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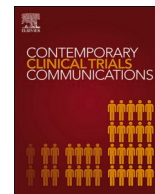
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## Implementing stakeholder engagement to explore alternative models of consent: An example from the PREP-IT trials

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### ABSTRACT

**Introduction:** Cluster randomized crossover trials are often faced with a dilemma when selecting an optimal model of consent, as the traditional model of obtaining informed consent from participant's before initiating any trial related activities may not be suitable. We describe our experience of engaging patient advisors to identify an optimal model of consent for the PREP-IT trials. This paper also examines surrogate measures of success for the selected model of consent.

**Methods:** The PREP-IT program consists of two multi-center cluster randomized crossover trials that engaged patient advisors to determine an optimal model of consent. Patient advisors and stakeholders met regularly and

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reached consensus on decisions related to the trial design including the model for consent. Patient advisors provided valuable insight on how key decisions on trial design and conduct would be received by participants and the impact these decisions will have.

*Results:* Patient advisors, together with stakeholders, reviewed the pros and cons and the requirements for the traditional model of consent, deferred consent, and waiver of consent. Collectively, they agreed upon a deferred consent model, in which patients may be approached for consent after their fracture surgery and prior to data collection. The consent rate in PREP-IT is 80.7%, and 0.67% of participants have withdrawn consent for participation.

*Discussion:* Involvement of patient advisors in the development of an optimal model of consent has been successful. Engagement of patient advisors is recommended for other large trials where the traditional model of consent may not be optimal.

## 1. Introduction

The Informed consent process is fundamental to protecting the rights and welfare of individuals who participate in clinical research [1]. In most prospective clinical trials, delegated member(s) of the research team obtains informed consent from each participant prior to initiating any study-related activities. However, in some circumstances, different models of informed consent may be appropriate, including a waiver of consent or deferred consent.

There are numerous circumstances in which the traditional consent model may be impractical or impossible [2]. For example, critically ill or injured patients may require immediate medical intervention. However, they may not be capable of providing informed consent for participation in a research trial and a proxy decision maker may not be present. In such circumstances, ethics committees or Institutional Review Boards (IRBs) may consider waiving some or all of the required elements of the consent process if the potential benefits of the proposed research outweigh the potential risks [2]. Specifically, ethics committees or IRB may grant a waiver of consent if the clinical research study meets the following provisions: 1) The research involves no more than minimal risk to the research participant; 2) The waiver or alteration will not adversely affect the rights and welfare of the research participant and 3) The research could not practicably be carried out without the waiver or alteration [3,4].

One concern associated with waivers of consent is that they may lead to participants never knowing of their involvement in research and therefore leaving no opportunity for participants to ask questions or request to withdraw their data or biological materials [2]. Consequently, it is important to consider whether it is feasible and appropriate to advise participants of their inclusion in the research study at a later time. In the deferred consent model, a member of the research team provides the participant or their proxy decision maker with information regarding the research study at some point in time after the initiation of study procedures, and obtains their informed consent to continue participation in the research [2]. The deferred model of consent may be appropriate when research participation aligns with the aforementioned provisions for a waiver of consent.

Different consent models have been used in prior cluster randomized crossover trials (CRXO), including traditional consent models [5,6], waiver of consent [7–9], and deferred consent models [10–12]. The selection of a consent model varies based on the patient population, the level of risk associated with the intervention, the study outcomes and the data collection requirements. When planning many CRXO trials, researchers face a decisional dilemma when determining which informed consent model to use. This paper describes the use of a model of stakeholder and patient engagement to inform the decision on which model of consent to use in a program consisting of two pragmatic CRXO trials. It also examines the participant consent rate and the proportion of participants that withdrew consent as surrogate measures of the success of the selected consent model.

## 2. Methods

### 2.1. The PREP-IT program

The master protocol for the Program of Randomized trials to Evaluate Pre-operative antiseptic skin solutions in orthopaedic Trauma (PREP-IT) has recently been published [13]. Briefly, PREP-IT is comprised of two trials that leverage similar methodology and infrastructure. Aqueous-PREP (A Pragmatic Randomized trial Evaluating Pre-operative aqueous antiseptic skin solutions in open fractures) compares 4% aqueous chlorhexidine versus 10% povidone-iodine in at least 1540 open extremity fracture patients and PREPARE (A Pragmatic Randomized trial Evaluating Pre-operative Alcohol skin solutions in fractured Extremities) compares 2% chlorhexidine in 70% isopropyl alcohol (ChlorPrep™) versus 0.7% iodine povacrylex in 74% isopropyl alcohol (DuraPrep™) in at least 1540 open extremity fracture patients and at least 6280 closed lower extremity or pelvic fracture patients. All patients presenting to participating hospital sites with an acute fracture are treated with the pre-operative antiseptic skin solution as per the current PREP-IT treatment allocation. Patients are subsequently approached after the intervention and consented for follow-up data collection. Consent may take place up to three weeks after injury in open fracture patients and six weeks after injury in closed fracture patients.

### 2.2. Patient and stakeholder engagement

One of the hallmarks of the PREP-IT trials is the engagement of patient advisors and stakeholders in the design, implementation conduct, and dissemination of the PREP-IT trials. This was facilitated through the engagement infrastructure of The PATIENTS Program, a diverse group of professionals at the University of Maryland dedicated to improving patient care and including patient perspectives in research and health care delivery. Multiple members of the PREP-IT team provide insight into different aspects of the trials. Team members include three patient advisors who had suffered a severe fracture or another medical trauma, research methodology experts, patient centered outcome advisors, infectious disease experts, operating room representatives, military representatives, trauma research coordinators, and orthopedic surgeons. There were regular meetings and conversations with the research team during the early phases of the trial. Collectively, they discussed and reached consensus on decisions regarding the trial concept, design, governance structure, and plans for study implementation, conduct, and dissemination. During these discussions, patient advisors provided valuable insight into how key decisions regarding trial design and conduct would be perceived by participants, and the impact these decisions would have on them. Given the pragmatic design of the trial, the patient population, and the large sample size, the stakeholders and the patient advisory group members invested considerable time into developing an optimal model for consent.

### 2.3. Statistical analysis

Our statistical analysis plan was determined a priori. Consent rates

were calculated and reported as frequencies and percentages for the PREP-IT trials. While the PREP-IT studies are not closed to enrollment, analyses were conducted using data from screened patients from the initiation of enrollment on March 12, 2018 to April 24, 2020. The proportion of participants that initially consented to participate and subsequently withdrew their consent during the follow-up period was calculated using all participants at least one year from their enrollment date as of April 24, 2020 and this was reported as a frequency and percentage for the PREP-IT trials. All analyses were performed using SPSS v21.

### 3. Results

#### 3.1. Establishing an appropriate model for consent

Early meetings involved discussions regarding the optimal model of consent for the PREP-IT program. The traditional consent model, the waiver of consent model and the deferred consent model were brought forth and discussion ensued regarding selection of the most appropriate model. Together the team determined that the traditional model of consent that involves obtaining consent before the trial intervention may not be the most appropriate approach based on the following rationale:

- PREP-IT trials compare surgical preparation solutions that are commonly used as standard of care and all patients would receive one of the current solutions being used regardless of their participation in the trial.
- Obtaining consent prior to the patient's initial surgery via the traditional consent approach could add undue decision-making stress to a patient who is awaiting surgical management of a serious extremity injury. Conversely, allowing consent after their surgery would facilitate an improved consent process by allowing the patient more time to consider their participation in a more relaxed environment.
- It would not be feasible to consent patients that are unconscious or critically injured, and therefore, proxy consent would be required.
- Per standard clinical procedures, the decision-making process regarding choice of surgical preparation solutions is conducted by the surgical team and the patient is not involved in this decision.
- Participants are informed of pertinent information throughout the duration of the trial and afterwards.

As a next step additional models of consent were considered including a waiver of consent and deferred consent. Consent is required to contact study participants to ask them about their health, which is a necessary component of the PREP-IT protocols. Therefore, a waiver of consent was not appropriate.

In a deferred consent model, participant consent may be obtained following the intervention. In this model, consent is obtained to contact the participants for data collection purposes. Patient advisors felt that deferred consent is the ideal approach for PREP-IT, as it avoids the undue stress associated with preoperative consent in urgent circumstances, potential participants would have time to consider their participation, and the necessary consent would be obtained for data collection. All parties agreed to this and a deferred consent model was implemented in which patients are approached after their fracture surgery and prior to data collection. Further consultation with ethics committee and IRB members during the study design phase confirmed the acceptability of this approach.

#### 3.2. Rate of consent to participate and withdrawal of consent

The overall consent rate across the 27 clinical sites participating in PREP-IT was 80.7% (5316/6588). The consent rate for Aqueous-PREP was 86.7% (1219/1407) and the consent rate for PREPARE was 79.1%

(4097/5181).

The proportion of PREP-IT participants that withdrew consent during the one-year follow-up period was 0.67% (9/1324). Of these participants, 0.17% (1/586) withdrew from Aqueous-PREP and 1.08% (8/738) withdrew from PREPARE. Seven participants withdrew consent because they found the study too burdensome and two participants elected not to provide a reason for their withdrawal of consent.

### 4. Discussion

The traditional model of consent, which entails approaching patients and obtaining their consent to participate in a trial before initiating any trial-related activities, is commonly used in clinical trials but has limitations in certain settings and trial designs. In these situations, implementing either a waiver of consent or a deferred consent process may be more appropriate.

The PREP-IT program engaged patient advisors and stakeholders in the development of the protocol and solicited their input regarding the development of an optimal model of consent. Their contributions helped identify foreseeable challenges with using the traditional model of consent and they worked together with the research team to develop an alternative model. Specifically, they provided a unique perspective in assessing whether the PREP-IT program met the requirements for an alternative model of consent. Additionally, the patient advisors expressed concerns with implementing a total waiver of consent given the requirement to collect outcome data directly from the participants. Ultimately, they advocated for a deferred consent approach which was unanimously agreed upon by the research team.

This approach, although uncommon, has been reviewed and approved by multiple ethics committees and IRBs in Canada and the United States. We believe that this consent model may have beneficial consequences for the PREP-IT program. First, we anticipate that the large windows for obtaining consent that are made possible by our alternative model of consent will improve reliability and generalizability of trial findings by minimizing the number of missed participants. Second, the deferred consent model in studies involving standard of care procedures could decrease stress for participants by decreasing additional decision making at a crucial time in their medical care and increase participant satisfaction and sense of altruism regarding the involvement in a trial that provides benefit for future trauma patients. Third, it is possible that this informed consent model may lead to improved satisfaction among site research staff that conduct informed consent discussions. The deferred consent model allows for a more predictable and defined work schedule and eliminates the need for informed consent discussions with patients on evenings and weekends that are often required in research involving fracture patients requiring urgent treatment. Additionally, it allows time for patients to think about the research study and to discuss their participation in the study with their families.

The PREP-IT program's consent rate of 80.7% falls within the ranges of other recent large randomized controlled trials in fracture patients which report ranges between 69% and 99% [14–19]. Disparities in consent rates between Aqueous-PREP and PREPARE may be attributed to differences in the fracture populations across participating clinical sites.

The PREP-IT trials have experienced a very low proportion of participants that have withdrawn consent for their participation. This may be partially attributed to the low burden associated with participation, including no requirement for in-person follow-up visits. However, since previous research suggests that patients' level of understanding of a research trial and their ability to make informed decisions are positively correlated [20], it is possible that the consent approach adopted in PREP-IT improved understanding of the trial during the informed consent discussion and contributed to the low proportion of participants that withdrew consent during follow-up.

## 5. Conclusion

The engagement of patient stakeholders played an integral part in the development of an appropriate model of consent for the PREP-IT program, namely a waiver of consent for the trial intervention and deferred consent for the collection of outcome data from participants. With the success of this consent model in PREP-IT, researchers should consider seeking feedback from patient advisors when developing a model of consent in other large-scale trials where a traditional model of consent may not be suitable.

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## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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