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Waiver of consent in non-interventional, observational emergency research: the PROMMTT experience

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Abstract

Background—In the PROspective Observational Multi-center Major Trauma Transfusion (PROMMTT) study, waiver of consent was utilized because previous literature reported low response rates and subsequent bias. The goal of this manuscript is to examine the rationale and tradeoffs of using waiver of consent in PROMMTT.

Methods—PROMMTT enrolled trauma patients receiving at least one unit of red blood cells within 6 hours after admission at ten US Level 1 Trauma Centers. Local Institutional Review Boards (IRBs) from all sites approved the study. Site 8 was required by their IRB to attempt consent, but was allowed to retain data on patients unable to be consented.

Results—Of 121 subjects enrolled at Site 8, 55 consents were obtained (46%) and no patient or legally-authorized representative refused to give consent. Thirty-six (30%) patients died and 6 (5%) were discharged before consent could be attempted. Consent was attempted but not possible among 24 patients (20%). Of the 10 clinical sites, six of the local IRBs approved collection of residual blood samples, one had prior approval to collect timed blood samples under a separate protocol, and three reported that their local IRBs would not approve collection of residual blood under a waiver of consent.

Conclusions—Waiver of consent was used in PROMMTT because of the potential adverse impact of consent refusals; however, there were no refusals. If Site 8's IRB had required withdrawal of patients unable to consent and destruction of their data, a serious bias would likely have been introduced. Other tradeoffs included a reduction in sites participating in residual blood collection, and a smaller than expected amount of residual blood collected among sites operating under a waiver of consent. Non-interventional emergency research studies should consider these potential tradeoffs carefully before deciding whether waiver of consent would best achieve the goals of a study.

Level of Evidence—Prospective, Level II

Keywords

PROMMTT; Massive transfusion; trauma; waiver of consent

INTRODUCTION

A history of ethical issues in research practices have led to evolving guidelines for recruitment and consent of subjects such as the Nuremberg Code, Declaration of Helsinki, Belmont Report, and the Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines for Biomedical Research Involving Human Subjects. Principal guidelines for proper ethical conduct hinge on respect for individuals, beneficence, justice and protection of those involved.¹ In particular, protection of study participants through written consent has been stressed.²⁻⁴ Clinical research among critically ill or injured patients is essential to improve treatment options and reduce mortality and morbidity. Written consent of patients is often required when the purpose of gathered data is for research; however, obtaining consent from patients under emergency situations is difficult because patients are often unconscious, in shock, in severe pain, or intubated due to their injuries.⁵ Others may have experienced a disturbing event or act of violence that causes an altered mental state, making them unable to comprehend details of a complex research study. Denying these patients research participation due to difficulty of obtaining consent would violate the core research principle of justice.

Emergency research without initial consent has been a widely debated issue.⁶⁻⁸ Exception from informed consent (EFIC) is primarily used in intervention studies, including randomized controlled trials, and requires that the research have the potential for direct benefit to the patient and must involve an investigational drug or device administered before informed consent from the patient or the patient's legally authorized representative (LAR) can be obtained.⁹ Waiver of consent may be an option for any minimal risk study, which by definition usually do not involve interventions.¹⁰ Little discussion in the literature exists describing the rationale and use of waiver of consent in individual emergency research studies and thus it is difficult to identify best practices.

In 2009-2010, the PROspective Observational Multicenter Major Trauma Transfusion (PROMMTT) Study was conducted. Because this study subjected patients to no more than minimal risk, patients were not directly contacted, data collection needed to be initiated at admission before all eligibility requirements could be known, and all data were collected by direct observation of clinical procedures, abstraction of medical records and residual blood sample collection, we requested a waiver of informed consent at each PROMMTT Consortium site and the Data Collection Center (DCC). At the time, a waiver of consent seemed like the most appropriate consent process to prevent consent bias, lower participation rates, and reduced power seen in other studies.^{4, 11-15} In this paper, we will describe the impact of using waiver of consent in PROMMTT, contrast the experience at one site where consent was not waived, and describe lessons learned regarding waiver of consent in non-interventional, observational emergency research.

METHODS

Study design

PROMMTT was a prospective, multicenter observational cohort study at 10 US Level 1 trauma centers and collected data from July 2009 to October 2010. Severely injured patients requiring the highest level of trauma activation were enrolled at arrival and prospective data collection was initiated. Information on timing and results of vital signs, laboratory and

diagnostic tests, infusions, and other treatments were collected by direct observation until active resuscitation ended or 24 hours had elapsed. Additional information on treatment, complications, and outcome was collected daily from the medical record until death or discharge. Collection of residual (left-over) blood drawn for routine clinical laboratory tests was also planned in order to help standardize diagnostic laboratory assays that were not uniformly performed across all clinical sites. Patients were withdrawn from the study and their data were destroyed if they met any exclusion criteria after enrollment. Exclusions included pregnancy, prisoners, inhalation injury, more than 20% burn injury, receiving more than 5 minutes of CPR during pre-hospital care or within 30 minutes of admission, or death within 30 minutes of admission. The study design has been previously described in more detail elsewhere.^{16, 17}

Waiver of consent for clinical data collection was approved by the Institutional Review Board (IRB) at the Data Coordinating Center (DCC), nine clinical sites, and by a secondary review by the US Army Medical Research and Materiel Command Office of Research Protection, Human Research Protections Office (HRPO). One site's IRB (Site 8) requested deferred consent from surviving patients or LARs, but allowed retention of data on all patients unable to consent as long as all consent attempts were documented. Site 8's informed consent documents were available in English, Spanish and Vietnamese.

RESULTS

The number of enrolled patients at each site and other site characteristics are listed in Table 1. Because their IRB allowed them to retain data on all patients unable to consent as long as all consent attempts were documented, Site 8 enrolled 100% of eligible patients. Of the 121 subjects enrolled at Site 8, consent was obtained from 55 patients or their legally authorized representatives (45.5% of the total enrolled) and no patient or LAR refused to give consent. Thirty-six (29.8%) patients died and six (5.0%) were discharged or left against medical advice before consent could be attempted. Consent was attempted but not possible among 24 patients (19.8%). Reasons for not obtaining consent included patients and LARs speaking languages other than English, Spanish or Vietnamese and patients not able to consent due to altered mental status and no available LAR.

Among the ten clinical sites, IRBs at six sites approved the collection of residual blood samples under the waiver of consent for PROMMTT (Table 1). Of these six sites, one site never collected any residual blood samples because of difficulties identifying a clinical lab to process the samples. Of the remaining five sites, residual blood sample collection was achieved in 2-56% of the total number of patients enrolled at each site and 92-100% of patients had at least one sample that was able to be analyzed (Table 1). Residual blood sample collection began 4-5 months after data collection and so not all patients were eligible for sample collection. Another common reason samples were not collected was that no residual sample was available. Reasons for samples not being analyzed included inadequate sample volume, hemolysis, age of sample, sample thawing, and improper shipping methods.

Three sites did not submit the residual blood collection protocol to their local IRB because the site clinical research staff had received informal information from their IRB that they were not likely to approve residual blood sample collection under a waiver of consent. One site collected timed blood samples under a separately approved protocol and was approved by their IRB to share the laboratory testing results with PROMMTT (Table 1).

DISCUSSION

Waiver of consent is an important tool that can enable non-interventional, observational research in traumatically injured patient populations early after trauma when it may not be possible or appropriate to consent patients or LARs and the study is minimal risk. For some minimal risk studies, deferred informed consent may be a better choice. The decision to apply for a waiver of consent or deferred informed consent in an observational study must be made considering the tradeoffs associated with both.

The decision to apply for waiver of consent for PROMMTT was discussed amongst the members of the DCC, including IRB and ethics experts, and principal investigators from the clinical sites over several months during the set-up phase of the study. Our rationale was that PROMMTT would subject patients to no more than minimal risk, a waiver would not adversely affect the rights and welfare of the patients, the research could not be practicably carried out without a waiver, and patients would be provided with additional information after participation through publically available reports and peer-reviewed journal articles.¹⁰

We considered PROMMTT to be a minimal risk study because the study did not alter patient care in any way and patients were not directly contacted at any point. All collected data were derived from clinically indicated procedures, were not sensitive in nature, and were recorded in the medical record solely for the purpose of medical treatment. Data collection was performed prospectively by direct observation of patient treatment up to 24 hours after admission and daily abstraction of the medical record thereafter until death or discharge. No identifying information except for dates of admission, treatment, and discharge/death (for time to event and survival analyses) was recorded in the study database and all patients were assigned a random study identification number to protect confidentiality.

PROMMTT did not adversely affect the rights and welfare of patients under waiver of consent because the study was wholly observational in nature, participation in this study did not change the care that patients received, and observations recorded solely for the study had no effect on the care of the patients being observed. Because few published prospective data are currently available that examine the timing, order, type, and ratios of blood products given to major trauma patients, we considered PROMMTT vital to help determine best clinical practice and allow the rational and ethical design of future transfusion intervention studies.

The practicability of informed consent among critically injured trauma patients was a major concern to investigators before PROMMTT began based on prior literature and experience. Severely injured trauma patients who receive blood and are in shock may be unconscious, intubated, sedated, in pain, and/or just experienced a psychologically disturbing event. As such, they may be unable to comprehend, and it may be inappropriate to discuss the details of a research study at that time. Previous studies have reported that 23% of trauma patients were not able to give consent or have a LAR available to do so within the first 30 minutes of arrival¹⁸ and that 43% of trauma patients appeared incapable of consent.¹¹ Of these patients unable to provide consent, 20% had no LAR available to potentially provide consent.¹¹ Other studies have confirmed that proxies are often unavailable¹⁹ and if an LAR is located early, s/he may also be injured or psychologically impaired due to emotional distress.^{20, 21} A study of patients with traumatic brain injuries showed that all LARs arrived more than 30 minutes after the arrival of the patient; 10% of available LARs declined consent for patient participation in research; and of those who did provide consent, the mean time to LAR consent was 4.3 hours.¹⁹ This same study also found that more prospective study participants were excluded than were actually enrolled because no LAR was identified within the defined therapeutic window.¹⁹

For these reasons, it was clear to PROMMTT Investigators that consent was not possible immediately after patient arrival to the ED, but it was less clear how best to handle consent after that. Deferred consent from the patient or an LAR may be obtained when the condition of the patient is less critical. Unfortunately, this process could either exclude early fatal cases, or cause more stress to the LAR if approached after the death of the patient.²¹ CIOMS recommends that consent be waived if the patient dies.²²

Our rationale for waiver of consent for the daily medical record abstraction from 24 hours post admission until death or discharge was that the variables collected were similar in nature to variables collected in a trauma registry (additional transfusions and other life saving interventions and complications subsequent to initial resuscitation), but these variables needed to be collected prospectively from the medical record because of the level of detail required and concerns about errors in trauma registry data,²³ hospital administrative databases,²⁴ and in retrospectively abstracted medical records.²⁵ For example, during planning for PROMMTT we identified inconsistent documentation of the sequence and timing of blood product transfusion. Additionally, the literature suggests that information regarding transfusions is incorrect in the medical record 39.4% of the time,²⁵ and one study found surgical procedure codes missing in 11-22% of records.²³ For these reasons, we considered it best to prospectively collect follow-up data, using daily rounding and chart review to ascertain the best information on transfusions, other life saving interventions, and complications in the ICU soon after the transfusion, intervention, or complication has occurred to ensure high quality data.

Another concern with the consent process in PROMMTT was consent bias. Enrolling only patients who have the capacity to consent would drastically limit sample size, create selection bias, and reduce validity and relevance of the research being conducted.¹² Characteristics of consenting patients are likely different from non-consenting patients with regards to health outcomes^{14, 26} and at least one study has presented differences in mortality greater than the difference expected in PROMMTT.¹² In addition, differences in demographic features of consenters and non-consenters,¹³ including age,^{27, 28} sex,^{4, 27, 28} and of socioeconomic status^{15, 28} have been reported. Studies on the magnitude and direction of consent bias have shown inconsistent results^{26, 29} and anticipated bias introduced by requirements of consent are unpredictable,¹³ thus they cannot be adjusted for. During planning, PROMMTT Investigators expected a 30-60% refusal rate^{4, 11, 12, 14, 15} which would have threatened both the validity and statistical power of the study, making PROMMTT unethical.³⁰ Biased, invalid results would also make it impossible to provide meaningful guidance for the design of future intervention trials of potential benefit to all severely injured trauma patients. For these reasons, we decided to apply for waiver of consent for PROMMTT.

The IRB for Site 8 requested deferred consent, but allowed all data to be retained as long as all consent attempts were documented. For this reason, Site 8 was able to enroll 100% of eligible patients and therefore no consent bias was introduced. If their IRB had required consent in order to retain data, consent bias likely would have been introduced because 55% of patients were unable to provide consent. Patients who experienced early deaths, which are more likely to be due to hemorrhage, would not have been included in the study and validity and power would have been affected negatively in this transfusion study. These data suggest that it is important to request that data be retained at minimum for patients who die or leave the hospital before consent can be attempted (35% of patients from Site 8) in a trauma study using deferred consent.

One unexpected finding was that of 55 patients or LARs able to be consented, none refused to participate in this non-interventional study. Such a high level of participation is not

common in any type of study and we attribute it to the very experienced staff at Site 8 and the lack of intervention in PROMMTT. Although it is unclear if 100% participation could have been achieved at the other nine clinical sites, it does raise into question our original assumption that refusals would be 30-60%. Most studies reporting refusal proportions are intervention studies or randomized trials. If the refusal proportion for non-interventional studies is closer to 10-20%, then bias caused by refusals to participate may not be as impactful.

IRBs at six sites approved waiver of consent for collection of residual blood samples. If PROMMTT Investigators had applied for deferred consent, it would have been likely that the other three sites would have also gotten approval and participated in blood sample collection. Another tradeoff resulting from the decision to waive consent was that the blood sample collection was required to be from residual blood to ensure that the study was minimal risk according to all participating local IRBs. We originally designed PROMMTT under the assumption that trauma teams would draw a large-volume syringe of blood and fill collection tubes for clinical laboratory tests from the syringe. Any left-over blood in the syringe would be considered residual and could be used for research. However, vacutainer systems are becoming more common because of needlestick concerns and these systems fill the exact number of tubes required for clinical labs with no residual blood. Because vacutainers were so commonly used at the participating clinical sites by the time PROMMTT sample collection began, we collected fewer residual samples than expected, and the samples that were collected were of extremely small volumes (less than 5 mLs). If PROMMTT had used delayed consent, then blood samples could have been collected from all eligible patients at volumes that would have allowed for more research assays to be performed. However, if the refusal rate is high, selection bias may be introduced.

Results of PROMMTT were communicated back to each clinical site at the end of the study, allowing the site PIs to make any changes to their future practice they deemed necessary. Additionally, study findings have been disseminated in publically-available reports to the US Army and in peer-reviewed journal articles.^{16, 17} Release of study findings to individual patients whose data and samples were collected in this study is not possible because the DCC received only de-identified data and samples from the ten sites.

In conclusion, waiver of consent can be a valuable tool for performing non-interventional observational emergency research but tradeoffs exist that must be weighed against study goals. Deferred consent may be a more appropriate strategy for some studies, but requires working closely with the local IRB to create a consent process that will maximize study validity and power. More information regarding refusal rates, consent bias and other potential issues exists in the literature regarding interventional studies compared to non-interventional studies and inferences made on the basis of interventional studies may not be generalizable to non-interventional studies. More studies, including observational ones, should publish details about the consent processes used in emergency research and about any lessons learned so that best practices are easier to identify when planning future studies.

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Table 1

PROMMTT site characteristics

Site	Waiver of Consent?	Number of patients enrolled in PROMMTT	IRB approved residual blood collection	Number (%) of patients from whom discarded blood samples were collected	Number (%) patients with at least one sample analyzed
1	Yes	308	Yes	173 (56.2%)	170 (98.3%)
2	Yes	138	Yes	21 (15.2%)	21 (100%)
3	Yes	61	Yes	1 (1.6%)	1 (100%)
4	Yes	128	Yes	6 (4.7%)	6 (100%)
5	Yes	143	Yes	0	0
6	Yes	110	No	0	0
7	Yes	107	No ^I	0	25
8	No	121	No	0	0
9	Yes	101	No	0	0
10	Yes	28	Yes	13 (46.4%)	12 (92.3%)

^I Site 7 was approved to collect timed blood samples under a separate protocol, and results were shared with PROMMTT