions, a staged approach minimizes the number of decisions patients (or their surrogates) are asked to make during the acute phase of the patient's illness. By limiting the scope of initial consent, staged consent also may offer a way to satisfy the research regulations for emergency care studies that involve significant follow-up procedures. Finally, if follow-up procedures introduce added research risks, it seems more respectful to ask patients to make decisions regarding these procedures when they are stable.

### **Targeted Consent versus Deferred Consent**

Some trials in the emergency setting randomize patients to a treatment arm and only later obtain the consent of the patient or a surrogate. Although this approach is sometimes described as 'deferred consent', the term is something of a misnomer since one cannot consent to something that has already occurred. Instead, this approach involves enrolling patients in research and randomizing them without consent, and then obtaining consent later for any follow-up procedures and use of the data. This approach might seem preferable to targeted consent. In particular, one might argue that there is no need to obtain consent to randomize patients between clinically indicated treatments, especially when investigators will later obtain consent to keep the patient in the trial and use their data for research purposes. Moreover, even a brief initial consent process can delay treatment, place additional stress on the patient or surrogate, and increase selection bias.

We have argued that targeted consent should be used only when it does not undermine patient care. In addition, while targeted consent may increase stress in some cases, this concern, at least when the stress is not significant, seems to be outweighed by the benefits of obtaining consent for research enrollment. Obtaining initial consent, even for studies that are limited to indicated treatments, shows greater respect for patients by informing them (or their surrogates) that they are being considered for research enrollment, allows those who are willing to choose to enroll, and allows those who object to research to decline to enroll. For example, the use of brief initial consent in the IMPROVE trial allowed patients who preferred no treatment or a specific treatment (6.4%) to decline enrollment. This greater transparency also avoids the possibility of conveying the impression that the patient is involved in clinical care only and provides some assurance that investigators are not taking advantage of the circumstances to enroll patients in research. And this approach may help to better maintain patient and public trust in research.

The benefits of targeted consent are even greater for studies that randomize subjects to qualitatively different interventions. In these cases, obtaining initial consent allows patients to determine whether they are willing to undergo either intervention. And when there is evidence to believe that one intervention may be better than the other, and when research procedures are performed as part of initial treatment, obtaining initial consent, unlike “deferred consent”, discloses the associated risks and burdens and allows potential participants to decide whether to accept them.

Future research should evaluate whether patients regard these benefits as sufficiently compelling to justify any increased stress that results from obtaining initial consent. Future research also will be needed to evaluate to what extent an initial consent process increases selection bias. Finally, it is important to note that, unlike targeted consent, approaches that do not obtain initial consent can be used only for studies that qualify for a waiver of the regulatory requirements for informed consent.

### **Waiver of Consent**

We have focused on standard-of-care studies that do not seem appropriate for a waiver of prospective consent under existing regulations. However, some standard-of-care trials may qualify for an exception from consent under the emergency regulations, particularly when even a slight delay to treatment initiation would undermine patient care. Similarly, although it may seem incongruent in the emergency setting, some trials of standard-of-care interventions may pose no more than minimal risk and may qualify for a waiver or alteration of consent under DHHS consent regulations.

The fact that a study is limited to standard-of-care interventions does not imply that it necessarily poses no greater than minimal risk. For example, there may be evidence that one intervention is better than the other and the trial is designed to evaluate this possibility. In this case, enrollment in the trial poses the risk of being randomized to the intervention that the existing data suggest may be worse. This seems especially important when the data concern major morbidity or mortality.

In other cases, enrollment in trials that are limited to indicated interventions may not pose any added risks compared to appropriate care. Such studies might be categorized as minimal risk and may qualify for a waiver or alteration of the DHHS consent requirements. However, even for these trials, review committees should consider using at least the verbal portion of targeted consent rather than waiving the requirement for initial consent entirely. While this disclosure does not describe all the elements of consent that are mandated by most regulations, it informs patients that they are being considered for research and allows them to decide whether to enroll.

## Conclusions

There has been significant debate over what type of consent is appropriate for standard-of-care trials. This debate is especially challenging in the emergency setting which involves a combination of tight timelines, distressed patients, and high stakes. Many standard-of-care trials in the emergency setting likely do not qualify for a waiver of the research consent requirements. We have argued that targeted consent offers a feasible and ethically appropriate way for these studies to satisfy the US regulations. This approach also might be used in countries whose consent requirements are similar to those in the US. For trials that do qualify for a waiver of consent, the verbal disclosure and discussion of targeted consent is ethically preferable to waiving initial consent entirely, provided a slight delay to intervention is consistent with appropriate care, and there is a capacitated patient or available surrogate.

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**Text Box 1****US required and additional elements of informed consent (45 CFR 46.116/21 CFR 50.25)****Required Elements**

1. A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental;
2. A description of any reasonably foreseeable risks or discomforts to the subject;
3. A description of any benefits to the subject or to others which may reasonably be expected from the research;
4. A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject;
5. A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained;
6. For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained;
7. An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject; and
8. A statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

**Additional Elements When Appropriate**

1. A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant) which are currently unforeseeable;
2. Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent;
3. Any additional costs to the subject that may result from participation in the research;

4. The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject;
5. A statement that significant new findings developed during the course of the research which may relate to the subject's willingness to continue participation will be provided to the subject; and
6. The approximate number of subjects involved in the study.

**Text Box 2****Targeted Consent****Possible Verbal Disclosure**

“Doctors do not know if [A] or [B] is better for [condition]. To find out, we are doing a study that compares [A] and [B] to each other. We believe this is an important study that has the potential to improve care for patients with [condition]. Whether you participate is up to you. If you decide to participate, you will receive either [A] or [B], both of which are indicated for your condition. [If applicable: add data that one intervention may be better and/or experiential differences]. If you decide not to participate, your doctor will choose one of these two treatments for you. Do you have any questions, or is there anything else you would like to know about the study?”

**Consent Form**

The patient (or surrogate) should be provided with a consent form that briefly describes: 1) purpose and duration of the study, 2) most important risks of A and B, 3) potential benefits of A and B, 4) availability of both treatments outside research, 5) confidentiality measures, 6) investigators' contact information, 7) statement that the patient will not be penalized for declining to enroll or deciding to stop participation.