Exploring ethical conflicts in emergency trauma research: The COMBAT (Control of Major Bleeding after Trauma) study experience

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Background. *Up to 25% of severely injured patients develop trauma-induced coagulopathy. To study interventions for this vulnerable population for whom consent cannot be obtained easily, the Food and Drug Administration issued regulations for emergency research with an exception from informed consent (ER-EIC). We describe the community consultation and public disclosure (CC/PD) process in preparation for an ER-EIC study, namely the Control Of Major Bleeding After Trauma (COMBAT) study.*
Methods. *The CC/PD was guided by the four bioethical principles. We used a multimedia approach, including one-way communications (newspaper ads, brochures, television, radio, and web) and two-way communications (interactive in-person presentations at community meetings, printed and online feedback forms) to reach the trials catchment area (Denver County's population: 643,000 and the Denver larger metro area where commuters reside: 2.9 million). Particular attention was given to special-interests groups (eg, Jehovah Witnesses, homeless) and to Spanish-speaking communities (brochures and presentations in Spanish). Opt-out materials were available during on-site presentations or via the COMBAT study website.*
Results. *A total of 227 community organizations were contacted. Brochures were distributed to 11 medical clinics and 3 homeless shelters. The multimedia campaign had the potential to reach an estimated audience of 1.5 million individuals in large metro Denver area, the majority via one-way communication and 1900 in two-way communications. This resource intensive process cost more than $84,000.*
Conclusion. *The CC/PD process is resource-intensive, costly, and complex. Although the multimedia CC/PD reached a large audience, the effectiveness of this process remains elusive. The templates can be helpful to similar ER-EIC studies. (Surgery 2015;157:10-9.)*

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New strategies to treat emergent conditions, such as trauma resuscitation[1] and trauma-induced coagulopathy (TIC)[2] have become a major research priority. Cohort studies in trauma resuscitation have been shown to be weakened by methodologic issues such as survivor and intervention biases.[3,4] For example, recent studies suggest that early plasma administration may mitigate TIC, but no randomized clinical trials have been conducted to test this hypothesis.[5-7] Therefore, randomized clinical trials are crucial to quantify better the effects of novel therapies, yet are difficult to implement in trauma emergency research. Trauma victims are a vulnerable population in immediate need of treatment and often are incapable of consenting to participate in a study.[8] Interventional studies in these patients

require the same level of protection afforded to persons able to exercise their right to consent or refuse participation. To study potential clinical interventions for this vulnerable population where consent cannot be obtained easily, the Food and Drug Administration (FDA) and the Department of Health and Human Services published regulations for emergency research with an exception from informed consent (ER-EIC) under Title 21, Code of Federal Regulation Section 50.24 in 1996.[9]

In a recent report,[8] our group published on the need for ER-EIC to evaluate novel therapies in the early resuscitation period and outlined in detail the required conditions to satisfy Title 21 Section 50.24. These federal regulations dictate a process of community consultation and public disclosure (CC/PD) in preparation for the ER-EIC trials. Despite heavy regulation surrounding ER-EIC, there is little guidance on how to conduct the CC/PD and no set goals to evaluate its effectiveness. The current report builds on the previous publication to expand the discussion of the ethical challenges while implementing the CC/PD and to provide an example of the CC/PD implementation and the application of the consent substitute model[10] for ER-EIC using the Control of Major Bleeding after Trauma (COMBAT) study as a model.

THE COMBAT STUDY

The Trauma Research Center in Denver, Colorado, has participated previously in two clinical trials under Title 21 Section 50.24 or ER-EIC: prehospital use of 7.5% hypertonic saline/dextran-70 (1991), and field use of polymerized human hemoglobin solution (PolyHeme) (2009).[11,12] Currently, we are preparing to undertake a third ER-EIC trial, funded by the Department of Defense, namely the COMBAT study.[13] The University of Colorado Denver, in collaboration with the Denver Health Medical Center, is one of three US institutions funded by the Department of Defense to study plasma administration in the field for severely injured patients with hemorrhagic shock. The COMBAT study is a randomized clinical trial to determine whether giving plasma in the field compared to standard crystalloid can attenuate TIC and improve adverse outcomes. Trauma patients in hemorrhagic shock defined by the Resuscitation Outcomes Consortium criteria (systolic blood pressure [SBP] <70 mm Hg or between 70 and 90 mmHg with a heart rate of ≥ 108 beats per minute) are eligible for enrollment.[14] Once eligibility is determined, patients will be randomized at the scene to receive in the ambulance en route to the hospital initial resuscitation with standard crystalloid fluid (standard group) or two units of frozen plasma, the experimental intervention. After arrival at the hospital, care is identical with serial blood sampling for physiology and coagulation assessment, ie, patients in both groups will receive crystalloid and blood products as determined by current management protocols.

COMBAT's therapeutic window for intervention is estimated to be only 8 minutes during when patient assessment, scene care, randomization, enrollment, and initiation of a saline or plasma infusion has to occur. This brief interval between contact and clinically beneficial treatment is the stage where we examine how conflicting ethical principles can be negotiated within ethical bioresearch.

BIOETHICAL PRINCIPLES AND ER-EIC UNDER TITLE 21, SECTION 50.24

Modern bioethics acknowledges four basic principles as follows: respect for autonomy, nonmaleficence, beneficence, and justice.[15] The first and overriding principle is *respect for autonomy*, meaning that the subject must be freely able to consent or decline participation in a study based on their values and beliefs without coercion and in circumstances that allow for appropriate communication of all available information and lead to truly informed consent. When the potential subject is incapable or unable to understand, the next of kin or designated legally authorized representative (LAR) must sign on behalf of the patient the consent with the details of the therapy being tested and the potential benefits and risks of participating. "Do no harm," or *nonmaleficence*, a vital principle of ethical research and a fundamental principle of medicine ("*Primum non nocere*") mandates that a scientific study should not result in harm to the participants. *Beneficence* is the bioethical principle that requires the research study to result in a benefit to the patient or society in general. *Justice*, the fourth principle, addresses the appropriateness of including/excluding vulnerable or incapacitated groups.

THE DILEMMA BETWEEN NONMALEFICENCE AND AUTONOMY IN EMERGENCY RESEARCH

All four research ethics principles must be applied in a prima facie manner, where each principle is obligatory unless there is a stronger or equal obligation, allowing for some negotiation.[15] In emergency research, autonomy and nonmaleficence may collide, making it difficult to advance science while maintaining an ethically sound study.

Typically in nonemergency research, investigators take time to communicate details of the study, discuss risks and benefits, and answer questions, but severe trauma requires immediate intervention to achieve stability within the "golden hour" for the best chance of survival with minimal morbidity. Paramedics remove patients safely from the scene and transport them rapidly to the nearest trauma facility. It is assumed that the patient wants aggressive, effective treatment to the injuries. Ideally, paramedics would contact a LAR or family member before study enrollment, but trauma sites are chaotic, and a considerable amount of patient care has to occur within the 8-minute therapeutic window. Respect for autonomy would literally require seeking family members in a crowd of bystanders, whom police are holding back away from the scene and searching an electronic database of people who opted out, risking nonmaleficence. Nonmaleficence mandates expeditious treatment of patients in hemorrhagic shock, which conflicts with the time and attention that would be devoted to respecting autonomy. Finally, paramedics themselves are not rarely at risk themselves at the trauma scene and must evacuate as quickly as possible.

CONSENT SUBSTITUTE MODEL

How then can we justify the enrollment of trauma patients in research investigations without their informed consent? The consent substitute model (CSM) consists of five conditions that are essentially restatements of 21 CFR 50.24 stipulations with more emphasis on honoring patients' values.[10] First, the experimental intervention must treat an urgent medical need in characteristically incapacitated patients. Second, the risk-benefit ratio of the experimental interventions must be comparable with standard emergency care of the patients' medical needs. Third, there should not be a conflict between the experimental intervention and patients' values, and if there is a conflict, there should be a mechanism in place for patients to exhibit their values, such as an opt-out bracelet. Fourth, the net risk should be minimal. Finally, consent for continued interventions should be obtained as soon as possible and research continued only after consent from the patient or surrogate has been directly acquired.

Applied to the COMBAT study, the first condition is met, because hemorrhage is a major cause for mortality in severe trauma patients and early administration of plasma may attenuate TIC. The second condition is satisfied because the eligible patients would likely receive plasma on arrival in the emergency department regardless of group assignment.

To satisfy CSM's third condition, in partnership with community groups and paramedics, we developed wearable opt-out identifiers (ie, study specific bracelet, dog-tag necklace) to ensure respect for autonomy and accommodate conflicting preferences. To meet the fourth condition, we ensured that the experimental group receives the same standard of care as the control group, except for the early administration of plasma. Both groups will follow standard algorithms for massive transfusion and critical care. We should emphasize the fact that in-hospital plasma is already part of standard trauma care, and timing (ie, in the field vs in-hospital) is the only change being tested in the study. In addition, despite lack of strong evidence supporting it, pre-hospital plasma is already standard of care in many locations.[16-18]

CSM's fifth condition requires prompt consent to be obtained for continued interventions. This is a major challenge in emergency research, where a LAR cannot be identified at the site of injury, and family members often cannot be identified for hours to days after injury. Laws regulating who can be a proxy decision maker (PDM) vary by state. In Colorado, if there is no previously identified LAR, all interested parties, including neighbors, friends, as well as biologically and legally related family members should gather to elect a PDM. Other states use an order of precedence to determine a PDM.

In a prospective study, Dutton et al[19] found that greater than 55% of patients with SBP <90 mm Hg could not be consented within 3 hours due to their own incapacitation and lack of an LAR or PDM. Similarly, only 7% of patients in the PROTECT trial of progesterone treatment for traumatic brain injury of patients could be enrolled within 3 hours using a proxy consent, and no consent could be obtained within 2 hours of the injury.[20]

Even proxy consent in the trauma population is challenging and requires major efforts to preserve the subject's autonomy and participation in the study. Furthermore, the existing solutions are somewhat imperfect. We are directing public attention to informing family members of one's wishes, encouraging person to wear opt-out emblems (which cannot be enforced), and respecting an uninformed "no!" from an undesignated surrogate. We are acutely aware that these are not altogether satisfying exits from this unavoidable dilemma.

MINIMIZING EXPOSURE TO RESEARCH-ASSOCIATED RISK

In any clinical study, we want to limit the intervention to those subjects who would benefit most from the intervention, because giving the intervention to those who will not benefit potentially violates the nonmaleficence principle by increasing exposure to the potential risks associated with the intervention. Unfortunately, predicting who will benefit is not an exact science. We can only use evidence from previous observations or published studies to define criteria or create prediction models of who will benefit from the intervention.

Ideally in the COMBAT study, all enrolled subjects would require plasma during resuscitation in the emergency department or intensive care unit, evading nonmaleficence by confining the difference between the standard and experimental groups to the timing of administration. Predicting who will receive plasma, however, is far from perfect. Despite advancements in our knowledge of TIC, we cannot predict accurately who will become coagulopathic and require blood product transfusions.[21]

These field criteria for eligibility are based on the multicenter Resuscitation Outcomes Consortium studies, the largest national effort for emergency research. After a previous, single institution pilot trial indicated that an SBP ≤90 mm Hg alone was not a good predictor of packed red blood cells transfusion, the criteria were modified to be SBP ≤70 mm Hg or SBP between 71 and 90 mm Hg with a heart rate ≥108 beats per minute.[14,22] By using Resuscitation Outcomes Consortium eligibility criteria in the COMBAT study, we minimize nonmaleficence by minimizing exposure of patients unlikely to require transfusion, which will satisfy the second condition of the CSM. In addition, we improve the generalizability of our findings and maximize the beneficence of the research study.

The necessity of justice. Justice requires that the benefits and risks be distributed equally and fairly. Trauma does not discriminate, allowing all patients to be enrolled for individual benefit. In the COMBAT study, subjects can benefit regardless of the group assignment. We are closely monitoring coagulation parameters, allowing early detection and prompt treatment of coagulopathy. To achieve justice in a study of ER-EIC, communities of all populations should have the opportunity to learn about the details of the study and to provide feedback about the study.

The COMBAT study excludes pregnant women and children. The risks and benefits of plasma in pregnant women and pediatric trauma patients are not yet known. Pregnant women physiologically are hypercoagulable with increased levels of clotting factors, decreased platelet counts, and decreased fibrinolytic activity.[23] Enrolling this susceptible population may subject them to greater risks of adverse effects such as blood clots. Similarly, the effects of early plasma in pediatrics are not yet known. The literature is beginning to show that pediatric trauma patients have evidence of coagulopathy,[24] but it is not clear whether children benefit from early plasma administration or from a greater packed red blood cells:fresh-frozen plasma ratio. Without evidence to support the risks and benefits of the early administration of plasma, these vulnerable populations were excluded from the study.

COMMUNITY CONSULTATION AND PUBLIC DISCLOSURE

According to 21 CFR 50.24, the COMBAT study requiring an exception from informed consent must be conducted under an Investigational New Drug or Investigational Device Exemption Application to the FDA. Thus, we began the regulatory process by contacting FDA for a pre-Investigational New Drug meeting, as well as informing our institutional review board (IRB) and the Research Ethics Consult Service of our intent to perform a study involving subjects who cannot consent, asking for insights they might have from other successful investigators, and seeking suggestions for study design refinements. These early involvements established good working relationships with the regulatory bodies from the start, a crucial step as we progressed toward FDA approval. The involvement of the IRB early on the process added the crucial element of community engagement, as the IRB composition includes members of the community (COMIRB Policies regarding Panel Membership: http://gcrc.ucdenver.edu/comirb/COMIRB-Policy-and-Procedures-Document.pdf, accessed March 22, 2013).

In preparation for ER-EIC, the FDA requires researchers to conduct a CC/PD. Despite heavy ER-EIC regulation, there is little guidance on conducting CC/PD and much less on evaluating its effectiveness.[25] Several experts have pointed out these difficulties and made repeated recommendations that clear outcomes be defined for the CC/PD process.[26-29] Yet, no consensus has emerged among researchers or trauma care providers regarding the CC/PD process. In contrast, the latitude in the regulations reflects the fact that

communities are unique; therefore, the process must be tailored to regional conditions and its effectiveness judged locally. Accordingly, the FDA recommends that, ultimately, the responsibility of determining how the CC/PD is conducted and its effectiveness be left to the local IRB.

The public disclosure component involves one-way communications to inform the community from which the sample will be drawn about the purposes, risks, and benefits of the study, whereas the community consultation component is a two-way communication approach where the community can voice their opinion and provide feedback on the study. During the latter, the investigators must be open to incorporate the community suggestions into the study design.

COMBAT's primary catchment region is limited to Denver County, which has an estimated population of 634,625 residents in 2012 (Colorado Division of Local Government, Demographic Section http://dola.colorado.gov/demog/, accessed March 22, 2014). Denver is an urban center to where suburban residents commute to work, play, and study, placing them "at risk" for traumatic events while in transit or at the destination; thus, our CC/PD was designed to encompass the larger Denver Metro area with a population of 2.9 million (Source: Colorado Division of Local Government, Demographic Section http://dola.colorado.gov/demog/, accessed March 22, 2014). Denver Metro has a large Latino population; therefore, the CC/PD included bilingual materials. We partnered with the Denver Health Marketing and Public Relations department and the local IRB (Colorado Multiple Institutional Review Board at http://www.ucdenver.edu/academics/research/AboutUs/comirb/Pages/comirb-home.aspx, accessed March 22, 2014) to devise a multimedia, bilingual approach illustrated in Fig. The Public Disclosure one-way communications involved: 1) bilingual (Spanish and English) brochures, 2) social and online media: study website at http://www.denverhealth.org/for-professionals/clinical-specialties/trauma-center/research-and-publications/combattrial and Denver Health Facebook page; and 3) traditional media (newspaper ads and articles, and television/radio interviews). The Community Consultation two-way communications were done via: 1) interactive presentations at ongoing gatherings at community-based organizations; all presentations were done by the study investigators followed by time for questions and answers, distribution of feedback forms, and opt out packages; 2) information phone hotline and e-mail; and 3) social and online feedback forms available at the COMBAT study website and the Denver Health Facebook page.

PUBLIC DISCLOSURE ONE-WAY COMMUNICATION

Brochure distribution. The brochure with a summary of the study and frequently asked questions was distributed at the community meetings, three homeless shelters, and 11 medical clinics within Denver City. These bilingual handouts were written at a middle school reading level and were translated into Spanish by native speakers (Supplementary File 1).

Social and online media. With the assistance of Denver Health Marketing and Public Relations, the COMBAT study website was created to be a central location for study information at http://www.denverhealth.org/for-professionals/clinical-specialties/trauma-center/research-and-publications/combattrial (accessed March 22, 2014). The bilingual (Spanish and English) brochures, a video about emergency research from the University of Michigan (with their permission), and the study presentation with audio recording were available for both viewing and downloading. The presentation was translated into Spanish by two native bilingual speakers and recorded in Spanish for viewing. Links to the website were posted on the Denver Health Medical Center Facebook page, and a blog was created where frequently asked questions and answers were posted.

Over 4 months, 1,835 people accessed the webpage. Web traffic peaked after our televised presentation to City Council and after our ad campaign (described in "Traditional media"). The website, email, and phone will continue to be monitored for the duration of the study.

Traditional media. We included more traditional media, such as print advertisements in the local newspaper and other citywide publications, including two Latino newspapers, one newspaper directed at the local African-American community, and a free, widely distributed newspaper listing local events around Denver. Table I depicts the characteristics of these media and their estimated circulation numbers. Our advertisement (Supplementary File 2) described the study briefly and directed the reader to the website for more information. The Public Relations Department suggested color advertisements on multiple days to draw attention to the advertisement and to expand the scope of the disclosure (Ad run schedule, Supplementary File 2). A press release statement was distributed to the local newspapers and networks. An article describing the study and including an interview with the Principal Investigator, Dr. Ernest E. Moore, by our local health

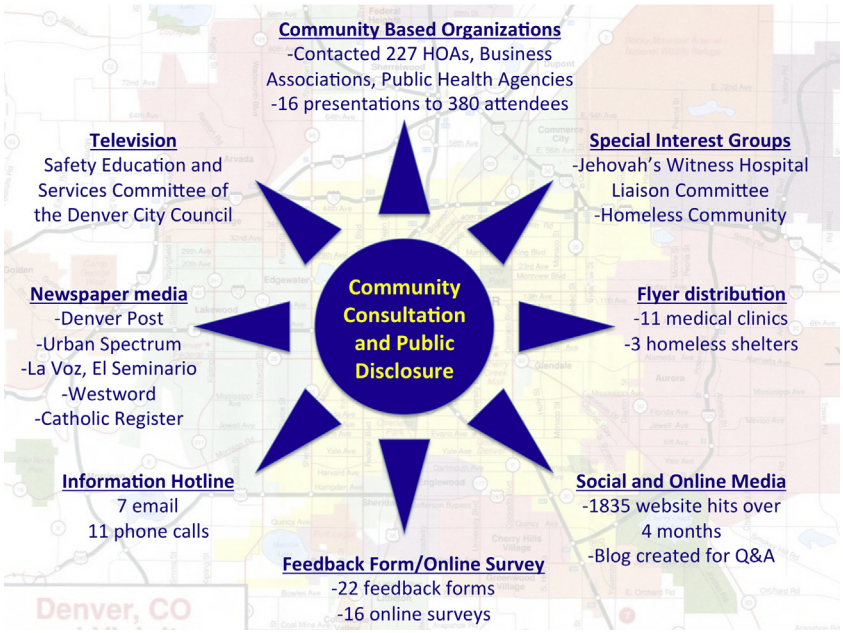

Fig. Community consultation and public disclosure chart.

Table I. News media reach

	Audience and general demographics	*Cost*	*Distribution and general description*
Denver Post	970,000 readers/Sunday	$6,900	Daily publication, general city newspaper
Westword	237,500 readers, 59% are ages 21–54 years	$750	Weekly publication, free paper of local news and events
Urban Spectrum	60,000 readers, primarily African American, ages 25–49 years	$523	Monthly publication, free distribution to the Denver metro area
El Semanario	50,000 readers, primarily Latino	$698	Weekly publication, free distribution to the Denver metro area
La Voz	100,000 readers, primarily Latino	$1,000	Weekly publication, free distribution to the Denver metro area
Denver Catholic Register	88,000 readers	$1,248	Biweekly publication, free distribution to the Denver metro area
Outside Marketing personnel cost		$3,000	
Total	Estimated 1.5 million readers	$14,119	

reporter was published in the local newspaper *The Denver Post* on February 4, 2013.

We presented the study to the Safety Education and Services Committee of the Denver City Council, which was televised on a local channel and is still available online linked from the study website.

COMMUNITY CONSULTATION TWO-WAY COMMUNICATIONS

Meetings at community-based organizations. We contacted 227 organizations within the study catchment area, including neighborhood and homeowner associations, chambers of commerce, clinics, and churches, as well as special interest groups (eg, Jehovah's witnesses, organizations serving the homeless) and the local Latino community. Supplementary File 3 contains a template of our e-mail/letter and the list of contacted organizations. The types of organizations are not unique to Denver, and entities with similar missions can be found in many urban centers. We chose to present the study at regularly held meetings in the community environment, to maximize attendance, and to use the community's time efficiently as recommended by Sauaia[30] in her proposed principles of community engagement.

A slide presentation (see Supplementary File 4) was created with heavy input from our IRB to familiarize the community meeting attendees with the study. Topics included the study's purpose and background, regulatory differences between COMBAT and other research studies, circumstances in which federal regulations allow exception from informed consent, risks/benefits, and opt-out opportunities.

Sixteen community organizations requested an in-person presentation at one of their meetings. The Principal Investigator (E.E.M.) delivered all of these presentations, and IRB members were invited to attend the meetings. Attendance varied from 5 to 50 persons, comprising a total of 380 attendees. All questions and comments were documented and submitted to the IRB for further review.

Information hotline and e-mail. A study-specific email address as well as a phone hotline was created to receive questions and comments. Over the CC/PD period, we received seven e-mails and 11 phone calls, primarily asking clarification about the specifics of the study.

Feedback forms. A feedback form (Supplementary File 5) was available at the project website and also dispersed at the community meetings. Of 16 respondents, 13 agreed to the study importance, the overall study, and the enrollment in the study without consent and 14 agreed that enough information was available to give an informed opinion about the study.

Opt-out methods. To comply with CSM's third condition, opt out methods were provided. Interestingly, opt-out methods are not required by FDA regulations, but an opt-out opportunity provides respect for autonomy based on the CSM. It is difficult to find a method to opt-out that is reliable in the acute trauma setting. Our Research Ethics Consult Service suggested more than one opt-out method to maximize respect for autonomy. Based on feedback from our IRB and from paramedics, we chose a bracelet and a "dog-tag" necklace that are easily visible in the acute trauma setting, minimizing the net risk, the fourth condition of the CSM. In addition, the bracelet and a dog tag-necklace could be worn discretely under clothing. We considered a wallet card, but when considered in the acute trauma setting, this method did not seem reliable. Paramedics are not always able to search for a wallet card and if required to do so, could jeopardize the clinical care of the patient, violating the ethical principle of nonmaleficence. An opt-out acknowledgement form was provided online and at community meetings (Supplementary File 6). Over 4 months, 98 opt-out packets were requested by 32 persons with different addresses, largely via website request. Interestingly, eight zip codes were within Denver City (the trauma center and paramedic catchment area), but the other 25 zip codes were from outside the catchment area in the greater Denver metro, probably reflecting the population who commutes to Denver for work, study, and leisure.

We specifically reached out to the Jehovah's Witness Hospital Liaison (JWHL) Committee because people of this faith refuse blood products, including plasma. Although most all Jehovah's Witnesses carry a durable power of attorney card in their wallet or purse, searching for a card did not seem to be a practical opt-out indicator, given the brief therapeutic window and the potential to increase the net risk, violating CSM's fourth condition. The feedback from the JWHL Committee was supportive, and they planned to encourage their congregations to use the opt-out methods provided by the COMBAT study. In addition, the JWHL Committee requested to participate in the paramedic training as an opportunity to educate health care providers about the beliefs of Jehovah's Witnesses and how to identify members of the congregation.

RESOURCES AND COST

This process is resource intensive. One study coordinator coordinated the 4-month long CC/PD process, resulting in costs of about $84,094 (Table II). There was intense time commitment of the Principal Investigator (E.E.M.), who attended all in-person meetings and edited all the documents before Colorado Multiple Institutional Review Board approval (64 hours) and 100 hours from Denver Health Marketing and Public Relations. The print advertisements cost approximately $14,000. In addition, there was in-kind support from native Spanish-speaking coinvestigators, who ensured an accurate translation of the informational materials. Overall, the CC/PD process was expensive and complex, providing a very real potential financial barrier for investigators interested in emergency research. The FDA does not specify who will bear the cost but assumes the sponsor or investigator will pay for these costs because the CC/PD is required to conduct the research study.[25]

DISCUSSION

The CC/PD phase for ER-EIC studies remains a challenge for which there is little guidance despite heavy regulation. A multimedia approach provides

Table II. Budget breakdown

Materials	
Advertisements	$14,119 (includes $3,000 for design and management of campaign)
Handout printing	$2,707
Opt-out materials	$3,065.25
Blog and website	$400
Translation of materials to Spanish	$160
Total materials cost	$20,451.25
Personnel	
Principal Investigator (64 hours)	
Study Coordinator (1,200 hours)	
Denver Health Marketing and Public Relations (100 hours)	
Study team members (128 hours)	
Total personnel cost	$63,643
Total estimated community consultation/public disclosure cost	$84,094.25

several modes to inform the community and for the public to voice an opinion concerning an ER-EIC study. In our previous experience and the experience of other ER-EIC studies,[31] public forum meetings are often poorly attended; thus, we felt that we could reach the "true" community better by attending scheduled meetings in the community rather than holding a public forum meeting at the hospital.

We focused a portion of our efforts on special interest groups, specifically Jehovah's Witnesses and the homeless community. It is difficult to estimate the portion of trauma patients who are homeless and the chance they could be enrolled in the study, although they are at high risk for trauma. It has been shown in the literature that homeless persons may have access to a computer or mobile phone and use the internet.[32-34] Although the access of internet and social media may vary by geography, social media and the internet have been explored as a means to reach the homeless population for public health purposes.[35,36] Although social media and the internet may not be the solution to reach the homeless population, it appears to be a viable alternative. Furthermore, we brought opt-out packets with us to the meetings at the homeless shelters and left additional packets for people who may not have access to the internet and wish to opt out of the study.

When we started planning the CC/PD, we anticipated receiving more opinions about the study. We thought our social media campaign would encourage more people to provide feedback. This was, however, not the case. Perhaps not as many people were reached as we had hoped, or rather, people may not have felt they were at risk for trauma and thus, may have been apathetic about the study and uninterested in spending time to give their opinion. Furthermore, people who are indifferent about the study may not be likely to provide feedback. Most people at community meetings showed interest in the study, but may not have provided feedback because their questions were answered adequately. Perhaps, people were not inclined to provide feedback because the COMBAT study is not testing a new product but instead examining the potential risks and benefits of early infusion of a product already approved by the FDA to treat bleeding trauma patients.

Previous studies of community consultation in this type of emergency research revealed similar low attendance to the community meetings and acknowledged that this process elicited few questions.[31,37-40] A recent successful CC conducted for study on burn victims reached close to 600 persons through community meetings for a target population of 4 million individuals, and a study on emergency anticonvulsant medications reached 317 individuals in Atlanta and San Francisco, suggesting that our numbers are similar for this type of CC activity.[41,42] Despite the low attendance at community meetings, there may be a ripple effect of dissemination of information about the study, such that people who attended the meeting may discuss the study with other people. Moreover, neighborhood organizations disseminated the information to their communities, reaching additional community members.

There is no metric to measure the effectiveness of our CC/PD process. The minimum amount of community participation or feedback necessary to proceed with the study is not specified in the regulation[9] or in the guidance for IRBs, clinical investigators, and sponsors.[25] The guidance allows for local IRBs to determine the appropriate amount of community activity based on the nature of the study and the local community. Our IRB was satisfied with the results of our CC/PD approach and has recommended this type of approach as a model for similar investigations in the Denver metro area.

Our description of the CC/PD process for the COMBAT study has limited generalizability

because it reflects the Denver metro area and is under the regulation of the Colorado Multiple IRB. Each IRB is unique to the local community and may have different requirements of investigators.

The challenges of research under exception from informed consent are daunting and, despite these efforts, evidence that the eligible public is truly informed and approving is lacking. As we seek assurance that we have planned an ethical study, we must balance the attractiveness of scientific advancement with the limitations and vexations of ethically conducted clinical research to gain maximal benefit for both the subjects and future patients.

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SUPPLEMENTARY DATA

Supplementary data related to this article can be found online at http://dx.doi.org/10.1016/j.surg.2014.05.021.

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