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Clinical paper

Variations in the application of exception from informed consent in a multicenter clinical trial

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Abstract

Background: Exception from infor med consent (EFIC) is allowed using federal regulations 21 CFR 50.24 and facilitates research on patients with critical conditions such as cardiac arrest. Little is known regarding the differences in the application of EFIC requirements such as community consultation (CC), public disclosure (PD) and patient notification. We sought to characterize variations in the fulfillment of EFIC requirements in a national multicenter clinical trial in the United States.

Methods: We determined the strategies for fulfillment of EFIC requirements at five regional coordinating centers of the Pragmatic Airway Resuscitation Trial (PART), a cluster-crossover randomized trial comparing airway devices in out-of-hospital cardiac arrest. We collected information from the including site demographics, how CC and PD were implemented, methods undertaken by the site investigative team to meet the local IRB's interpretation, and patient notification timing (post-enrollment). We analyzed the data using descriptive statistics.

Results: Sites had multiple approaches to CC, including social media advertising, random digit dialing surveys, working with city officials, and websites with embedded surveys. All sites used more than one approach for conducting CC. Public Disclosure activities included press releases through various means, website documentation, and letters to community members and local officials. Time from CC to study approval ranged from 42 days to 253 days.

Conclusion: EFIC implementation varies across sites and highlight community and regional variation. Different EFIC approaches may be needed to effectively accomplish the goals of community consultation, public disclosure, and patient notification.

Keywords: Clinical trials, Public disclosure, Exception from informed consent, Community consultation

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Introduction

Prospective research on acutely ill and injured patients is challenging because obtaining informed consent, due to the nature of the critical illness, is often impossible or impracticable. To address this, the US Department of Health and Human Services (DHHS) and the Food and Drug Administration (FDA) developed regulations allowing such research to occur, Federal Regulation 21 CFR 50.24, called exception from informed consent (EFIC) under emergency circumstances.[1]

The additional requirements of 21 CFR 50.24 include community consultation (CC) and public disclosure (PD). According to the FDA Guidance for Institutional Review Boards (IRBs), Clinical Investigators, and Sponsors, community consultation "means providing the opportunity for discussions with, and soliciting opinions from, the community in which the study will take place" with the goals of "showing respect for persons by informing the community about the study in advance", "provide a means for affected communities to provide meaningful input to the IRB before its decision to approve, require modifications to, or disapprove the study", "identify potential community-level concerns and effects of the research", and "obtain input from a group that is expected to be similar to the eventual study subjects".[2] Public disclosure has been interpreted by the FDA to mean dissemination of information by the sponsor (i.e., one-way communication) to the community, the public, and researchers about emergency research. It occurs before initiation of the clinical trial, after the trial has been completed, and whenever the IRB determines that new disclosures are appropriate.

An additional requirement of 21 CFR 50.24 is that "IRBs must ensure there are procedures in place to provide information at the earliest feasible opportunity about the subject's inclusion in the clinical investigation, the details of the investigation and other information contained in the informed consent document".[2]

Because of local cultural, population demographics, and IRB differences, optimizing these required processes of federal regulation 21 CFR 50.24 may vary in each community. Currently, there is limited understanding of the variation that occurs with any given multi-center EFIC study. For these reasons, we utilized an established clinical trials network (Resuscitation Outcomes Consortium; ROC) to describe the variation in implementation of CC and PD by all participating study sites in the Pragmatic Airway Resuscitation Trial (PART), a multicenter randomized clinical trial using exception from informed consent under emergency circumstances comparing the effectiveness of endotracheal versus laryngeal tube airway insertion on outcomes after out-of-hospital cardiac arrest.[3]

Methods

We report the CC and PD performed at each site involved in PART, a multi-center, prospective, randomized cluster with crossover clinical trial comparing two airway devices in out-of-hospital cardiac arrest (OHCA). Details of the study methodology have been described previously.[3] Briefly, PART compared 72-h survival from OHCA in adult patients initially managed with either endotracheal intubation or a supraglottic airway.[4] Because of the nature of the condition of cardiac arrest, 21 CFR 50.24, exception from informed consent under emergency circumstances was used for this study. PART was performed in 27 EMS agencies surrounding five US cities: Birmingham, Alabama; Dallas-Fort Worth, Texas; Milwaukee, Wisconsin; Pittsburgh, Pennsylvania; and Portland, Oregon. The IRB for each site approved the parent study and, when required, the IRBs of other local hospitals also reviewed and approved the study.

Data were collected during regular discussions between the site principal investigators and study authors and verified by the lead study coordinators for the parent study at the sites. We report CC and PD requirements regarding local demographics (number of EMS agencies, number of local IRBs that reviewed the protocol), IRB requirements for CC, PD, and patient notification, how the local investigators completed CC and PD, and timeliness of patient notification after study enrollment for each of the five sites. We analyzed the data using descriptive techniques.

Results

Sites had multiple approaches to CC, including social media advertising, random digit dialing surveys, working with city officials, and websites with embedded surveys (Table 1). All sites used more than one approach for conducting CC. The time from initiation of CC to local IRB approval ranged from 42 to 253 days. Public Disclosure activities included press releases through various means, website documentation, and letters to community members and local officials. The median interval (interquartile range [IQR]; % unable to be notified) across sites for notifying patients who had been enrolled was 21 days (IRQ: 15–23 days; 6.8%) for patients who did not survive to be transported, 24 days (IRQ 18–42 days; 3.3%) for patients who died within 72 h of ED arrival, and 8 days (IRQ: 3–25 days; 3.2%) for those who survived for 72 h or more post-arrival (Table 2).

Discussion

Within the context of a national multicenter clinical trial, we observed variations in the strategies used to fulfill the EFIC requirements. Sites reported different EFIC approaches, suggesting that the EFIC process may be impacted by regional demographics, epidemiology and outcomes of the studied event, local or regional course of care, variations in interpretation of the FDA guidance and cultural differences. While it is unknown why these differences occur, it is important to recognize this variability and future work will be needed to understand why the approach varies across different sites for the same study.

Our sites have completed multiple prospective, randomized clinical trials[4–10] over the last 10 years incorporating EFIC and have likely refined the CC, PD and notification practices over time to what has proved most successful. They have also integrating newer technologies (e.g. social media) when available, suggesting an iterative and adaptive methodology focused on a site or region's specific makeup.[11] Even with this experience, there remains great variability in the time from CC initiation to IRB approval to enroll patients and all sites required IRB review of proposed CC activities before conducting CC. These time intervals (ranging from 42 to 253 days) can represent significant challenges in terms of resources; specifically investigator time and cost. While we did not examine the financial or individual time resources (i.e. number of hours required to completed these tasks) associated with these activities, future work may be needed to help develop efficient strategies across sites to help reduce time and labor while ensuring the ethical treatment of human

Table 1 – Variation in EFIC processes.

	Total sites (n = 5)
Satellite IRBs	Yes (n = 5, 16 total)
IRB Required activities for CC	Not defined (n = 4)
	One 'town hall' style meeting in each county (n = 1)
Methods for conducting CC	– Facebook ads (n = 4)
	– Random digit dialing surveys (n = 3)
	– Contact local city officials (n = 2)
	– Website with survey (n = 3)
	– Booth at festivals/health fairs (n = 1)
	– Town hall' style meeting with a survey (n = 1)
IRB Required activities for PD	Not defined (n = 4)
	Press release announcing study start date (n = 1)
Methods for conducting PD	– Press release via any method(n = 4)
	– Press release via newspaper (n = 3)
	– Press release via radio (n = 2)
	– Press release via TV (n = 1)
	– Press release via bus ads (n = 1)
	– Press release via web ads (n = 1)
	– Website (n = 4)
	– Letters to local officials and community members (n = 1)
IRB Required sequence of CC/PD activities	CC and PD performed simultaneously (n = 3)
	CC then PD (n = 2)
Time from initiation of CC to study approval in days	Site A – 42
	Site B – 164
	Site C – 141
	Site D – 253
	Site E – 209

IRB — Institutional review board.
CC — Community consultation.
PD — Public disclosure.
TV — Television.

subjects. However, our work helps to better describe the techniques undertaken to achieve CC and PD in an EFIC trial while also reporting the successes with notification of enrollment in a mature research network.

While EFIC guidelines require patient notification as soon as feasible post-enrollment to allow an opportunity for the patient or a legally authorized representative (LAR) to opt-out of continued participation, there is a paucity of published guidance for these activities. In the PART study, ongoing participation was only in relationship to the collection of hospital-based data. Given the high mortality of OHCA, it was important to consider notification to the next of kin for patients who did not survive their cardiac arrest. Most sites adopted a strategy to notify and consent patients surviving to 72 h post-admission in-person, while sending letters to known next of kin for patients who died prior to EMS transport for ongoing treatment, or those who died in the ED or within the first 72 h of hospitalization. Given this timing, sites must have the ability to quickly know of and monitor patient status post-enrollment to identify availability of

Table 2 – Time from enrollment to notification in days.

	Died in pH[a]			Admitted to ED died <72 h[b]			Admitted to ED survived ≥72 h[c]		
	25th%ile	50th%ile	75th%ile	25th%ile	50th%ile	75th%ile	25th%ile	50th%ile	75th%ile
Site 1	12	14	18	11	14	18	7	15	31
Site 2	19	22	28	4	15	25	2	6	11
Site 3	21	21	22	23	39	57	3	7	36
Site 4	12	16	21	10	15	19	3	13	24
Site 5	21	24	27	22	24	27	3	11	25
All sites	15	21	23	18	24	42	3	8	25

pH — Prehospital setting.
ED — Emergency department.
Note — Sites A–E (Table 1) are different from sites 1–5 (Table 2) to maintain site confidentiality.
[a] 6.8% of these patients were unable to be notified.
[b] 3.3% of these patients were unable to be notified.
[c] 3.2% of these patients were unable to be notified.

patients or LARs for notification and consenting for ongoing participation, and to consider the clinical status in the timing.

As more studies have been completed using EFIC, greater focus has been spent understanding stakeholder impact of CC and PD, including EMS providers[12] and IRBs[13,14], and examinations of ethical implications of this research.[15,16] Previous work has described EFIC application in multi-site trials.[3,17–20] The methods described in these previous trials include newspaper, radio, or television advertisements, direct letters to community groups or individuals, presentations at community meetings or health fairs, random digit dialing surveys, and, more recently, the inclusion of technology and social media through internet advertising, web-based surveying and comment collection, and specifically-targeted Facebook advertising. These and other specific methods have been increasingly shared[21–26], and most note the variation in approaches given community needs and responsiveness.

These observations may have implications for future EFIC trials. As researchers and institutions at all study sites of NIH-funded multi-center clinical trials will soon be required to use a single, centralized IRB for approval, such as proposed for the Strategies to Innovate EmeRgENcy Care Clinical Trials Network (SIREN), stakeholders need to better understand and consider how this will affect execution of CC and PD. Recognizing and honoring local variation in implementing CC and PD may be crucial to optimize these processes locally. A 2018 study systematically reviewed FDA-reported CC and PD activities for 34 trials[27], indicating similar variability as our study, and concluded that there is a need to identify best practices and less uncertainty as to the implementation of CC and PD. With the current local variation in implementing CC and PD processes, there may be misunderstandings of what is required for CC and PD between local and centralized IRBs. Uniform, standard approaches to CC and PD, while potentially helpful to centralized IRBs, may fail to address the nuances of local CC and PD processes necessary to address local cultural and demographic differences. Future work will be needed to detail the ideal approach to local CC and PD with centralized IRBs.

Limitations

There are several limitations to our work. We report the CC and PD process of several sites in one trial. Our results were derived from five study sites. A larger sample size involving a greater number of sites over multiple trials may result in different findings. However, these sites have participated in multiple previous trials through the ROC network. As such, we believe they have a refined approach to CC and PD that may be beneficial for other sites that have less experience conducting CC and PD for EFIC trials. The EFIC approach in sites without extensive experience may be different. There was variability in both the approach to EFIC and the time from CC to IRB approval. Understanding why these differences occur, will require future study. Individuals who died in the prehospital setting or who were admitted to the ED and survived <72 h had longer time to notification than those who were admitted to the ED and survived ≥ 72 h. We believe this is related to the challenges in notification the LAR when an individual dies while recognizing the balance between these challenges and respecting the grieving period of families however, the ideal methodology and time interval for identifying and notifying LARs in these cases is unknown. All sites were relatively large metropolitan centers, and how these findings extrapolate to smaller communities and rural areas is unknown. The parent study (PART) focused on airway management in OHCA. As a result, these findings may not be generalizable outside clinical trials studying pre-hospital interventions for OHCA. The current EFIC study involved only adult study subjects and our findings do not necessarily apply to the pediatric study population.

Conclusion

Significant variability exists in implementation of CC and PD as well as the methods utilized to achieve these but less so with notification. The drivers of this variability are likely multifactorial but may be related to community factors such as demographics and cultural needs; regulatory factors such as interpretation of the FDA guidance variation; and other considerations including feasibility, convenience and study specific issues. Further study will be needed to determine the driving factors behind local variability. Recognizing and honoring local variation in implementing EFIC may be crucial to optimize these processes locally if centralized IRBs are utilized for future multi-centered EFIC trials. Future work will be needed to establish the ideal methods for recognizing local variability within the context of centralized IRBs.

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