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Enrollment in Research Under Exception from Informed Consent: The Patients' Experiences in Emergency Research (PEER) Study

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Abstract

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Background—Resuscitation research requires an exception from informed consent (EFIC). Despite concerns that patients may find EFIC unacceptable, the views and experiences of patients enrolled in an EFIC study are largely unknown.

Methods—The Patients' Experience in Emergency Research (PEER) Study was nested within the Rapid Anticonvulsant Medication Prior to Arrival Trial (RAMPART) for pre-hospital treatment of status epilepticus. PEER included 61 EFIC enrollees or their surrogates from 5 sites. Interviews used a structured, interactive guide focusing on acceptance of EFIC enrollment in RAMPART and existing regulatory protections. Simple statistics were generated, and textual data were analyzed for common themes.

Results—24 enrolled patients and 37 surrogates were successfully interviewed. 49/60 (82%) were glad they or their family member were included in RAMPART; 54/57 (95%) felt research on emergency seizure treatment is important. 43/59 (73%) found their inclusion under EFIC acceptable; 10 (17%) found it unacceptable, and 6 (10%) were neutral. There were no statistically significant interactions between enrollment attitudes and demographic characteristics, though there were trends toward lower acceptance among interviewees who were non-white, less educated, or had prior research experience. The most common concerns related to lack of consent prior to RAMPART enrollment. Positive responses related to perceived medical benefits, recognition of the impracticality of consent, and wanting doctors to do what needs to be done in emergencies. Many participants had difficulty understanding the trial and EFIC.

Conclusions—Most subjects had positive views of enrollment, and acceptance generally correlated with results of community consultation studies.

Introduction

Federal regulations allowing an exception from informed consent (EFIC) for research in emergency settings have facilitated pivotal trials, but EFIC research remains challenging and controversial.^{1,2} Some challenges stem from requirements for community consultation and public disclosure, but fundamental concerns remain about attitudes of the public and enrolled patients. Patients' attitudes are particularly relevant, because EFIC regulations are designed to facilitate research in settings where consent is not possible but not to take advantage of incapacity in order to enroll patients against their wishes.³

There is a body of literature addressing attitudes toward EFIC, mostly in the context of community consultation efforts and surveys of the general public.⁴ Approval of the concept of EFIC ranges widely (from 36% to 81%).⁵⁻⁹ Acceptance of hypothetical personal EFIC enrollment scenarios has also varied significantly (from 45% to 94%).^{7,10,11} In contrast, several studies involving patients who have survived conditions such as stroke, traumatic brain injury, and cardiac arrest have reported greater support.^{12,13} A recent Finnish study similarly found broad EFIC support among individuals, physicians, and surrogates involved in a pre-hospital trial of hypothermia induction after cardiac arrest.¹⁴ However, these patients had been enrolled in the hypothermia trial under surrogate consent rather than under EFIC.

While informative, these studies have thus reported hypothetical views on EFIC enrollment. Moreover, most have utilized closed-ended survey instruments offering little insight into reasons for particular views or attitudes. It is unknown whether these data reflect views of patients (or surrogates) actually enrolled in an EFIC trial. The Patients' Experiences in Emergency Research (PEER) study was nested within the Rapid Anticonvulsant Medication Prior to Arrival Trial (RAMPART) by Silbergleit et al. and was designed to address these knowledge gaps.¹⁵

Methods

The principal objective was to assess the views of actual EFIC subjects and surrogates regarding acceptability of EFIC enrollment. Other goals were to assess patient and study factors predicting acceptance of EFIC enrollment and to evaluate the accuracy of community consultation in predicting enrollees' concerns. PEER was nested within RAMPART, a double-blind, randomized, noninferiority trial comparing intravenous lorazepam with intramuscular midazolam in pre-hospital treatment of status epilepticus (clinicaltrials.gov NCT00809146).¹⁵ RAMPART was an EFIC trial conducted within the Neurological Emergencies Treatment Trial (NETT) network.¹⁶

Five geographically diverse RAMPART hub sites were selected for PEER: Atlanta, GA; York, PA; Minneapolis, MN; San Francisco, CA; and Cincinnati, OH. All RAMPART enrollees over age 18 at participating sites were eligible. Subjects under 18 or incapable of being interviewed due to impairment or death could not be included. However, parents or other surrogate decision-makers (identified locally) for these populations were eligible in order to represent the views of all enrolled subjects. All interviews were conducted in English, though a Spanish-speaking interviewer was available.

Participants were identified by local study staff. Eligible participants were asked for permission to be contacted about PEER or sent an opt-out letter stating they would be contacted unless they wished otherwise. Oral informed consent was obtained at the time of interview. Participants were given a \$35 gift card for participating, regardless of whether they finished the interview. Each site maintained a trained interviewer. Interviews were conducted in-person or by telephone and were audio-recorded and transcribed verbatim.

The PEER study was reviewed and approved by each site's institutional review board (IRB).

Interview Methods

This study employed a structured interview guide containing open and closed-ended questions with three principal goals: 1) to obtain quantitatively meaningful data with reliable estimates of prevalence of particular views; 2) to allow subjects to ask content-related questions to maximize understanding of and develop views on content being discussed; and 3) to qualitatively assess reasons for responses and subjects' level of understanding. This interview method, derived from prior work, suits the complex nature of the content and the study's descriptive aims.¹² The interview guide was cognitively pre-tested with RAMPART enrollees to ensure that questions were understandable. Interviewers were trained by one investigator (ND).

The interview guide (Appendix 1) contained 11 domains: prior research experience, knowledge of RAMPART, views on personal EFIC inclusion, views on acceptability of EFIC generally, views on randomization, interactions with RAMPART staff, views on community consultation, impact of public disclosure, trust in researchers, subject demographics, and medical background. Each core domain featured an introduction and opportunity for clarification, followed by a five-point Likert Scale question (see Box 1) and probes regarding reasons for the response. Interviews generally lasted 20-30 minutes.

Analysis

Closed-ended responses and pre-defined codes for text data were entered into a database. Data were analyzed using SAS 9.3 (SAS Institute Inc., Cary, NC, USA), with answers "1" and "2" collapsed as "agree," "3" as "neutral," and "4" and "5" as "disagree." Descriptive statistics and bivariate analyses (Chi-Square for proportions, Fisher's Exact test for dichotomized questions, and Kruskal-Wallis test for ordinal categorical answers) were

calculated, consistent with hypothesis-generating goals. Textual data were redacted for errors and analyzed using MAXQDA 10 (VERBI GmbH, Berlin, Germany). Qualitative analysis focused on identifying common themes and contextualizing quantitative responses. A multi-level coding strategy was employed; data were principally coded by one author (VM). Domain-based codes were used to allow sorting. A priori codes were developed based on expected responses. Inductive codes were developed through reviewing data. Once the codebook was finalized, all interviews were reviewed using the complete codebook. Three rounds of verification were performed to ensure reliability. First, 15 challenging interviews were double-coded (VM and ND). Discrepancies were discussed, and the codebook was revised as needed. All interviews were reviewed based on changes. A second round of double-coding was performed on 15 additional interviews. Finally, instances of all major codes were reviewed (VM and ND) to ensure consistency among coded segments.

Results

Study Population

In total, 62 interviews were conducted. One could not be analyzed due to a recording failure. Two were terminated prematurely for reasons unrelated to interview content, though available data were included. The sample size for most questions is thus 59. The denominator for each question reflects the number of individuals asked that question.

Total RAMPART enrollment at PEER sites was 245; however, accurate contact information was not available for many subjects, and some sites were able to contact only individuals who were enrolled after PEER was initiated. The eligible population was thus substantially less than 245. At the two leading sites, accounting for over 2/3 of PEER participants, 39% of total RAMPART enrollees/surrogates were successfully interviewed. Most non-responders were never successfully contacted. The median time between RAMPART enrollment and PEER interview was 29 days (range 1-245, IQR 4-108).

Thirty-nine percent of interviewees were RAMPART enrollees; 61% were surrogates. 66% were female, 23% were white, and 57% were black. Five surrogates were parents of minors. Several notable differences existed between PEER interviewees and RAMPART enrollees network-wide (Appendix 2). The percentage of females was higher in PEER (66% vs. 45%), due to a large number of female surrogates. RAMPART also enrolled more white patients (39% vs. 23%). The age distribution reflected the RAMPART population (minors were ineligible for PEER). About half the interviewees had a high school education or less, and about half who reported income had a family income of \$40,000 or less. Most enrollees (86%) had prior seizures. All but 6 (11%) reported multiple hospitalizations or ER visits within the previous 2 years. About a quarter (n=15) had previously participated in research; 11 had previously declined research participation.

Attitudes Toward EFIC and Enrollment in RAMPART

Almost all interviewees (95%) believed pre-hospital seizure research is important, and 49/60 (82%) were glad that they or their family member was included in RAMPART (Table 2). Importantly, the latter question was asked after a description of RAMPART but before explicit discussion of EFIC. When asked about EFIC enrollment, 43/59 (73%) interviewees felt it was acceptable to have enrolled them (or family member) in RAMPART. 39/58 (67%) felt it was acceptable, *in general*, to enroll patients in RAMPART under EFIC. Eight interviewees explicitly stated they accepted EFIC enrollment for themselves/family member but could not make that assessment for others. Four objected to enrollment for themselves/family member but felt that conducting the study under EFIC was acceptable.

We examined interactions between major demographic variables and attitudes toward EFIC and RAMPART inclusion (Table 3). No relationship was statistically significant, but there was a trend toward lower acceptance of EFIC (personal and general enrollment) among non-white interviewees. Less-educated interviewees and males were more accepting of personal enrollment and less accepting of EFIC in general than more-educated or female interviewees, respectively. Surrogates interestingly were somewhat more often “glad” their family member had been included but slightly less often accepting of EFIC enrollment. There was also a trend toward lower acceptance of EFIC enrollment (personally and in general) among individuals who had previously participated in research compared to those who had not.

Reasons for Views and Understanding of Study Content

The most commonly cited reasons for positive attitudes toward enrollment (Table 4) related to potential medical benefit. In some cases, interviewees felt the trial offered quicker seizure resolution; others mistakenly believed it offered long-term benefit such as reducing recurrence. Other commonly cited positive reasons included recognition of the inability to get consent in emergencies, altruistic desire to advance science, believing that study risks were low and no harm was done, and general support for research. Ten interviewees specifically stated that interactions with RAMPART study staff at enrollment positively influenced their attitudes.

Six of 59 interviewees (10%) believed that they (or a surrogate) had provided consent for RAMPART participation. In some cases, they confused consent for data use and follow-up with consent for enrollment and treatment. However, in several cases, a surrogate reported being told about the trial by paramedics and felt they had given permission. These interviewees appreciated being asked, though the nature of these interactions is unknown, and this practice was not part of the RAMPART protocol or paramedic training. In contrast, 5 interviewees reported that they (or their surrogate) had not been notified of the trial or asked about participation despite being present at enrollment. These interviewees thought the available surrogate should have been involved.

The most common concerns related to absence of consent. Some interviewees believed enrollment should only take place if a surrogate or patient has consented. Other interviewees simply felt they could not speak for others or that others would be more likely to disagree. 11/59 interviewees (19%) reported dissatisfaction with the amount of information they received about the study. Finally, some interviewees expressed specific concerns about risks, particularly potential drug interactions or allergies. Only two participants felt they were harmed by enrollment; one experienced pain at an injection site; the other (a surrogate) stated her husband could not transfer hospitals due to enrollment.

Overall, 38/61 (62%) interviewees appeared not to understand some relevant study detail despite re-direction, opportunities for questions, and probing of answers. Three types of misunderstanding predominated. 29/59 (49%) participants did not appear to understand randomization. 15/61 (25%) revealed a misunderstanding of the nature of RAMPART, often confusing it with long-term seizure treatment. Finally, 8/61 (13%) could not describe the RAMPART study in their own words following a detailed explanation.

Other EFIC elements and Attitudes

Interviewees were administered a 4-question scale of trust in researchers. The average composite score was 16.04 (maximum possible = 20), higher than the national sample in which the scale was validated (mean score 12.4)¹⁷ and higher than community consultation participants at two PEER sites for RAMPART (mean score 14.4).¹⁸

Interviewees were also asked their views on community consultation and public disclosure practices (table 5). Most interviewees supported community consultation for EFIC research and commonly suggested that it should target patients with the condition and healthcare providers. Only two interviewees had heard of RAMPART before enrollment; one was previously enrolled. Four individuals stated they would have been interested in a bracelet that was offered to allow members of the public to “opt out” of inclusion, but only 1 understood the opt-out purpose of the bracelet.

Finally, the interview contained questions specific to randomization. Most interviewees (86%) accepted it, but about half did not demonstrate understanding of randomization.

Discussion

This is the first study to interview individuals and surrogates included in an EFIC study and employed a design allowing insight into respondents' understanding and reasoning. In these respects, these data are novel and begin to fill an important knowledge gap.

One goal of this study was to assess whether acceptance of EFIC enrollment is similar among EFIC enrollees and participants in community consultation efforts required by U.S. EFIC regulations. The rate of EFIC acceptance almost exactly matches one recent report of focus group and community meeting-based consultation efforts for RAMPART at 2 PEER sites and was substantially higher than acceptance of personal enrollment in a survey at another PEER site.^{7,18} Other published community consultation reports have demonstrated acceptance in similar ranges, with some surveys showing lower acceptance.^{6,9-11,19,20} It is encouraging that community consultation feedback generally does not appear to overestimate acceptance. However, given that community consultation results can impact study approval, further research to understand sources of variability among responses is important to help investigators and IRBs in designing community consultation and interpreting its results.

The concerns and views of PEER interviewees were consistent with expectations based on community consultation experience. Several novel insights, however, emerged from their unique perspective. In particular, interactions with RAMPART study staff were important to their views of the study and EFIC, consistent with the centrality of trust in researchers. We did not directly observe subject-staff interaction, but this finding suggests this is an important element for investigators to consider in training staff, and further research may clarify how to optimize these interactions. Most participants described their interactions with RAMPART study staff as positive; however, several individuals mentioned that discussing the research study and asking for continued consent while the patient was still critically ill was problematic from their perspective. In these cases, the patient had been enrolled in RAMPART in the field and no further study medication was planned. Consent was only for follow-up data collection. Staggering or postponing consent when no treatment-related research decisions are necessary may improve patients' or surrogates' experience or perceptions though may be logistically challenging.

In contrast, surrogates present at initial RAMPART enrollment (and randomization) had strong feelings about being involved in that decision. This situation poses a dilemma. True consent is not practical in this context. However, exploration of approaches to inform surrogates of what is happening and to recognize appropriate refusals when present are important topics to address.

A distinctive aspect of PEER was the interactive interview guide designed to maximize engagement and participants' understanding of this complex topic. However, more than half the interviewees did not seem to understand some element of RAMPART or the EFIC

process. Misunderstanding of randomization is widely reported and is not surprising.^{21,22} However, the extent of general misunderstanding that we observed may call into question the depth of understanding driving patient or public views on these topics during community consultation efforts, particularly in less interactive settings in which misunderstanding is presumably more pronounced. The reasons for misunderstanding may be multifactorial, but these findings suggest cautious interpretation of community consultation feedback and recognition that consultation data may reflect public reaction more than informed public opinion.

Finally, these data suggest a need for further research to examine associations between particular patient characteristics and views of EFIC. There was only a suggestion of a difference in this small study, but it is interesting that minorities tended to be less accepting of EFIC enrollment (both personally and in general) than white subjects despite similar responses to the initial question “I am glad that I/my family member was included in this research study.” This pattern suggests that the difference may be more related to EFIC than to a generic difference in attitude toward research. A similar pattern was observed with lower education levels and prior research experience (the latter contrary to expectations). These and other associations warrant further assessment, because they may impact the conduct and interpretation of future community consultation and disclosure efforts.

PEER was a small, exploratory study, and recruitment was challenging. Many patients were enrolled in RAMPART prior to initiation of PEER, recruitment depended on local study teams, and because RAMPART did not otherwise involve contact with subjects after discharge, contact information was often unreliable or unavailable. There is thus potential for response bias. Additionally, information about individual subjects' medical outcomes from RAMPART participation was unavailable. Individuals or surrogates for individuals with bad outcomes may have been less willing to be interviewed or may have had more negative views toward the study. We did not observe this phenomenon and did interview several surrogates whose family members had died. Moreover, the study enrolled more surrogates than patients, suggesting that we did not preferentially enroll those with good outcomes. While differences between surrogates' and patients' views in this study were minimal, more could emerge in larger populations.

Having multiple interviewers provides an opportunity for interviewer bias. We attempted to mitigate these biases by training interviewers, reviewing technique, and limiting the number of interviewers, but interviewer effects are inevitable with this design.

The RAMPART study was also a relatively low-risk, active-controlled, noninferiority trial of commonly used drugs. Furthermore, mortality and major morbidity in treated status epilepticus is lower than in conditions such as traumatic brain injury. These factors may affect participants' assessments of risks and benefits of participation or the importance of consent. Research is underway to assess whether similar attitudes exist in other EFIC trials.

Conclusion

This study is the first to report attitudes of actual EFIC enrollees and surrogates. Interviewees were generally accepting of enrollment and, while sometimes concerned about lack of consent, generally accepting of EFIC. Our findings suggest community consultation efforts do not systematically over-represent acceptance among enrollees; however, we caution against over-interpretation of community consultation acceptance rates given prevalent misunderstanding of study content. Important topics for future work include optimizing interactions between patients, surrogates, and staff, characterizing responses in

other EFIC studies, and further examination of associations between patient characteristics and attitudes toward EFIC.

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Appendix 1: Interview guide for family members

1. Prior research experience and general attitude toward research

1.1. Have you ever been a part of a medical research study other than the study we are talking about today? *PROBE: This could be a study of medications or procedures or could involve answering questions like you're doing today.* **IF NO, SKIP to 1.2**

1.1.1. If so, what kind(s) of study(ies) and what was involved for you?

1.1.1.1. How would you describe your experience being part of research?

1.1.1.1.1. *PROBE:* Would you say it was a good experience, a bad experience, or are you neutral about it?

1.1.1.2. (Probe for reasons for positive or negative experiences)

1.1.1.3. Have you ever been asked to be a part of a research study and decided not to be in the study? **IF NO, SKIP to 1.3**

1.1.1.3.1. What kind(s) of study(ies) and what would have been involved for you?

1.1.1.3.2. What was your reason for choosing not to be a part of that study?
SKIP TO 1.3

1.2. Have you ever been *asked to be a part of* a medical research study? (**IF NO, SKIP TO 1.3**)

1.2.1. If so, what kind(s) of study(ies) and what was involved for you?

1.2.2. What was your reason for choosing not to be a part of that study?

1.3. To your knowledge, has (*your family member*) ever been a part of a research study?

1.3.1. If so, what kind(s) of study(ies) and what was involved?

1.4. On a scale of 1 to 5 with 1 being very important and 5 being not important at all, how important do you think it is to do medical research studies?

1	2	3	4	5
Very important at all			Not important	

2. Knowledge of the RAMPART study

2.1. We're interviewing you today because (*your family member*) was included in a research study for people having seizures.

2.2. Before this interview today, were you aware that (*your family member*) was included in a research study for people having seizures? **IF “NO” or “uncertain,” SKIP TO 2.3.**

2.2.1. What was this research study about?

2.2.2. What do you think was being tested in this research study (If not answered by prior response)?

2.2.3. How did you find out that (*your family member*) was included in this research study?

2.3. Read Regardless of Response, Acknowledging that They Were Correct If Answers to 2.2.1- 2.2.2 Were Correct

(*Your family member*) was included in a research study called the RAMPART study where doctors are trying to figure out which of two medicines is better at treating seizures in the ambulance. One of these drugs is given by a shot in the muscle and the other is given by a shot in the vein. Both drugs are medicines that are currently used to treat seizures but it is not clear which one works better or faster. In this study, people like (*your family member*) are given one or the other treatment in the ambulance at random like by the flip of a coin. In other words, the paramedics do not pick and choose who gets which of the two treatments. They open up a box that contains one or the other treatment and give that treatment first without knowing which of the two treatments it is. So every patient will be treated with one of the two study medicines. If the seizure doesn't stop, paramedics then give whatever medicine they normally use to treat seizures. Just to make sure that what I said made sense to you, can you tell me in your own words what the RAMPART study involved?

- Suggested re-phrasing for subjects who don't understand the initial description

Doctors are not sure which of two commonly used medicines are better at treating seizures in the ambulance. In this study, patients having a seizure will get one medicine or the other (doctors and paramedics won't know which one they get) as their initial treatment. If that medicine doesn't stop the seizure, paramedics give whatever they would normally use. This will help doctors learn whether one medicine is better than the other at treating seizures in the ambulance.

- Some may ask about how IM vs IV is blinded. If they do, the following is a possible response

Each patient will actually be given 2 shots. One will go in the vein and one in the muscle. Only one will contain the real medicine, though. The other will just be salt water. Paramedics won't know which shot was real medicine and which one was just salt water. So all patients will get one of the 2 medicines.

2.4. Do you remember being told about any risks associated with being included in this study?

2.5. What do you think the potential benefits were to (*your family member*) of being included in this study?

2.6. On a scale of 1 to 5 with 1 being strongly agree and 5 being strongly disagree, how does the following statement apply to you: I am glad that (*your family member*) was included in this research study.

1		2	3	4	5
Strongly Agree	Disagree				Strongly

PROBE (ALL): Can you tell me how you decided on this answer?

2.7. Do you think that (*your family member*) would feel the same way? *PROBE WHY IF DIFFERENT*

2.8. On a scale of 1 to 5, please tell me how much you agree the following statement. It is important to do research comparing which treatments for seizures work best in the ambulance.

1		2	3	4	5
Strongly Agree	Disagree				Strongly

PROBE (IF DISCREPANT ANSWERS to 2.6 and 2.8): Why different?

3. Views on having been included in RAMPART)

3.1. As I mentioned, the study (*your family member*) was included in is called the RAMPART study, and it was testing two different medicines used to treat patients having a seizure in the ambulance. Normally, people are only included in research studies after they (*or someone who makes decisions for them*) have been asked for permission to be included in the study. But because (*your family member*) was having a seizure, you didn't find out about (*your family member*) being included in the RAMPART study until (*your family member*) was doing better. Is that right?

3.2. When you first found out that (*your family member*) was included in this study without you or (*your family member*) having been asked, what were your reactions?

3.3. When researchers do research studies to test treatments for emergencies like seizures, they can't ask patients for their permission or consent. This is because patients are very out of it or are unconscious. In addition, family members are not always around and decisions about how to treat people with these conditions have to be made very, very quickly. Does it make sense why researchers who do research like the RAMPART study have to include patients without asking them or their family members for consent or permission?

- Suggested re-phrasing if necessary

-Normally, people are asked if they want to be included in research studies, but a patient having a seizure can't make decisions, and family members are not always

around to make treatment decisions for the patient. This is why research studies testing treatments for conditions like seizure sometimes have to include patients without asking their permission first.

3.4. The rules that allow research in emergencies without consent have some special requirements. First, medical experts have to review the research to make sure it is safe to do. Second, there has to be some chance that patients may benefit from being in the study. Third, researchers have to talk with community members in the places where they would do the research to ask for their opinions on the research study before the study is started. Do you have questions about these rules?

I want to ask you now for your opinion about (*your family member*) being included in the RAMPART study. On a scale of 1 to 5 with 1 being strongly agree and 5 being strongly disagree, how would you rate the following statement? I think that it was ok for researchers to include (*your family member*) in the RAMPART research study without asking me or (*your family member*) first for permission.

1		2	3	4	5
Strongly Agree	Disagree				Strongly

PROBE (ALL)- How did you decide on this answer?

PROBE (IF ANSWERS to 3.5 DIFFER FROM 2.6) WHY for any discrepancies between this and earlier answer

3.6. Do you think that (*your family member*) would feel the same way?

3.6.1. PROBE any differences

4. Views on acceptability of the use of EFIC in research (in RAMPART and in general)

4.1. The last question asked about your thoughts on (*your family member*) in particular having being included in the RAMPART study. Not thinking specifically about (*your family member*)'s situation, I now want to ask you about your thoughts, in general, on whether it was ok for researchers to do this study where people are included without being asked for permission first. On a scale of 1 to 5 with 1 being strongly agree and 5 being strongly disagree, how would you rate the following statement? I think that it was ok for researchers to include people in the RAMPART research study without asking them for permission.

1		2	3	4	5
Strongly Agree	Disagree				Strongly

PROBE (IF DIFFERENT FROM ANSWER TO 3.5): Can you tell me why you answered this question differently from when I asked about your family member being included in the RAMPART study?

FOR PEOPLE WHO EXPRESS CONCERN ABOUT “NOT SPEAKING FOR EVERYONE:” Ask what they think should be done instead given that we can't know who would want to be in a study and who wouldn't..

5. Views on randomization

5.1. Now I want to ask you a few questions about having treatments picked at random. As I mentioned earlier, in this study, paramedics did not decide who got which of the 2 treatments. This was decided at random, like by the flip of a coin. Researchers decide treatments at random like this so they can tell whether one or the other treatment works better. If the paramedics decided on their own which patients to treat with each of the 2 medicines, they might not give equal numbers of people each medicine or might only give certain types of patients one medicine or the other. Does that make sense to you?

PROBE (IF THEY DO NOT UNDERSTAND RANDOMIZATION): Correct any clear misunderstanding about what randomization is

- For people who ask about the need for randomization:

Randomization ensures that doctors don't give different medicines to different types of patients

Randomization allows researchers to compare results across multiple sites.

Randomization and blinding avoids bias on the part of doctors and paramedics in assessing which patients do better

If they dispute the need for randomization, this is fine, just ask for their reason and move on.

5.2. On a scale of 1 to 5 with 1 being strongly agree and 5 being strongly disagree, how much do you agree with the following statement: I think that it was acceptable for researchers to assign treatments at random like this in this study?

1	2	3	4	5
Strongly Agree	Disagree			Strongly

5.2.1. How did you decide on this answer?

PROBE (IF THEY DISAGREE BUT WERE PREVIOUSLY SUPPORTIVE of enrollment). How did learning about randomization affect your assessment of whether this study was ok to do?

6. Views on conversations with investigators about the study

6.1. Did someone from the research team come to talk to you or (*your family member*) about (*your family member*) having been included in the RAMPART study while you were in the hospital? (If no, SKIP to 6.1.1.5).

6.1.1.1. (If yes) How would you describe your conversation with that person about this study?

6.1.1.2. Would you say that conversation was helpful?

6.1.1.3. Did you feel as if you got too much information, just the right amount of information, or too little information about the study at that time?

6.1.1.4. Did they ask your permission to review (*your family member*)'s hospital chart for this study? (If Yes, go to 6.1.1.4.1. If NO, SKIP to 7.1)

If they ask for clarification, can re-phrase as: Did they ask if it was ok to use the results and records from (your family member)'s treatment in the ambulance and hospital as part of the study?

6.1.1.4.1. What did you say? (**SKIP to 7.1**)

6.1.1.5. (**If no to 6.1**) How did you hear (*your family member*) was part of a study?

6.1.1.6. Do you wish that someone from the study had come to talk with you about the study?

7. Views on the community consultation process

7.1. As I described earlier, when researchers want to do a study like this where people have to be included without being asked, the rules of research require researchers to ask members of the community before starting the study for their thoughts about the study. In other words, the researchers have to ask the community for input on the study the researchers want to do. Does this seem like something important to do?

7.1.1. *PROBE(ALL)*: Tell me more about this.

7.1.2. What groups of people do you think researchers ought to talk to before doing studies like the ones we've been talking about?

7.1.3. In the RAMPART study specifically, the one (*your family member*) was included in that was testing ways to treat seizure, who are the particular people or groups of people that you think researchers should have talked to in trying to get the community's thoughts on the study?

8. Impact of public disclosure

8.1. These researchers also tried to inform people in the community about the RAMPART study so that they would know it was going on. Were you aware of the RAMPART study, the one in which (*your family member*) was enrolled, before (*your family member*) was brought to the hospital? (**IF NO, SKIP to 8.3**)

8.2. (If yes), how did you hear about the study?

8.2.1. Were you aware that you could call in and get a wrist band that would let people know you didn't want to be included in this study if you had a seizure and were picked up by the ambulance? (**IF NO, SKIP TO 8.3**)

8.2.2. (If yes), did you call? Why or why not? (ASK 8.3 and then SKIP to 9)

8.3. As far as you know, was (*your family member*) aware of the study before being included in it?

8.4. People who heard about the study could call in and get a wrist band that would let people know that they didn't want to be included in this study if they had a seizure and were picked up by the ambulance. Is that something you would have done if you had known about the study? (*PROBE REASONS* and ask for yes/no)

For people given a wrist band AFTER enrollment, clarify that they received that wrist band because each person can only be included in the study once. Other people who have never been enrolled in RAMPART can also call and get a wrist band to say they don't want to ever be a part of it.

Before you were included, if you had known you could get a wrist band to let people know you wouldn't ever want to be included, would you have wanted one?

Do you think that (*your family member*) would feel the same way?

9. Trust in researchers and in clinical research

I want to ask you some questions now about your thoughts about doctors and researchers. On a scale of 1 to 5 with 1 meaning you strongly agree and 5 meaning you strongly disagree, how much would you say you agree with the following statements?

9.1. Doctors who do medical research care only about what is best for each patient

1	2	3	4	5
Strongly Agree			Strongly Disagree	

9.2. Doctors tell their patients everything they need to know about being in a research study

1	2	3	4	5
Strongly Agree				
Strongly Disagree				

9.3. I completely trust doctors who do medical research.

1	2	3	4	5
Strongly Agree				
Strongly Disagree				

9.4. Medical researchers treat people like “guinea pigs.”

1	2	3	4	5
Strongly Agree				
Strongly Disagree				

9.5. **(PROBE:** For those with negative answers to any of the above questions) Can you tell me about your reasons for thinking _____?

10. Demographics and medical background

- 10.1. **Interviewer:** Is the respondent Male or Female? _____(1) Female
 _____(2) Male
- 10.2. In what year were you born? _____
- 10.3. Which of the following best describes your marital status?
 Single _____ (1)
 Married _____ (2)
 Divorced or Separated _____ (3)

- Unmarried living with a partner _____ (4)
- Widow or Widower _____ (5)
- 10.4. Do you consider yourself Hispanic or Latino? _____ (0) No
_____ (1) Yes
- 10.5. Which of the following best describes you? Are you ...
- Asian, Hawaiian, or Pacific Islander _____ (1)
- Black or African American _____ (2)
- Native American/Aboriginal _____ (3)
- White _____ (4)
- Some other race, specify: _____ (9)
- 10.6. What is the last grade or year that you completed in school?
- Less than high school _____ (1)
- Some high school _____ (2)
- High school graduate or GED _____ (3)
- Some college _____ (4)
- College graduate _____ (5)
- Some post-graduate _____ (6)
- Post-graduate or Professional degree _____ (7)
- Other, specify _____ (9)
- 10.7. Which of the following best describes your employment or student status?
- Are you employed..(Read options out loud.) _____ (1) Empldy FullTime
_____ (2) Empldy PartTime
_____ (3) Retired
_____ (4) Not Empldy
_____ (5) Disabled
_____ (6) Student
- 10.8. Which category best describes your combined family income in the last year (before taxes)? Was it _____ (1) < \$5,000
_____ (2) \$5,000 - \$19,999
_____ (3) \$20,000 - \$39,999
_____ (4) \$40,000 - \$59,999
_____ (5) \$60,000 - \$79,999
_____ (6) > \$80,000
_____ (8) Don't know
_____ (9) Refused
- 10.9. How important to you are your religious/spiritual beliefs?
Would you say they are ... _____ (0) Not applicable
_____ (1) Not important
_____ (2) Slightly important
_____ (3) Somewhat important
_____ (4) Very Important
_____ (5) Extremely important
_____ (6) Refused
- 10.10. Do you currently have medical insurance coverage of any sort? _____ (0) No
_____ (1) Yes
- 10.11. **Interviewer:** Is (*family member*) Male or Female (if not already known)? _____ (1) Female

- 10.12. In what year was (*family member*) born? (or age if they don't know birth year) _____
 _____ years
- 10.13. Which of the following best describes (*family member*)'s marital status?
- Single _____ (1)
- Married _____ (2)
- Divorced or Separated _____ (3)
- Unmarried living with a partner _____ (4)
- Widow or Widower _____ (5)
- 10.14. Does (*family member*) consider him/herself to be the same race/ethnicity as you (SKIP to 10.14 if YES) _____ (0) No
 _____ (1) Yes
- 10.14a. Does (*family member*) consider him/herself Hispanic or Latino _____ (0) No
 _____ (1) Yes
- 10.14b. Which of the following best describes (*family member*)?
- Asian, Hawaiian, or Pacific Islander _____ (1)
- Black or African American _____ (2)
- Native American/Aboriginal _____ (3)
- White _____ (4)
- Some other race, specify: _____ (9)
- 10.15. What is the last grade or year that (*family member*) completed in school?
- Less than high school _____ (1)
- Some high school _____ (2)
- High school graduate or GED _____ (3)
- Some college _____ (4)
- College graduate _____ (5)
- Some post-graduate _____ (6)
- Post-graduate or Professional degree _____ (7)
- Other, specify _____ (9)
- Don't Know _____ (10)
- 10.16. Which of the following best describes (*family member*)'s employment or student status
- Are you employed..(Read options out loud.) _____ (1) Employd Full-Time
 _____ (2) Employd Part-Time
 _____ (3) Retired
 _____ (4) Not Employd
 _____ (5) Disabled
 _____ (6) Student
 _____ (7) Don't know
- 10.17. Does (*family member*) currently have medical insurance coverage of any sort? _____ (0) No
 _____ (1) Yes
 _____ (2) Don't know
- 10.18. What is your relationship to ____?
- _____ (1) Spouse
 _____ (2) Child (of patient)
 _____ (3) Parent (of patient)

- ____ (4) Sibling
 ____ (5) Other _____
- 10.19 Has (*family member*) ever had a seizure before the time when he/she was enrolled in the RAMPART study? ____ (0) No
 ____ (1) Yes
 ____ (2) Don't know
- 10.20 Does (*family member*) take medications regularly for seizures? ____ (0) No
 ____ (1) Yes
 ____ (2) Don't know
- 10.21 How many times in the past 2 years has (*family member*) had to come to the hospital or emergency room because of seizures or for other reasons? _____

Appendix 2: Comparison of PEER and RAMPART populations

		PEER Population n (%) total=61*	RAMPART Population n (%) total=893
Sex	Female	40 (66%)	405 (45%)
	Male	21(34%)	488 (55%)
Race*	White	13 (23%)	348 (39%)
	Black	32 (57%)	453 (51%)
	Other	11 (20%)	92 (10%)
Ethnicity*	Hispanic	5 (9%)	106 (12%)
	Not Hispanic	50 (88%)	600 (67%)
	Unknown	2 (4%)	187 (21%)
Age*	Mean (SD)	48.41 (14.14)	43.50 (22)
	Range	24-83	0-102
	0-5 years	0 (0%)	61 (7%)
	6-10 years	0 (0%)	35 (4%)
	11-20 years	0 (0%)	49 (5%)
	21-40 years	20 (36%)	226 (25%)
	41-60 years	24 (43%)	338 (38%)
	>= 61 years	12 (21%)	184 (21%)
History of seizure*	Yes	46 (82%)	588 (66%)
	No	9 (16%)	214 (24%)
	Unknown	1 (2%)	91 (10%)

* Totals less than 61 for PEER reflect non-response to this item

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Sample interview question

When researchers do research studies to test treatments for emergencies like seizures, they can't ask patients for their permission or consent. This is because patients are very out of it or are unconscious. In addition, family members are not always around and decisions about how to treat people with these conditions have to be made very, very quickly. Does it make sense why researchers who do research like the RAMPART study have to include patients without asking them or their family members for consent or permission?

I want to ask you now for your opinion about (your family member) being included in the RAMPART study. On a scale of 1 to 5 with 1 being strongly agree and 5 being strongly disagree, how would you rate the following statement? I think that it was ok for researchers to include (your family member) in the RAMPART research study without asking me or (your family member) first for permission.

Strongly Agree 1 2 3 4 5 Strongly Disagree

Follow-up probe- How did you decide on this answer?

Table 1

Demographics of Interviewees

		n (total=61)*	%
Interviewee Type	Patient	24	39%
	Surrogate	37	61%
Sex	Female	40	66%
	Male	21	34%
Race *	White	13	23%
	Black	32	57%
	Other	11	20%
Ethnicity *	Hispanic	5	9%
	Not Hispanic	50	91%
Age	<30	10	16%
	31-50	22	36%
	51-70	26	43%
	>70	3	5%
Education *	High School or Less	29	54%
	Some College or More	25	46%
Income *	<\$5,000	7	13%
	\$5,000 - \$19,999	11	20%
	\$20,000 - \$39,999	9	16%
	\$40,000 - \$59,999	5	9%
	\$60,000 - \$79,999	1	2%
	> \$80,000	7	13%
History of seizure *	Refused/Don't know	16	29%
	Yes	46	84%
	No	9	16%

* Totals less than 61 reflect non-response to this item

Table 2

Acceptance of EFIC and RAMPART trial

	Agree	Neutral	Disagree
I am glad that I/my family member was included in this research study. * (n=60)	49 (82%) 95% CI: 72%-91%	9 (15%)	2 (3%)
It is important to do research comparing which treatments for seizures work best in the ambulance. (n=57)	54 (95%) 95% CI: 89% -100%	1 (2%)	2 (3%)
Personal enrollment- I think that it was ok for researchers to include me/my family member in the RAMPART research study without asking me/my family member first for permission. (n=59)	43 (73%) 95% CI: 62% - 84%	6 (10%)	10 (17%)
General enrollment- I think that it was ok for researchers to include people in this research study without asking them for permission. (n=58)	39 (67%) 95% CI: 55% - 79%	10 (17%)	9 (16%)

* Asked before explicit EFIC discussion

Table 3

Acceptance by demographic categories*

Demographics		Accepts personal EFIC enrollment n (%)	Accepts general EFIC enrollment n (%)	Glad about inclusion n (%)
Respondent Type	Patient	17 (77%)	15 (71%)	16 (70%)
	Surrogate	26 (70%)	24 (65%)	33 (89%)
Sex	Male	14 (74%)	11 (58%)	16 (80%)
	Female	29 (73%)	28 (72%)	33 (83%)
Age	<30	6 (75%)	4 (57%)	7 (78%)
	31-50	15 (68%)	15 (68%)	17 (77%)
	51-70	20 (77%)	18 (69%)	24 (92%)
	>70	2 (67%)	2 (67%)	1 (33%)
Race	White	11 (85%)	12 (92%)	11 (85%)
	Black	24 (75%)	20 (63%)	27 (84%)
	Other	6 (55%)	6 (55%)	9 (82%)
Education	High School or <	22 (76%)	18 (62%)	27 (93%)
	Some College or >	17 (68%)	18 (72%)	18 (72%)
Prior Experience with Research	Yes	9 (64%)	7 (54%)	12 (80%)
	No	34 (76%)	32 (71%)	37 (82%)

* No differences were statistically significant using Chi-Square test for proportions.

Table 4

Positive and negative reasons for views*

<i>Positive reasons given</i>	# Participants	% (n= 59)
Direct medical benefits	30	51%
Recognizing the inability to get consent given the situation	16	27%
In case of an emergency, do what needs to be done	14	24%
Part of life saving efforts	12	20%
Desire to improve scientific knowledge and help others	10	17%
Importance of research	10	17%
Positive interaction with RAMPART staff	9	15%
Risks of study are low/no harm done	9	15%
Trust in researchers/doctors to do what is best	8	14%
<i>Negative reasons given</i>		
Concerns about absence of consent	20	34%
Dissatisfaction with amount of information given	11	19%
Other people may not be as accepting	11	19%
Concerns about allergies/interactions	7	12%
Negative interaction with RAMPART staff	6	10%
Should only include patients who consent (or surrogate)	6	10%
Believes there was missed opportunity for consent	5	8%
Legal concerns	5	8%
Unsure about balance of risks/benefits in trial	5	8%
Concerned about being experimented on	4	7%
Does not remember enrollment or consent	4	7%

* Respondents may have given more than one response

Table 5
Other questions

Randomization (n=58)		n (%)
I think that it was acceptable for researchers to assign treatments at random like this in this study?	Agree	50 (86%)
	Neutral	3 (5%)
	Disagree	5 (9%)
Opt Out Bracelet (n=51)^a		
People who heard about the study could call in and get a wrist band that would let people know that they didn't want to be included in this study if they had a seizure and were picked up by the ambulance. Is that something you would have done if you had known about the study?	Yes	4 (8%)
	No	47 (92%)
Community Consultation (n=57)		
Do you think community consultation sounds like something important to do?	Yes	56 (98%)
	No	1 (2%)
What groups of people do you think researchers ought to talk to before doing studies like the ones we've been talking about?	People w/condition and their families	35 (57%)
	Medical community	10 (16%)
	General public	10 (16%)
	Other ^b	25 (41%)
Public Disclosure (n=56)		
Researchers also tried to inform communities about the RAMPART study so that they would know it was going on. Were you aware of the RAMPART study (the one in which you/your family member was enrolled) before you/your family member was brought to the hospital?	Yes	2 (4%) ^c
	No	54 (96%)

^aSome interviewees refused or were unable to give an answer to this question.

^bIncludes such groups as low socioeconomic status persons, racial/ethnic minorities, community leaders, churches, elderly, people at risk for getting disease of interest, support/health groups, and research groups, among others.

^c1 subject was enrolled twice in RAMPART, 1 received a letter from epilepsy foundation.