

THE BIROS SECTION ON RESEARCH ETHICS

Implementation of the Exception From Informed Consent Regulations in a Large Multicenter Emergency Clinical Trials Network: The RAMPART Experience

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Abstract

Clinical trials investigating therapies for acutely and critically ill and injured patients in the earliest phases of treatment often can only be performed under regulations allowing for exception from informed consent (EFIC) for emergency research. Implementation of these regulations in multicenter clinical trials involves special challenges and opportunities. The Rapid Anticonvulsant Medication Prior to Arrival Trial (RAMPART), the first EFIC trial conducted by the Neurological Emergencies Treatment Trials (NETT) network, combined centralized resources and coordination with retention of local control and flexibility to facilitate compliance with the EFIC regulations. Specific methods used by the NETT included common tools for community consultation and public disclosure, sharing of experiences and knowledge, and reporting of aggregate results. Tracking of community consultation and public disclosure activities and feedback facilitates empirical research on EFIC methods in the network and supports quality improvements for future NETT trials. The NETT model used in RAMPART demonstrates how EFIC may be effectively performed in established clinical trial networks.

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The Neurological Emergencies Treatment Trials (NETT) network was created in 2007 by the National Institute of Neurological Disorders and

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Stroke (NINDS) to perform clinical trials of interventions given in the earliest phases of care for patients with acute neurological illness and injury, such as stroke or neurotrauma.¹ Because patients with these conditions are often unresponsive, and the treatments being studied are taking place in the ambulance or immediately on arrival in the emergency department (ED), many trials in the NETT can only be performed using a special set of federal regulations that govern emergency research. These regulations allow for an exception from informed consent (EFIC) for certain emergency circumstances and are described in the Code of Federal Regulations at 21 CFR 50.24.² In addition to specifying which types of studies are eligible for EFIC, these regulations require substantial pretrial community consultation and public disclosure (CC/PD) activities.^{2,3}

Although many EFIC studies have been performed, the processes of CC/PD remain poorly described and poorly understood. While sometimes used in other contexts, CC/PD are not required by regulation for any other type of research. In particular, little guidance exists with regard to implementing EFIC processes within large multicenter trials. Multicenter trials are more complicated than single institution trials because

CC/PD is conducted in more locations, interpretations of many diverse institutional review boards (IRBs) must be addressed, and results must be tracked and aggregated across centers for reporting to oversight bodies (IRBs, Food and Drug Administration [FDA], etc.).³⁻⁶ The presumption that processes should be customized to meet the needs of local communities, coupled with a lack of consensus about optimal CC/PD practices, or even the goals of such efforts, makes it difficult to standardize EFIC activities across a network. It is unknown whether central coordination within a network helps to address these issues.

The first NETT trial performed using EFIC is the Rapid Anticonvulsant Medication Prior to Arrival Trial (RAMPART). RAMPART compares intravenous (IV) versus intramuscular (IM) benzodiazepine anticonvulsants for the prehospital treatment of status epilepticus in adult and pediatric patients. Because establishing IV access can be challenging in convulsing patients in the field, IM midazolam has become increasingly popular for emergency medical services (EMS) use, but its safety and efficacy in this context have not been demonstrated in a clinical trial. RAMPART is a randomized double-blind, double-dummy multicenter noninferiority clinical trial designed to provide this information (clinicaltrials.gov identifier NCT00809146). The trial is being conducted at all 17 NETT “hub” hospitals, each of which is an academic medical center that coordinates research activities at a number of “spoke” hospitals and EMS systems.

We describe here the EFIC activities that took place within the NETT in preparation for the RAMPART trial, with emphasis on the special role an established network infrastructure can play in improving such efforts. The strategy was intended to optimize the protection of human subjects, enhance regulatory compliance, support local autonomy, and improve efficiency. This strategy, which employed novel methods of oversight and collaboration, may serve as a model for other EFIC trials conducted within large multicenter networks.

RAMPART TRIAL

Resources and Planning

At the outset, RAMPART investigators, as well as relevant regulatory bodies, recognized that the RAMPART trial would necessitate the use of EFIC. An EFIC plan was thus developed centrally and was included in the trial protocol,⁷ (also see Data Supplement S1, available as supporting information in the online version of this paper) and in an investigational new drug (IND) application to the FDA.

Concurrent with the development of RAMPART EFIC activities, a human subjects protections working group was formed to coordinate and optimize NETT EFIC activities. Members of the working group were drawn from the NETT steering committee and study coordinator group and from NETT sites based on interest and expertise. The purpose was to coordinate and foster empirical research related to EFIC.

RAMPART EFIC Meeting. Because participating sites had varying levels of experience conducting EFIC

trials, the RAMPART trial leadership convened a pretrial meeting to provide education on the regulatory aspects of 21 CFR 50.24. Investigators and study coordinators from each site were invited to attend. IRB members from NETT sites were also invited.

The meeting agenda included presentations from investigators experienced in emergency research with EFIC, ethicists, federal regulatory personnel, and IRB directors. The full agenda of the meeting is included in Data Supplement S1. Over the course of the 2-day meeting, there was extensive discussion about EFIC and opportunities for interaction between novice investigators and those with prior experience. The meeting also served as a forum to create a strategy for addressing potential barriers identified during implementation of the proposed trial. An opportunity was also available for site investigators to record custom video introduction footage for use in later community consultation activities. Finally, the meeting proceedings were used to inform the next steps in implementation of EFIC within RAMPART and the NETT.

Network Central Resources. EFIC implementation was coordinated centrally by the NETT Clinical Coordinating Center, and a full-time human subjects protection coordinator (HSPC) was hired for this task. Initially, the Clinical Coordinating Center developed generic templates for CC/PD activities that could be customized by sites for local implementation. This material was based on existing information from experienced investigators and from advice given by federal regulators.^{5,8} Educational videos, advertising templates, sample IRB applications, and documents were also developed by the Clinical Coordinating Center and were placed in a Web-based repository alongside materials developed by individual sites to promote sharing and reduce duplication of work.

The template EFIC plan included an overview of the EFIC regulations, the rationale for conducting RAMPART under 21 CFR 50.24, how the investigators planned to fulfill the requirements of the regulations, and how the results would be summarized and submitted to the IRB for its consideration. The EFIC plan also included a menu of options for CC/PD activities as suggested by the FDA draft guidance document and prior use in EFIC trials. Activities were categorized by method of communication and the potential targeted audience, and the pros and cons of each were described. The intention was for sites to choose activities that were most likely to be locally feasible within a reasonable time frame and which would yield the best information for IRBs to use in their deliberations. Sites were advised to consider the characteristics of their local populations and community resources and to choose a variety of complementary activities. Each site was expected to submit a local EFIC plan to the Clinical Coordinating Center for review and comments. Clinical Coordinating Center staff worked with sites to refine their plans and allowed for variability in EFIC plans as deemed appropriate by local sites.

In addition to serving as a central contact and facilitator for EFIC within the network, the HSPC was able to leverage the collective experience of the entire

network to address individual site issues as they arose. To provide oversight and assistance to sites, the HSPC traveled to each site and directly observed community consultation activities. She also participated in site readiness telephone calls to assure that community consultation was completed and that there was recent public disclosure activity in relation to trial start date. These activities allowed the HSPC to identify problems and variances as they arose and seek rapid solutions or intervention before significant regulatory or safety issues developed.

Metrics of EFIC Progress. The progress of the EFIC approval was tracked with a set of predetermined milestones that were attached to a payment schedule (Data Supplement S1, figure). Completion of milestones was documented in a tracking database. This system allowed for identification of sites having difficulty with EFIC processes and allowed the HSPC to interact with those sites to identify potential solutions.

Local investigators were encouraged to meet in advance of protocol submission with their IRB to discuss their proposed EFIC plan and to seek further input for CC/PD activities. Once finalized, the EFIC plan was submitted for formal IRB approval. After IRB approval of the EFIC plan was obtained, sites performed CC/PD activities. Throughout the CC/PD process, the HSPC provided regular updates and shared information on novel or unique approaches or findings with the steering committee.

Community Consultation and Public Disclosure. The human subjects protection working group recommended the creation of a database to track EFIC CC/PD activities. The database consisted of electronic data summary reporting forms that allowed for standardizing, aggregating, and sharing information collected during CC/PD activities. Summary data were entered in the network's centralized clinical trial management and data system. Sites provided estimates of the population reached through public disclosure activities that were based on the reported audience reach of media outlets. The database was accessible by any interested investigator for regulatory or academic purposes. A member of the human subjects protection working group was appointed to serve as a member of the trial's operations committee.

Experience and Outcomes

Timeline. Funding for the NETT Clinical Coordinating Center, including resources to conduct RAMPART as an EFIC trial and to conduct other trials, was awarded from the NINDS and the Office of the Director. The IND application was submitted to the FDA in April 2008 and approved in October 2008. The FDA raised no concerns about the use of 21 CFR 50.24 in RAMPART or the proposed EFIC plans. Among the 17 hub sites, local EFIC plans were submitted to IRBs in the first half of 2008 at seven hubs, in the second half of 2008 at seven hubs, and in 2009 at three hubs. An investigator training meeting was held in January 2009; enrollment in the study began in June 2009.

RAMPART EFIC Meeting. The RAMPART EFIC meeting held in January 2008 was attended by 21 IRB representatives (at least one from each hub); five invited external presenters experienced in regulatory and ethical aspects of emergency research; and 74 other investigators, coordinators, and NIH representatives.

Video. Three videos were developed as central resources. These 1) described the RAMPART study, 2) described the nature of clinical emergency medicine research, and 3) addressed a series of likely questions and answers. Investigators attending the RAMPART EFIC meeting were given the opportunity to record custom video introductions, and investigators from all 17 sites did so. The videos were created for a general public audience. They were posted to the national trial website and several hub-specific websites (links available in Data Supplement S1). Sites also used the videos to create public service announcements for television; as a multimedia aid in community consultation events; and in social networking environments, including Facebook and YouTube. Ten of the 17 sites ultimately used the video for online streaming, with live presentations, or for broadcast purposes. Complete Internet tracking reports for online viewing of the videos are not available, but the combined number of viewings for RAMPART videos on YouTube is currently 946 (through September 12, 2010). The videos were provided in short segments that could be combined or reordered and were otherwise customized to the needs of each site or use. The cost to create the videos, using a professional academic producer (Michigan Productions, Ann Arbor, MI), was \$22,000.

Toolbox. The Web-based toolbox containing both materials developed centrally and shared materials developed at hub sites included 153 unique documents including templates for community consultation presentations and public disclosure materials (slide sets, brochures, advertisements, and surveys in English and other languages). EFIC plans, IRB applications, informed consent documents, and related resources for training and enrollment were also uploaded to this shared site.

Examples of the most commonly used centrally provided resources include the detailed EFIC plan template, based on the plan submitted with the FDA, that explained how the trial met criteria for use of EFIC and provided a menu describing CC/PD options along with the rationale, advantages, and disadvantages of each approach. Although sites customized their own EFIC plans to address local IRB expectations, all sites used the text from the provided EFIC plan template as their starting point and chose approaches from the menu. All sites also cut and pasted language from centrally prepared templates for IRB applications and consent forms, including descriptions of the protocol, descriptions of risk and benefit, background, and other common components. The centrally provided slides and brochures were also commonly used by study sites.

Examples of successful centrally facilitated site-to-site sharing of EFIC community consultation resources included a common script and survey shared by sites

doing random-digit dialing, frequent exchanges of slides and advertising copy between sites, and frequent sharing of community consultation meeting survey questions and focus group instruments.

Metrics of EFIC Progress. Hub sites were provided monetary resources necessary to engage in a robust EFIC process. Three payments were contingent on achieving explicit prespecified milestones: 1) submission of a local EFIC plan to the participating site IRB, 2) completion of a schedule of CC/PD activities, and 3) local IRB approval to begin enrollment. The interval between the RAMPART EFIC meeting and the first EFIC milestone ranged from 1 to 19 months with median of 5 months (interquartile range [IQR] = 2 to 8 months) and a mean (\pm SD) of 7 (\pm 6) months. The interval required for community consultation from approval of local EFIC plans to final IRB approval to start enrollment ranged from 2 to 14 months, with a median of 7 months (IQR = 5 to 9 months) and a mean (\pm SD) of 7 (\pm 3) months.

The trial protocol was reviewed and approved by 43 unique IRBs (many institutions and all EMS systems deferred to other local IRBs). One municipal IRB reviewed but did not approve an application to conduct RAMPART in its city EMS system, citing liability and other concerns. As required by 21 CFR 50.24(e), this nonapproval was reported to other reviewing IRBs and the FDA.

Community Consultations. For RAMPART, 225 NETT community consultation activities at 17 hubs have been reported, involving over 23,898 participants. Feedback from 6,846 individuals included 50,275 closed-ended responses and 2,635 open-ended responses and comments. Qualitative coding of responses expressing support or concern for EFIC identified 79% of closed-ended answers and 77% of open-ended comments as supportive. Table 1 describes the frequency of various types of community consultation events and the number of reported participants by type. The most common types of community consultation activities included visits to existing group meetings (43%) and focus groups or interviews (19%).

Table 1
Frequency and Number of Participants in RAMPART Community Consultation Activities by Event Type

Type of Community Consultation Event	<i>n</i>	(%)	Participants
Existing group meeting	97	(43)	4,405
Focus group/face-to-face interview	43	(19)	604
Unscheduled feedback	35	(16)	59
Town hall style meeting	21	(9)	256
Booth/table/exhibit	19	(8)	16,850
Internet survey	6	(3)	704
Random-digit dialing telephone survey	2	(1)	1,003
Other (call-in radio show)	2	(1)	17

RAMPART = Rapid Anticonvulsant Medication Prior to Arrival Trial.

Other types of activities included a booth or table at events (8%), town hall meetings (9%), phone surveys (using random digit dialing) or Internet surveys (4%), and call-in radio talk shows (1%). Unscheduled feedback (phone calls, e-mail, etc.) was also collected. Table 2 shows how these activities and participation were distributed by hub. Events were directed toward geographical communities 68% of the time and seizure risk-related communities in 32%. Groups involved included the general public (56%), parents (13%), children (8%), medical professionals (19%), ethnic or racial groups (6%), religious groups (2%), civic leaders (8%), and others (these add up to more than 100% because some events involved multiple categories of participants). Participants in community consultation activities self-assessed their comprehension of key elements of EFIC as being quite strong (detail provided in the Data Supplement S1).

There was no important or statistically significant interaction between the numbers of reported participants in community consultation activities by hub, the number of events, the timing of IRB approval, or the number of subjects eventually recruited at that hub hospital. For submission to oversight bodies, aggregate reports of community consultation results were prepared using an automated standardized template that both includes a "high-altitude" overview of summarized findings and then includes detailed listings of individual responses. The report, including both numerical and graphical presentations of the community consultation results from throughout the network, is included in Data Supplement S1. A more detailed exploration of the community consultation experience in RAMPART is beyond the scope of this report and will be reported separately.

Public Disclosure. There were 289 public disclosure activities over 22 months reported at 17 hubs, with a cumulative estimated potential target audience of 12,978,315 people. Pretrial activities took place between April 26, 2008, and February 17, 2010, and the median disclosure date was April 10, 2009 (IQR = November 21, 2008, to September 1, 2009). Further ongoing and post-trial public disclosure activities are not reported here. Traditional media were commonly used, including newspaper stories or announcements in 18% and radio and television broadcasts in 10%. These accounted for 75% of the estimated target audience. Electronic media including e-mail distributions, on-line postings, and website visits constituted another 19% of activities, and contributed 11% of the estimated target audience. Other methods of public disclosure included brochures, posters, fliers, direct mailings, billboards, information booths, presentations, and other communications. Disclosure activities were sometimes directed toward the epilepsy community through stories or announcements in epilepsy support or advocacy newsletters or through the use of advertisements on public transportation, since those with frequent seizures are less likely to drive.

The estimated total cost to hubs for public disclosure activities (excluding study team time or manpower hours) was \$105,711, although this underestimates

Table 2
Community Consultation Events and IRB Approval Details by Hub

Hub	Types of CC Events Reported, Ordered by Frequency at Hub	Number of CC Events	Number of Participants	Months to Approval of CC Plan	Months to IRB Final Approval	Months From CC Plan to Final Approval
A	EGM, B/T, FG	5	130	19	24	5
B	EGM, B/T, FG, I	22	11,245	6	11	5
C	EGM, B/T, I	23	574	8	22	14
D	EGM, B/T, RS	11	212	7	15	9
E	EGM, B/T, THM, FG, S, US	20	215	7	17	10
F	EGM, FG	8	180	7	14	7
G	EGM, I	8	1,635	18	21	3
H	EGM, I, THM, B/T, S, US	14	751	12	17	5
I	EGM, I, THM, FG, S, US	18	288	8	22	14
J	EGM, THM, FG, S, US	16	560	8	17	9
K	EGM, US	15	148	3	9	7
L	FG, EGM	13	193	8	14	5
M	FG, EGM, I	9	260	5	12	6
N	RDD, EGM	2	506	20	27	8
O	RDD, EGM, US	8	514	9	12	3
P	S, FG, US	6	124	5	12	7
Q	THM, B/T, EGM, US	30	6,475	3	12	9

Intervals are the number of months: 1) from the RAMPART EFIC meeting until reported IRB approval of a plan for performing community consultation, 2) from the RAMPART EFIC meeting until final IRB approval to enroll subjects, and 3) from reported IRB approval of a plan for performing community consultation to final IRB approval to enroll subjects.
 B/T = booth or table at event; CC = community consultation; EFIC = exception from informed consent; EGM = existing group meetings; FG = focus groups; I = face-to-face interviews; IRB = institutional review board; RAMPART = Rapid Anticonvulsant Medication Prior to Arrival Trial; RDD = random-digit dialing telephone survey; RS = call-in radio show; S = Web or mail surveys; THM = town hall meetings; US = unscheduled feedback.

the true dollar value of these activities since many sites were able to leverage publicly funded or donated media access. Public disclosure activities were reported to be associated with a total of 14 requests to opt out of the trial. If one interprets the purpose of public disclosure as a means to allow potential subjects to opt out, this is a remarkably low total that could reflect a low level of concern about the trial or low penetration of the message. If, however, the purpose of public disclosure is primarily to ensure transparency in and of itself, then the low number of opt-outs is a less important finding because transparency per se does not require high message penetration.

EMS Participation and EFIC. Thirty EMS services operating in 14 states participated in the trial. The majority of hubs worked with a single EMS agency, but others involved as many as six. Two thirds of the systems were fire-service based, and the rest were private, third-service, or hospital-based services. Participating systems ranged widely in size, with 27% performing <5,000 runs/year and 20% performing >100,000 runs/year. EMS participation in EFIC community consultation activities was variable, but was infrequent at the majority of sites. In several systems, however, paramedics or EMS system leadership participated with the investigators and other study team members in visits to existing meetings or in presentations at town hall meetings. No quantitative data on the frequency of this participation were collected. One site obtained additional NIH funding (5RC1NR011536-02) for a robust and successful multifaceted approach to community consultation and engagement that included use of EMS personnel as community liaisons.^{9,10}

On another level, administrative approval of the trial including EFIC was obtained from all participating agencies. All EMS entities had or obtained a Federal Wide Assurance (FWA) designating an IRB of record or were explicitly covered under the FWA of the institution housing the IRB. Hub institutions coordinated participation and approval with these disparate organizations through a combination of collaborative protocol approvals and implementation activities, ongoing training activities that often involved a paramedic educator supported by the study, and ongoing screening of EMS run logs for evaluation of potential missed enrollments. Support for a national EMS coordinator for the study, for local EMS coordinators at each hub, and for leadership effort and payment of training costs as needed was critically important to this success.

DISCUSSION

The complexities and novelty of the EFIC regulations are widely thought to have had a chilling effect on the conduct of emergency research trials, especially multicenter trials where many IRBs will be involved. The recent creation of federally funded emergency clinical trials networks, like the NETT (as well as the Pediatric Emergency Care Applied Research Network [PECARN] and the Resuscitation Outcomes Consortium [ROC]), offers an opportunity to address this concern through implementation and evaluation of innovative practices.

Building processes for performing EFIC trials within a clinical trials network has several advantages compared to implementation for a single multicenter trial. Because the EFIC processes will be repeated and refined for future trials, the network can justify greater

initial investments of time, energy, and resources in their development. Based on our experience with EFIC in RAMPART, we refined our database structure and standardized survey questions for community consultation for the next EFIC trial being conducted in the NETT. Furthermore, the network provides an incubator for empirical investigation in research ethics. These include an NIH-funded ancillary trial (5R03NS066378-02) to qualitatively assess RAMPART subject attitudes about having been enrolled with EFIC. Additional funding has been obtained to extend this investigation in the next NETT EFIC trial. These projects, and their continuity from one trial to the next, directly benefit from the concerted network approach to EFIC. Similarly, participating institutions in a network are able to simultaneously develop or refine their own expertise in the review and oversight of EFIC research. Perhaps most importantly, our model, which emphasizes strong central resources and guidance but allows flexibility and individualization at the local level, provides a dynamic laboratory for comparing the various experiences of different sites. For example, a wide array of community consultation activities was conducted within the NETT around the same EFIC trial; this “federated” model ultimately may allow identification and recommendation of best practices.

The cornerstones of the NETT model for network implementation of EFIC research are 1) development of central resources, 2) sharing of information and experiences between sites, and 3) central tracking of results. Central resources including the NETT HSPC, study media, and regulatory templates promote efficiency and help ensure a common and accurate message. The HSPC and network information technology are also central resources that enable site-to-site information and resource sharing. Sharing of information and experiences between sites began with the IRB investigator meeting at the outset of implementation and continued into the trial. Sites shared solutions to common challenges and exchanged additional tools they created. Central tracking of EFIC-related activities allows the NETT to provide consolidated reporting across the trial to better meet sponsor FDA and IRB reporting obligations. It also permits comparisons among sites and event types and allows the network HSP working group to monitor activities and advise the trial and network leadership. As seen in our data, the time to achieve certain EFIC requirements varied widely. Investigation of the reasons why some sites require more time to fulfill the same requirement for the same study may provide useful information that can inform NETT investigators planning future EFIC trials.

Key to the timely and cost-effective implementation of EFIC in the NETT is adequate and strategically allocated funding. Sites received milestone payments for completion of essential steps in the EFIC process. A uniform budget of \$50,000 per site was provided to complete the EFIC-related milestones; this was separate from the cost of centrally available NETT materials. This budget was based on the anticipated costs of CC/PD activities. Actual costs may vary, but a trial of the magnitude of RAMPART will always require significant

up-front funding to adequately meet the obligations of EFIC and the desired community engagement and penetration.

LIMITATIONS

There are several limitations to the description of the model presented here. While we believe these central resources reduced the burden of fulfilling the EFIC requirements, we have no comparative data to verify our impression. No similar system has published data from its experiences. We also do not know which central resources were most frequently used or were the most useful. CC/PD activities were self-reported by the sites and could not be independently monitored for accuracy. Most of the central resources provided in the toolbox do not have a metric for their actual utility. Because the purpose of CC/PD is still not objectively defined, there is no authoritative way to describe whether any particular practice is more “effective” than any other. Available metrics of the performance of community consultation and public disclosure are purely observational.

CONCLUSIONS

A coordinated approach to implementation of exception from informed consent trials within a multicenter clinical trials network promises to improve the quality, efficiency, and accountability of these efforts. The Neurological Emergencies Treatment Trials provides a model of network exception from informed consent implementation in which best practices of community consultation/public disclosure may be identified and disseminated. Key elements of successful networkwide EFIC activities are the provision of central resources with retained local control and flexibility, sharing of information and resources between sites, and central tracking of site activities. Adequate funding and strategic management of timelines are also important. The Neurological Emergencies Treatment Trials model of EFIC implementation in a large multicenter clinical trials network was successful in allowing the trial to be performed on time at all hubs. Although there are no consensus metrics for exception from informed consent performance, the model appears to be effective and efficient and will continue to be refined in future trials in the network.

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APPENDIX

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Supporting Information

The following supporting information is available in the online version of this paper:

Data Supplement S1. Links.

The document is in document format.

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