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Exception From Informed Consent: Lessons From a Consensus Conference

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Overview of the Exception from Informed Consent Regulations for Emergency Research

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Background

- Controversy regarding deferred consent, implied consent, 2-tiered consent, discrepancies in wording between FDA and DHHS
- Recognition that discrepancies and inconsistencies within the federal regulations could lead to misunderstanding and misapplications when regulations applied to emergency research
- Recognition of the need to advance the science of emergency care and without alternative informed consent procedures, the safety and efficacy of emergency treatments could not be determined

Important historical events

- Society for Academic Emergency Medicine formed the “Coalition of Acute Resuscitation and Critical Care Researchers” representing many national organizations and held a national consensus conference
- Coalition recommendations presented at an FDA and NIH-sponsored public forum
- FDA develops a Proposed Rule that was open for 2 months for public comment
- All public comment formally addressed
- FDA issues Final Rule for Exception to Informed Consent for Emergency Research
- FDA and DHHS Final Rule harmonized and went into effect November 1996
- FDA issues Draft Guidance document 2000 and 2006

FDA has subsequently held several forums on EFIC; most recent public hearing October 2006

FDA Final Rule 21 CFR 50.24

- The IRB responsible for the review, approval, and continuing review of clinical investigation may approve that investigation without requiring that informed consent of all research subjects be obtained if the IRB (with the concurrence of a licensed physician who is a member of or consultant to the IRB and who is not otherwise participating in the clinical investigation) finds and documents each of the following:

FDA Final Rule 21 CFR 50.24

- Human subjects are in a life-threatening situation
- Available treatments are unproven or unsatisfactory
- Collection of valid scientific evidence, is necessary to determine the safety and effectiveness of particular interventions

FDA Final Rule 21 CFR 50.24

- Obtaining informed consent is not feasible because:
 - Subjects are incapacitated as a result of their medical condition
 - Intervention must be administered before consent from the subjects' legally authorized representatives is feasible
 - There is no reasonable way to prospectively identify eligible individuals for participation

FDA Final Rule 21 CFR 50.24

- Participation in the research holds out the prospect of direct benefit
 - Subjects are in a life-threatening situation that necessitates intervention;
 - Information derived from animal and preclinical studies support the potential for the intervention to provide a direct benefit to the individual subjects
 - Risks associated with the investigation are reasonable in relation to what is known about the medical condition of the potential class of subjects, the risks and benefits of standard therapy, and what is known about the risks and benefits of the proposed intervention or activity

FDA Final Rule 21 CFR 50.24

- Clinical investigation could not practicably be carried out without the waiver
- Research plan defines the length of the therapeutic window based on scientific evidence
 - Investigator has committed to attempting to contact a LAR within that window of time and, if feasible, to asking for consent within that window rather than proceeding without consent. The investigator will summarize efforts made to contact LARs and make this information available to the IRB at the time of continuing review
- The IRB has reviewed and approved informed consent procedures and an informed consent document
 - The informed consent procedures and document are to be used with subjects or their LAR in situations when feasible and the IRB has reviewed and approved procedures and information to be used when providing an opportunity for a family member to object to a subject's participation in the clinical investigation

Additional protections of the rights and welfare of subjects

- Consultation (including, where appropriate, consultation carried out by the IRB) with representatives of the communities in which the clinical investigation will be conducted and from which the subjects will be drawn
- Public disclosure to the communities in which the clinical investigation will be conducted and from which the subjects will be drawn, prior to initiation of the clinical investigation, of plans for the investigation and its risks and expected benefits
- Public disclosure of sufficient information following completion of the clinical investigation to apprise the community and researchers of the study, including the demographic characteristics of the research population, and its results;

Additional protections of the rights and welfare of subjects

- Establishment of an independent data monitoring committee
- If obtaining informed consent is not feasible and a LAR is not reasonably available, the investigator has committed, if feasible, to attempting to contact within the therapeutic window the subject's family member who is not a LAR, and asking whether he or she objects to the subject's participation in the clinical investigation. The investigator will summarize efforts made to contact family members and make this information available to the IRB at the time of continuing review.
- The IRB is responsible for ensuring that procedures are in place to inform, at the earliest feasible opportunity, each subject, or if the subject remains incapacitated, a LAR of the subject, or if such a representative is not reasonably available, a family member, of the subject's inclusion in the clinical investigation and that he or she may discontinue the subject's participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

Additional protections of the rights and welfare of subjects

- If a LAR or family member is told about the clinical investigation and the subject's condition improves, the subject is also to be informed as soon as feasible
- If a subject is entered into a clinical investigation with waived consent and the subject dies, information about the clinical investigation is to be provided to the subject's LAR or family member, if feasible

Community Consultation: What is it intended to do?

- To “ensure that the relevant communities have opportunity for input into the IRB’s decision-making process before initiation of the study” .
- Provide an opportunity for community to:
 - Understand the proposed investigation and it’s risks & benefits
 - Discuss the investigation

Community consultation

- **Community consultation ≠ community consent**
 - Process is meant to elicit input from the community regarding the study and process
 - IRB makes the final determination as to study approval using information obtained in the process

Community Consultation

- Many methods used in trials conducted under 21 CFR 50.24
- No proven superior method
- Few studies evaluating the feasibility, adequacy or cost-effectiveness of various methods
- Prior experience with community consultation suggests that targeted consultation within a specified time period may be the most appropriate to obtain community feedback
- Sites that serve a patient population that is multicultural and multilingual will have additional challenges in performing community consultation and public disclosure activities
- Investigators should determine from which if any of these communities the IRB will be interested in hearing specific feedback as it will not be practical or efficient to conduct trial activities with every representative group.

Public Disclosure

- Definition
 - “dissemination of information about the emergency research sufficient to allow a reasonable assumption that communities are aware of the plans for the investigation, its risks and expected benefits and the fact that the study will be conducted”
 - Also includes “dissemination of information after the investigation is completed so that communities and scientific researchers are aware of the study’s results”

Public Disclosure

- Clear statement that informed consent will not be obtained for most subjects
- Information about the test articles use including a balanced description of the risks and benefits
- Synopsis of the research protocol and study design
- How potential study subjects will be identified
- Participating sites/institutions
- Description of the attempts to contact LAR
- Suggestions for “opting out”

Public disclosure

- Public disclosure must continue throughout the study period
- May need to include relevant study updates
- Many methods used in previous trials
- Few data or reports of adequacy or (cost) effectiveness
- Requirement to submit materials to the FDA docket

Key Concepts

- Very narrow exception to the requirement to obtain prospective informed consent
- Not indicated when there is sufficient time for informed consent
- Only applies to life-threatening conditions or emergency research
- Community consultation (before study) and public disclosure (before and after study) are performed
- Family members are given a chance to “opt out”
- Notification of subject/family occurs, when feasible
- Written FDA approval is required (IDE or IND)
- IRB is responsible for approving this process in addition to approval of the research protocol

Barriers and Solutions to Conducting EFIC Research

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Public Perceptions

- Patients have an “illusion of efficacy” about emergency treatment.
- Sensational articles in lay press about EFIC research.

“I am personally troubled,” Sen. Grassley wrote, “that for all intents and purposes, the FDA allowed a clinical trial to proceed which makes the inhabitants” of these communities “potential guinea pigs, without their consent and, absent consent, without full awareness of the risks and benefits of the blood substitute.”

– *Wall Street Journal* 2006 March 14

Cardiac Arrest and Resuscitation

An Opportunity to Align Research Prioritization and Public Health Need

Ornato JP, Becker LB, Weisfeldt ML, Wright BA. *Circulation* 2010; 122:1876-9

Disease	Published RCTs	Deaths/Year	RCTs/100,000 deaths/year
STEMI	7,691	157,000	490
Stroke	3,639	150,000	243
Heart failure	4,108	284,000	145
Cardiac arrest	177	310,000	6

43x

82x

EFIC Consensus Conference

- Sponsored by
 - National Association for EMS Physicians (NAEMSP)
 - National Highway Traffic Safety Administration (NHTSA)
- Funded by
 - Agency for Health Care Research and Quality (AHRQ)
- Held in Washington DC in February 2007 to discuss the principles in emergency research.

IRB Responsibilities

- Weigh the risks and benefits of participation in the proposed research and substitute its judgment, with input from the community, for the judgment of the potential subjects.
- Investigator and IRB leadership meet prior to submitting the protocol for formal approval :
 - Seek feedback on the general research protocol
 - Discuss the preliminary plan for community consultation.
- Consider requesting that an independent ethics expert review the protocol to decide whether the protocol meets the requirements for the EFIC process.
- Investigators might consider including in the protocol the health outcomes that could potentially be lost if a study of a successful intervention is significantly delayed.

IRB Responsibilities

- Many IRBs approve the community consultation and public disclosure plan first.
- Then decide final approval of the overall study once the community consultation process is complete.
- Proposal for a structure for determining a reasonable balance between the need for public disclosure and community consultation and the relative risks of the proposed research (Halperin *Circulation* 2007;116:1855-63).

Public Disclosure

- Enforces transparency for all parties
 - Threat of widespread negative publicity will deter the vast majority of investigators from conducting unacceptable experiments.
- Provides information that could improve public knowledge of important health issues.
- Target the population of interest
- Offers a means of providing opt-out information
- Provides the investigator an opportunity to work with the local news media in a proactive manner prior to initiation of the study

Community Consultation

- Iterative process rather than an isolated event
- Actively seek information from communities and their representatives.
 - Explicitly inviting individuals to participate is vital
- Explore potential issues surrounding the proposed trial
- Elicit concerns and suggestions

Measuring Community Consultation

- **Process evaluation:**
 - How were the communities selected?
 - How were community members engaged?
 - What the appropriate information discussed?
 - Did the community consultation actively elicit comment?
 - How was feedback shared with the IRB?

Measuring Community Consultation

- **Impact evaluation:**
 - How many people participated in the process?
 - How many comments were received?
 - Did the community members engage in the process?
 - Was the feedback constructive and useful?
 - Were all appropriate groups reached?

Measuring Community Consultation

- Outcome evaluation:
 - Is there improved understanding and mutual trust between the communities and investigators?
 - Was information obtained during the community consultation process used to guide public disclosure or the process for objecting to participation in the study?
 - Did any concerns arise that led to changes in the study protocol or implementation process?

Consent

- When it is acceptable to forgo efforts to contact a legally authorized representative?
 - Therapeutic window is so short (e.g., a few minutes in the case of cardiac arrest or severe hemorrhagic shock).
- The window in stroke might be an hour or two, but the LAR still may not be able to arrive at the hospital in time.
 - Consent cannot be obtained solely by telephone in studies conducted under the current EFIC rules.
 - E-mail or fax can be used to send documents.

Consent

- Paramedics provided the legally authorized representative and the patient with written information about the study while still in the patient's home.
- Paramedics called a study investigator, and the patient and family were able to ask the investigator questions about the study.
- Final documentation of informed consent was completed after hospital arrival.

Consent

- Evidence from animal research or other clinical uses can help estimate the rate of decline in the study drug's effectiveness
- The IRB can use that estimate to guide a decision about abandoning efforts to contact a family member and using EFIC instead.

Notifying the Family

- If active study procedures are ongoing, then the family or LAR shall give permission to continue the subject in the study within a few hours.
- If active study procedures are completed, the IRB needs to make a judgment about the least intrusive means of informing the family of the subject's participation in the study.
- Waiting some reasonable amount of time for the family to come to terms with the events before informing them about the study seems much gentler.
 - The patient may regain the ability to provide consent.
 - IRB has to decide what timeline best protects the interests of the subject while being mindful that the HHS regulations state the notification should happen “at the earliest feasible opportunity.”

Opting Out

- EFIC rules do not require that potential subjects be given the opportunity to express objection to participation in advance.
- Scope of public disclosure activities should be commensurate with the likelihood of objection.
- As of November 2007, 1079 individuals had opted out of ROC studies.

Objecting at Enrollment

- An individual who is aware of an EFIC trial might express objection to participation.
 - Such objections must be honored.
- IRBs may decide that providing incomplete information at the time of the emergency in order to stimulate potential objections truly protects neither subjects nor the integrity of the trial.

Discontinuing After Enrollment

- FDA and OHRP issued guidance in the fall of 2008 about retention of data at the time of subject withdrawal from research.
- The FDA position is that data collected on study subjects up to the time of withdrawal must remain in the trial database.

Conclusion

- Conducting research using the EFIC rules is challenging.
- This research is most appropriate for life-threatening conditions with extremely high mortality and morbidity rates.
- Better treatments need to be identified.
- High quality research must test the effectiveness of those treatments.

Submissions to FDA under § 50.24

Highlights for Sponsors and Investigators

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Office of the Commissioner
Office of Good Clinical Practice
2/28/11

Study design

Preliminary considerations (1 of 6)

- Can the necessary scientific information be obtained in a consenting population?
 - Affect on scientific validity?
 - Affect on generalizability of results?
- Can risks be minimized by studying a less sick population?
- Protocol needs to contain a justification for:
 - Conducting the study in subjects who cannot provide informed consent
 - Selecting the therapeutic window
- Plan ahead—consider all aspects of the trial up front (e.g., biomarkers)

Study design

Qualifications (2 of 6)

- Life-Threatening Situation
 - Need not be immediately life-threatening or immediately result in death, however, death likely unless course of disease is interrupted, and intervention required before consent is feasible
 - Must be an emergent situation (e.g., not long-term or permanent coma)
- Available treatments unproven or unsatisfactory [a state of clinical equipoise must exist]
 - Unproven: lack of substantial evidence that a treatment is effective for the condition of interest
 - Unsatisfactory: drawbacks to the treatment (safety, poor survival rate, only partially effective, takes too long to work, treatment has limitations in the setting in which it is needed)
- Intervention must hold out the prospect of direct benefit to the subject receiving the intervention

Study design

Prospect of direct benefit (3 of 6)

- Subjects are facing a life-threatening situation that necessitates intervention;
- Information from appropriate animal and other preclinical studies support the potential for the intervention to provide a direct benefit to the individual subjects; and
- The risks associated with the investigation are reasonable in relation to what is known about the medical condition of the potential class of subjects, the risks and benefits of standard therapy, if any, and what is known about the risks and benefits of the proposed intervention or activity.

Study design

Endpoints (4 of 6)

- Mortality endpoints
- Morbidity endpoints may be acceptable
 - Severe morbidity is clinically relevant and closely associated with mortality
 - Study of stroke which can lead to permanent disability or death
 - Study to improve treatment of status epilepticus might focus on reduced time to seizure control

Study design

*Sponsors need to provide rationale for the selected design
(5 of 6)*

- Active-controlled trial
- Non-inferiority trial: to make the study interpretable, the submission needs to include clear data about the effectiveness of the control treatment and about known safety problems (or other concerns) associated with the control treatment
 - Might be used when PCT is unethical or when the currently available therapy is known to be effective but has a serious safety concerns
- Placebo-controlled trials may be acceptable
 - In virtually all cases, standard care, if any, is given to all subjects, with subjects randomized to receive, in addition, the test article or a placebo*
 - * an exception may be made in a situation in which the trial is to determine whether the standard treatment is, in fact, useful

Study design

Sponsors need to provide rationale for the selected design (6 of 6)

- The “phase” of a trial is not the focus of § 50.24 regulation: rather, the intervention must hold out the prospect of direct benefit:
 - Generally, PK studies would be done in consenting subjects
 - Generally, phase 2 controlled trials in consenting subjects may be needed to explore dose response for safety or biomarkers (e.g., multiple organ failure free days, degree or extent of acidosis) before an investigation proceeds under § 50.24

Pre-IND or pre-IDE meetings encouraged

- Provides an opportunity for FDA to comment on the protocol development plan and the adequacy of the IND/IDE submission
- Provides an opportunity for FDA and sponsor to discuss specific aspects of the draft protocol, if submitted, including:
 - Scientific considerations (e.g., study design, biomarker assays)
 - Ethical concerns (e.g., applicability of 50.24)

When is an IND needed for a study conducted under § 50.24?

- Always: A clinical investigation involving exception from informed consent (EFIC) is not exempt from the requirements of part 312 (§ 312.2(b)(6)).
- Protocols involving EFIC must be performed under a separate IND that clearly identifies such protocols as protocols that may include subjects who are unable to consent (§ 312.23(f) and § 50.24(d)).
- The submission of those protocols in a separate IND is required even if an IND for the same drug product already exists (§ 50.24(d)).

When is an IND needed for a study conducted under § 50.24?

21 CFR 312.20(c)

- Reiteration: A sponsor shall submit a separate IND for any clinical investigation involving EFIC under § 50.24.
- Such a clinical investigation is **not permitted to proceed without the prior written authorization from FDA**. FDA shall provide a written determination 30 days after FDA receives the IND or earlier. [In contrast to a clinical investigation not involving EFIC: the IND goes into effect 30 days after FDA receives the submission, unless FDA notifies the sponsor that the IND is subject to a clinical hold. (§ 312.40(b)(1))]

How are EFIC studies involving drugs processed?

- After the IND is submitted, FDA will review the study protocol under the applicable IND regulations (Part 312) and § 50.24.
- The study is not permitted to proceed without the prior written authorization of FDA and IRB approval.
- Questions should be directed to the FDA review division.

When is an IDE needed for a study conducted under § 50.24?

- Almost Always: A sponsor shall submit an application to FDA if it intends to use a SR device in a clinical investigation involving EFIC (§ 812.20(a)).
- Protocols involving EFIC must be performed under a separate IDE that clearly identifies such protocols as protocols that may include subjects who are unable to consent (§ 812.20(a)(4)(i) and § 50.24(d)).
- The submission of those protocols in a separate IDE is required even if an IDE for the same device product already exists (§ 50.24(d)).

How are EFIC studies involving devices processed?

- A sponsor is usually required to complete and submit an IDE application describing the proposed study. However, if the device would otherwise meet the criteria of the abbreviated requirements under 21 CFR 812.2(b), or the proposed protocol involves a device that has already been cleared or approved for marketing and is being used in accordance with its cleared/approved labeling, the sponsor or investigator should contact FDA for clarification regarding requirements for the submission of an IDE application.
- If an IDE is required, FDA will review the study protocol under the IDE regulations (Part 812) and § 50.24.
- The study is not permitted to proceed without the prior written authorization of FDA (§ 812.20(a)(4)(i)) and IRB approval.
- Questions should be directed to the FDA review division.

What are some other sponsor responsibilities for a study conducted under § 50.24?

- Submission of public disclosure materials to FDA docket number 95S-0158, prior to initiation of the clinical investigation
- Public disclosure of sufficient information following completion of the clinical investigation to apprise the community and researchers of the study
- Establishment of informed consent procedures and an informed consent document consistent with § 50.25
- Establishment of an independent data monitoring committee
- Ensuring that procedures are in place to **inform-at the earliest feasible opportunity- each subject or the subject's legally authorized representative** if the subject remains incapacitated

What information must a sponsor submit to FDA for a study conducted under § 50.24? (Slide 1 of 2)

- Contact the review division directly about the submission process.
- The separate IND or IDE submission should be completed as described in the pertinent regulations.
- Information previously submitted to FDA may be incorporated by reference. The location of information incorporated by reference should be specifically identified, for example, by application number, date of submission, volume, page and section. If the information was submitted by someone other than the current applicant, a letter from the person who holds the files authorizing reference to the information must be provided.
- The submission should include the informed consent document(s).
- In addition, the submission should address the specific requirements for studies conducted under § 50.24 (e.g., plans for community consultation, plans for public disclosure).

What information must a sponsor submit to FDA for a study conducted under § 50.24? (Slide 2 of 2)

- In addition to the information that sponsors customarily provide, the sponsor should also include:
 - justification for conducting the study in subjects who cannot consent
 - justification as to why the investigational intervention may be better than existing, available treatment
 - a description as to why existing, available treatments are unproven or unsatisfactory
 - a rationale for selecting the therapeutic window in which the investigational product is to be used
 - a description of the investigator's commitment to attempting to contact a legally authorized representative for each subject within that window of time (21 CFR 50.24(a)(5)).

Who can I ask for help at FDA?

- **CDER:**
 - Chief, Project Management Staff in the appropriate review division (i.e., for the therapeutic area being studied)
 - If the relevant review division is not known then contact CDER's Division of Drug Information, barry.poole@fda.hhs.gov, (301) 796-3400
- **CDER:**
 - Applications division of the appropriate review Office
 - If the relevant review division is not known then contact CDER's Division of Manufacturer's Assistance and Training at matt@cber.fda.gov, (301) 827-1800, 1-800-835-4709
- **CDRH:**
 - Office of Device Evaluation, IDE Staff, 301-796-5640
- **CFSAN:** David Hattan, 301-436-1293

Question & Answer Period

Please complete the evaluation immediately following this webcast. Thanks for joining us today!