

## **Introduction:**

Community Consultation is a required element of 21 CFR 50.24 and 45 CFR 46 [1]. Investigators have reported that it may be the most difficult aspect of the Rule to implement when conducting a trial using Exception from Informed Consent (EFIC) [2]. The literature on the subject of community consultation has been sparse since the implementation of the Rule in 1996. In the 2006 Draft Guidance [3], the FDA asks several questions:

- a) What are the costs, benefits, and feasibility of community consultation as currently required under 50.24?
- b) What aspects of community consultation as currently practiced are effective mechanisms for human subject protection?
- c) Are there additional practices that could enhance human subjects' protection?
- d) Are there elements of community consultation both procedural and substantive that should, at a minimum, be required?
- e) Would opt-out mechanisms to identify individuals who do not wish to be included as subjects in particular emergency research studies provide a necessary protection for human subjects? If so, are they feasible?
- f) Who should use the information obtained from the community consultation process and how should they use it? Should the regulation be more specific on this point, and if so, what should it provide?
- g) Are there others beside the IRB who should play a role in determining the adequacy of the plan for community consultation and the material to be publicly disclosed?
- h) Should the regulation require documentation of meeting activities and discussions in sufficient detail to show the information that was disclosed and the community reaction to the clinical investigation? If so, who should be responsible for such documentation?
- i) Should the regulation also require that documentation of community consultation activities be submitted to FDA, for example by being placed in the public docket? If so, who should be responsible for doing this?
- j) Should this information also be available elsewhere such as on [clinicaltrials.gov](http://clinicaltrials.gov)?

Many, if not most of these questions simply cannot be answered without research on the Rule itself, focusing on community consultation activity both within the context of the trial itself, and as a theoretical construct for obtaining needed information. This contribution to the FDA docket in response to the 2006 Draft Guidance on Exception

from Informed Consent consists of a critical appraisal of the currently available literature on community consultation and provides some answers to the questions raised above, based on expert opinion and the experience of preparing and conducting trials using 50.24.

This information is being submitted primarily to illustrate the overall lack of published information on experience with the community consultation process and an even greater lack of analytical information examining the effectiveness and adequacy of the process. Without studying the process of community consultation itself, we may never be sure that it meets its intended objectives. Because of the relative paucity of information on the community consultation process since the implementation of 50.24, any change in the regulations will not be evidence based. Therefore, we highly encourage the FDA to consider mechanisms to encourage rigorous, scientific inquiry on the application of 50.24's special protections, particularly the required elements of community consultation and public disclosure.

To date there are 8 published articles which describe community consultation activities [4-11]. Six of these were conducted within the context of a clinical trial using EFIC [4,5, 7,8,10,11]. The predominant method used was the hosting of public meetings where presentations were made about the study and participants were provided an opportunity to ask questions. Other methods that were found to be feasible were random digit dialing telephone interviews, face to face interviews and focus groups [11]. Communities were defined both broadly and specifically with activities targeting both types. The remaining two studies offered suggestions for community consultation methods although they did not take place concomitantly with a trial using EFIC. One of these conducted a survey of a proxy population for the population "at-risk" in a hypothetical trial using EFIC [6] and the other used focus groups and telephone surveys to obtain the needed information for a future planned trial [9]. The study by Baren et al, informally consulted with ethicists and IRB chairpersons who endorsed this particular method [9] whereas the Morris study ultimately did receive IRB approval to use the information as the community consultation in preparation for the actual trial which remains in the protocol design stage [6]. Two additional studies have examined the attitudes of individuals toward the process of community consultation [12,13] by conducting surveys and focus groups. One study performed a content analysis of the FDA docket in 1999 when only 4 studies had been approved for use of the Rule [14]. There may be additional experiences with community consultation that are not published and therefore are not included in this analysis.

Information from these studies is presented in detail below. Additional unpublished data and expert opinion is presented afterward. This will serve as supplementary information and is primarily directed at the specific questions posed by the FDA that cannot be answered by the review of the available literature.

#### 1. Diaspirin cross-linked hemoglobin study [4]

This study involved the use of a blood substitute in the resuscitation of trauma patients with hemorrhagic shock. To fulfill the community consultation requirements, the community relations staff at the hospitals involved assisted in identifying key members of the high volume trauma communities around the hospital. These individuals were invited to participate in a community council which received a presentation from the researchers. Other key individuals and members of the community were invited to public meetings. For public disclosure, information was disseminated via flyers, in-house publications, and newspapers and there were also radio public service announcements and a 24-hour hotline was set up to facilitate feedback.

Presentations to community councils were advertised to hospital personnel and the local and regional community 3 weeks prior to 4 scheduled public meetings. The research team, an IRB member, a hospital public relations coordinator and community relations coordinator were in attendance. An overview of study was presented and general information was distributed, question period. As an additional activity, a talk radio program was arranged with a local station highlighting the research project.

Attendance was documented as follows: There were 12 individuals present at the hospital community council meetings and 83 at public meetings. Only five calls were made to the live radio program and 16 to the 24-hour hotline. Feedback from the community indicated general acknowledgment of the need for study but also general skepticism about risks, motives, profit. The African American community in particular was very sensitive to the issue of “shouldering a large proportion of the research burden” and this concern was highlighted by concurrent media coverage of President Clinton’s apology to the victims the 1932 Public Health Service study on syphilis. There were isolated concerns regarding the loss of decision-making liberties but this was seen as little deviation from the norm during any presentation for emergency care. Initial skepticism was felt to be reduced by frank discussion and clarification of medical terminology.

These activities required 80 person hours but no direct cost estimates were provided and there was no discussion of IRB concerns. Only a small portion of the community actively participated as indicated by this data. A number of important feelings surfaced. It is reasonable to assume that this was costly in terms of human resources. No measure of the adequacy of these activities was provided. This was the very first study to publish their experience in this area.

## 2. Multicenter Vest CPR study [5]

This was a randomized protocol investigating the benefit of circumferential chest compression provided by a pneumatically inflated vest compared with standard manual cardiopulmonary resuscitation (CPR). It was done on hospitalized patients who experienced cardiac arrest refractory to an initial defibrillation. The study was first attempted in 1995 with prospective informed consent from inpatients but abandoned due to low numbers of actual patients enrolled. Only 18 of 2131 individuals approached gave consent and 7100 were screened for eligibility with considerable resources expended.

Once investigators attempted to conduct the study under 21 CFR 50.24, they indicated that their IRB did not initially approve it as their community consultation activities were not thought to be adequate. Their initial proposal was to advertise the study in the newspaper without any plans for community input, therefore not meeting the definition of community consultation.

They revamped their proposal offering these subsequent methods: Call-in line, hospital presentations, posting large posters on hospital units, placing brochures in patient rooms, and having one on one nurse-patient discussions about the study. They held a single public forum with the chair of the IRB in attendance, offered free parking, and demonstrated the use of the vest device followed by questions and answers.

Twelve individuals called the hotline, 25 attended the public forum with all 25 indicating “approval” of the study. The IRB granted approval of the protocol after 4 months but first requested revision of patient oriented brochures. However, no patient asked for information based on contact with the brochure. Estimated direct cost was \$5600. This protocol was ultimately performed on only 4 patients in 4 months and then abandoned due to escalating cost despite 1750 potentially eligible patients admitted over that time period.

The community consultation activities were poorly attended and poorly utilized at a significant expense. Over 1750 patients were admitted during this time and only one requested to be exempted from the study. Enrollment was slow and the trial was terminated due to escalating costs. Notification of the study termination and results were published in a local newspaper in compliance with the Rule.

### 3. Feasibility of a Proposed Method of Performing Community Consultation [6]

A randomized controlled trial of phenytoin vs. placebo for post-traumatic seizures in children with head injury using the “deferred consent” mechanism was placed on hold during development and discussion of the federal regulations governing research without consent in 1996. In response to the regulations, and prior to resumption of the trial, the investigators designed a separate study to determine the feasibility and utility of a particular method of community consultation. They conducted a survey of parents of children seen in 3 emergency departments for minor head injury in an attempt to approximate the potential community from which subjects would be drawn. The investigator described a hypothetical scenario (the actual randomized trial) and asked whether they would agree to allow their child to participate if the situation were real. They were also asked about their reasons for their responses.

227 interviews were conducted and 61% of the parents indicated that they would give consent had the situation been real. Parents who would have agreed to give consent cited benefit to their child, future children and contribution to medical knowledge as reasons for their consent decision. Parents who would not have consented cited fear of an adverse event, that they did not want child to be research subject, that they needed to consult with other family members, or that they couldn’t decide unless they were in a real situation.

Parental ethnicity (Caucasian and Hispanic) and household income (<\$50,000) were associated with the decision to consent but child's age, child's gender, parent's age and gender, parent's religious affiliation, level of education, language and number of children in the family were not.

Prior to publication, the authors discussed the results with selected ethicists and IRB chairpersons and although the study results and discussion do not reflect the views of these individuals, the method proposed was found to be quite acceptable and was thought to be able to be performed at a low cost, on a targeted population, yielding specific and important information about this community.

#### 4. The Prehospital Treatment of Status Epilepticus Trial [7]

This trial compared the use of lorazepam and diazepam in the prehospital control of status epilepticus in patients over the age of 18 years. The study was conducted from 1994-1999 spanning the time period when the Rule was being discussed and finalized. The investigators published the details of the study design and methodology distinct from the results. The study was approved under the DHHS regulations for Waiver of Informed Consent (45 CFR 46). Since both drugs were approved for this indication, the risk of the study was felt to be no more than minimal and related primarily to randomization. There was no request to obtain an IND at that time either by the approving IRB or post November 1996.

To target the population of potential subjects with neurological disease or preexisting seizure disorders, the investigators posted announcements in the neurology and epilepsy clinics describing the study and included information to contact the investigators. The article describes this as "community consultation" but there was no evidence of two-way communications. They also "targeted the community at large" by posting an announcement in an edition of the local newspaper and had one investigator provide study information to a local community representative of the Epilepsy Foundation of Northern California. These activities are consistent with public disclosure, but not with community consultation and clearly illustrates the confusion and misinterpretation that can occur both on the part of the investigator and the IRB.

#### 5. Content analysis of the FDA docket [14]

This study was an attempt to see how this aspect of the Rule was being documented and if it seemed to be effective. Since only information about public disclosure is mandatory to report to the FDA docket by a study sponsor, there was no focus on obtaining information particular to community consultation. Four trials had been reported at that time and were analyzed. Two studies reported both their community consultation and public disclosure activities in the literature [Santora and Kremers]. Two additional studies operating under the Rule did not publish any information related to informed consent, community consultation, or public disclosure (a monoclonal antibody trial in patients with hemorrhagic shock and a randomized double-blind study of magnesium sulfate,

diazepam or both, or neither for out of hospital cardiac arrest) and only published the results of the trial itself.

Information contained in the docket showed that most communications with communities were “one-way” in the sense that they were directed toward getting information to the community and not back from the community. Many 2 way communications that appeared in relation to these trials were not directed toward lay persons and many involved fewer than 15 persons. Some of the issues raised by communities were the inability to refuse study participation, potential racial biases affecting study design and execution, and ambiguity regarding how the community input would be used. Investigators concluded that much could be learned from creative approaches to meet these requirements but it is imperative to continue to monitor the suitability and appropriateness of different measure that are used in obtaining waiver of consent.

#### 6. Attitudes of ED patients and visitors toward EFIC [12]

This survey was conducted on a population of emergency department patients and visitors asked about their attitudes toward EFIC. The survey obtained a high response rate and was conducted by trained research assistants using a convenience sample in the waiting room of a Level 1 Trauma Center ED waiting room.

530 surveys were completed (82% response rate). 49% of respondents believed that enrolling subjects without prior consent in an emergency situation would be acceptable to them and 70% would not object to being entered. Informing and consulting the community as a substitute for patient consent in emergency research was felt to be reasonable by 45% of respondents and most indicated that they would prefer to be informed by radio and television (42%) or by attending a community meeting (49%).

Although this data validates the preferences of community members and the methods that have already been used to perform community consultation, the study was not linked to a particular trial and the inferences that can be drawn regarding these preferences in limited. This study is one of only two to provide a broad understanding of the attitudes toward the Rule. Of interest, is that the study was conducted in a community that actually had an ongoing study using EFIC – the Public Access Defibrillation Trial - but only 5% of those surveyed were aware of this raising further questions about the effectiveness of public disclosure.

#### 7. Public Access Defibrillation (PAD) Trial [8]

The PAD trial was a prospective multicenter randomized clinical trial comparing two prehospital resuscitation strategies (on-site layperson CPR and 9-1-1 activation with and without deployment of Automated External Defibrillators for patients with out-of-hospital cardiac arrest). The aim of this study was to describe the IRB approval process and the number and type of community consultation and public disclosure activities associated with the trial. It was the largest scale effort to date on a trial using EFIC.

There were 24 primary sites which conducted the trial and all 101 IRBs involved, approved of the study. Overall, the investigators conducted about 12,000 activities to achieve community consultation and public disclosure and these activities varied greatly from site to site in type and quantity. These included 1030 meetings attended by 8169 individuals (mean 88/meeting), 475 press releases, distribution of 9270 letters, brochures, newsletters or emails, 231 radio, TV or print advertisements, 286 feature news stories, and 75 radio or television appearances.

1502 comments were received by investigators of which 96% were interpreted as “positive.” The study failed to document additional costs associated with these activities but personnel time, print, and media accounted for most of the estimated cost. The length of time to obtain IRB approval and the extent of the other activities suggests that more specific guidance may be useful and that the determination of effective strategies is needed as these large scale and impressive efforts to conduct community consultation essentially were accepted without any independent evaluation process. Any trial of similar scope and expense would likely use this information to design community consultation and public disclosure activities without the benefit of knowing the effectiveness and true costs associated with them.

#### 8. Brain Cooling After In-hospital Pediatric Cardiac Arrest [9]

The objectives of this study were to perform a community consultation and public disclosure activity that was specific to a trial of induced hypothermia in children who were just resuscitated from cardiac arrest and to determine whether EFIC was applicable to trials that examined interventions after in-hospital pediatric cardiac arrest.

Investigators used focus groups, information notices, emails and telephone conversations to gather data from several groups of individuals: parents of critically ill children, hospital staff, and hospital administrators. In focus groups, parents and hospital staff both acknowledged that prospective informed consent was not feasible for such a trial. Parents endorsed exception from informed consent as long as study information was prospectively accessible and there was an opportunity to decline participation with a verbal conversation before enrollment. 100% of parents and 50% of hospital staff who provided written opinions endorsed the use of EFIC for the study while 12% of the hospital staff disapproved and 38% were neutral.

The trial remains in the protocol planning phase but the information from community consultation activities have been found to be acceptable to the IRB if the trial proceeds with a request to operate under EFIC.

#### 9. Effectiveness of an Innovative Emergency Department Procedure for the Initial Management of Brain Trauma Compared with Standard Procedure [10]

This trial compared an “innovative” emergency department procedure for the initial management of TBI compared to a standard protocol. A waiver of informed consent was

sought under the DHHS regulations (45 CFR 46). In preparation of community consultation the IRB assigned a “community liaison” to work with the research team. This individual attended all public community presentations and administered post-presentation questionnaires. The investigators updated each subsequent presentation based on feedback from the previous meeting. These techniques were aimed toward both the broad and more narrowly targeted communities in which the trial was taking place.

Presentations were made statewide at regularly scheduled meetings of civic organizations (broad community) and also at targeted, strategic meetings in areas where traumas occurred. Presentations lasted 20-45 min followed by questions. Post-presentation surveys assessed knowledge of study methodology and willingness to participate. There were 5 initial meetings held and then the IRB asked for two more targeted to a specific group.

There was a high level of understanding of study methodology except for the concept of random assignment to treatment group. When asked if they wanted to be enrolled in the study if they suffered brain trauma, 93% were in agreement, 95% were willing to have family member participate, and 100% were willing to have study done in their community. One year after initial review the IRB approved the study to enroll patients and requested quarterly reports of ongoing community consultation efforts in an attempt to verify continued community support. Although not part of the current regulations, this request for ongoing information may be of interest to the regulatory community and also warrants further exploration. This is the only study to mention such activity extending beyond the pre-trial phase, but no information is given beyond that.

#### 10. Views on Informed Consent in Emergency Situations (VOICES) Study [13]

In association with the PAD trial, focus group participants were recruited from residential sites in New York City and were asked about the ethical issues raised by the conduct of research without consent. The information obtained in this study was not collected as part of the community consultation process for the PAD trial; rather it was an exploration of community attitudes following the conduct of this trial. It’s intent was to examine the appropriate and relevant definition of the community, and effective methods of communication for purposes of consultation and public disclosure related to EFIC studies.

There were 42 bilingual participants who provided wide definitions of community and had no overall consensus regarding the definition of community. The most frequently cited definitions of community were references to a common geography but also “belonging to a group” with a common interest like religion.

No strategy for community consultation was consistently endorsed. No particular leaders or individuals were thought to be authoritative in terms of who investigators could consult with before the start of a research study although health care workers and clergy were most frequently suggested. There was a tendency to trust deliberative group process

rather than individuals for example, community boards rather than a single elected official.

No participant spontaneously suggested consulting individuals with the disease being studied or their family members but when asked specifically about this, some thought it was essentially while others continued to believe that the community should be viewed more broadly.

The only consistent predictor of views associated with the acceptability of performed research without consent was personal experiences with researchers or health care professionals both good and bad. These preliminary qualitative findings based on a small sample, suggests more research needs to be done to understand who to speak with during community consultation. This may differ for each study conducted and these responses may be unique related to where a trial is conducted and the composition of the focus groups providing input.

### 11. L-arginine Trial [11]

This trial of the use of L-arginine for reduced cerebral blood flow following traumatic brain injury used three methods of community consultation designed to target three different definitions of community. To date, this was the most systematic approach to community consultation and the most well designed of the studies on this topic. C

Community was defined in three ways and the investigative team developed methods to correspond to each. For population based assessment, random digit dialing survey of county residents was used. To assess the at-risk population of those who were likely to present to the hospital conducting the study, interviews in hospital waiting and treatment areas were conducted and finally individuals responding to an invitation to attend a series of public meetings were thought to represent self-selected, highly interested individuals. Sampling techniques were designed to match the demographics of the study location and the same evaluation instruments were used throughout the techniques.

Each of the methods was determined to be feasible as they had large number of attendees but telephone surveys were deemed the most efficient and guaranteed the desired geography. The cost per respondent was estimated at \$55 for the telephone survey and \$63 for a community meeting but they did not account for staff time (30 min/interview). The time to completion was 2 weeks for the telephone survey and 9 weeks to 1 year for the meetings and interviews.

This was the only study with the size and diversity to answers questions about the effect of the method, framing, and demographics on the rate of agreement between respondents. Overall, 80% approved of the research, 68% agreed that benefits justified the risks, 54% agreed that randomization was justified, and 58% agreed that waiver was justified

There remained a substantial level of concern even when the risks of the study were low and the concept of randomization poorly understood as noted by the investigators who

also expressed concern about lack of guidance on these issues. Their overall conclusion was that community consultation activities are feasible but the results depend heavily on the method of consultation

## 12. Supplemental information [15]

Jason Karlawish, an expert on medical decision-making in cognitively impaired individuals, has conducted focus groups with community members to better understand their attitudes toward community leaders and how trusted they are to speak for community members. His work showed that people identify with communities in different ways and that they often identify with multiple communities. His results indicated the following:

- That people can identify community leaders that can represent their views. It is possible that consulting with local government, medical, neighborhood, and religious leaders may be a viable way to perform community consultation for EFIC.
- Information about the research should be disseminated through media channels most accessible to the community: local health care providers, basic cable, radio, and free periodicals.

This work has some important implications. This may be a more viable and cost-effective way to conduct community consultation.

### **Conclusion:**

Since the regulations have been finalized in 1996, there have been few studies using EFIC and even fewer reports on the conduct of community consultation and public disclosure activities associated with implementing EFIC. The available small body of literature on this topic shows that the scope and breadth of these activities are wide and that the effectiveness of these activities has not been adequately evaluated. Future versions of the FDA Guidance should incorporate any available existing data on the process of community consultation and public disclosure. Community consultation activities should be mandated to appear in the FDA Docket in association with a trial using EFIC and methodologies should be made available to other investigators through [clinicaltrials.gov](http://clinicaltrials.gov).

In addition, the FDA should consider independently developing an assessment tool or evaluation procedure that assures the adequacy of the community consultation process. This tool should be developed by an expert panel of thought leaders and researchers that have proposed, performed and researched the community consultation aspect of the Rule. Such a tool has great potential for facilitating the IRB approval process of studies using EFIC.

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