Planned Emergency Research and EFIC Information

What Is Planned Emergency Research?

- Clinical investigation
- Subject incapacitated
- Life threatening situation
- No time to obtain traditional consent
- No way to identify subjects in advance
- Not practical to conduct research without an exception to informed consent

Example:
Experimental blood plasma product for trauma patients

Regulation 21 CFR 50.24—Summary of Key Points

See the full text of the regulation here:
https://www.govinfo.gov/content/pkg/CFR-2012-title21-vol1/pdf/CFR-2012-title21-vol1-sec50-24.pdf

- 50.24(a)—IRB can approve a clinical investigation with an exception to informed consent *under certain circumstances* and in consultation with a licensed physician not involved in the research *[paraphrased]*
- The IRB must find and document a lot of items…

The Requirements—Summary of Key Points

- 50.24(a)(1)—Life threatening situation, unproven or unsatisfactory standard treatments, collection of safety and efficacy data is necessary. *[paraphrased]*

- 50.24(a)(2)—Obtaining prospective consent is not feasible because there is no reasonable way to identify in advance who will become eligible. *[paraphrased]*

- 50.24(a)(3)—Research holds the prospect of direct benefit to the incapacitated subject who is in an emergency situation and the risks are reasonable in relation to their situation. *[paraphrased]*

The Requirements—Summary of Key Points

- 50.24(a)(5)—Investigator must commit to attempting to obtain consent from subject's LAR during the potential therapeutic window before initiating intervention without consent; these contact efforts must be summarized for the IRB at continuing review. *[paraphrased]*

- 50.24(a)(6) & (7)(v)—If LAR is not available, the investigator must also commit to attempting to contacting a family member to ask if they object to the subject's participation; these efforts likewise must be summarized for the IRB. *[paraphrased]*

The Requirements—Summary of Key Points

- 50.24(b)—Process must be in place to consent the subject, their LAR, or a family member at the earliest feasible opportunity. *[paraphrased]*
- 50.24(b)—Subject, their LAR, or a family member at the point of being told of the study may discontinue the subject's participation. *[paraphrased]*
- 50.24(b)—If it was the LAR or family member who was provided the after-intervention consent discussion; when the subject regains capacity they must be informed of the research and given their own opportunity to consent. *[paraphrased]*

The regulation emphasizes strongly that the consenting plan must make every feasible attempt to seek consent for the research.

The Requirements—Summary of Key Points

- 50.24(a)(7)(i-iii)—IRB must approve a community consultation and disclosure (CC/PD) plan to include at a minimum i) consultations with the community to obtain their input and provide opportunity to ask questions, ii) public disclosures prior to initiation of the research activity, and iii) public disclosures to the community following completion of the research. [paraphrased]

  ** Details of what constitute an adequate community consultation and public disclosure plan, as well as how the IRB is supposed to review such plans, are covered in detail by FDA's 60+ page guidance Exception from Informed Consent Requirements for Emergency Research. The IRB is required to review a lot of materials. This is an involved process befitting the nature of the research.

- 56.109(g)—IRB must provide a copy of the publicly disclosed information to the sponsor. The sponsor in turn is required to provide a copy of the public disclosures to the FDA. [paraphrased]

The Requirements—Summary of Key Points

- 50.24(d)—A separate IND or IDE must be obtained for planned emergency research even if the same drug or device already has an IND/IDE. [paraphrased]

- 50.24(e)—The IRB has additional disclosure requirements when disapproving planned emergency research with an exception to informed consent. If the IRB cannot approve the exception to informed consent it must document its findings as to why, and the IRB must communicate these findings to the investigator and the sponsor. The sponsor in turn is required to disclose this information to the FDA, to the sponsor's clinical investigators who are or may be carrying out similar investigations, and to other IRBs the sponsor has asked to review this or similar clinical investigations. [paraphrased]

Enrollment of Minors

- The IRB will apply Subpart D during its review
  - Generally will find the study to meet 50.52, due to the FDA requirement that studies under 50.24 hold out the prospect of direct benefit
- The IRB will take into consideration whether there is enough existing information to support the enrollment of minors initially
- Assent will not be required

What About Federally Funded Research?

- Planned Emergency Research subject to HHS regulation 45 CFR 46 (Common Rule) may also be approved with an exception to informed consent per letter number 97-01 from OPRR dated Oct 31, 1996.

Source: https://www.hhs.gov/ohrp/regulations-and-policy/guidance/emergency-research-informed-consent-requirements/index.html

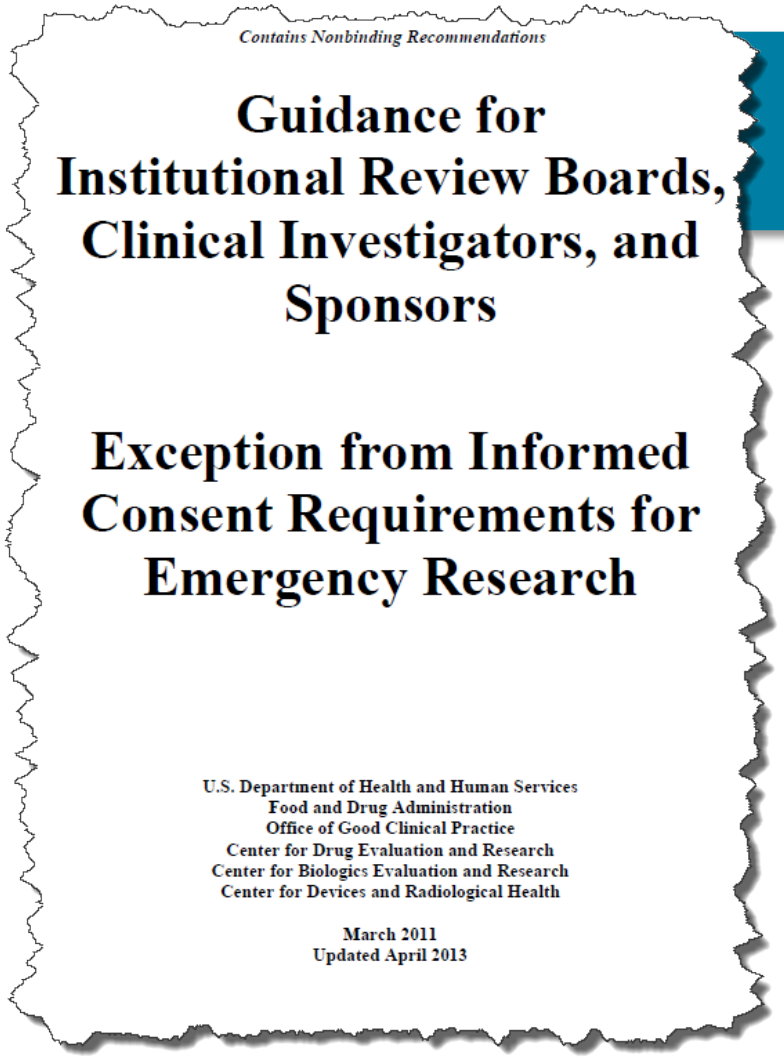
FDA U.S. FOOD & DRUG ADMINISTRATION

DEPARTMENT OF HEALTH & HUMAN SERVICES · USA

OHRP
Office for Human Research Protections

If the emergency research is subject to 45 CFR 46, then it may not involve pregnant women or prisoners.

More Details in FDA Guidance



Contains Nonbinding Recommendations

Guidance for Institutional Review Boards, Clinical Investigators, and Sponsors

Exception from Informed Consent Requirements for Emergency Research

U.S. Department of Health and Human Services
Food and Drug Administration
Office of Good Clinical Practice
Center for Drug Evaluation and Research
Center for Biologics Evaluation and Research
Center for Devices and Radiological Health

March 2011
Updated April 2013

FDA guidance dated April 2013 available here:
https://www.fda.gov/media/80554/download

We don't have time today to delve into the guidance, but it is a good resource for investigators and study team members and provides a relatively clear road map on what is required.

Read the guidance!

Community Consultation and Public Disclosure

Community Outreach: Two Components

- Community Consultation (CC)
- Public Disclosure (PD)

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    - Different columns with different types of event
      - » E.g., for CC, focus groups (column A), social media events (column B), survey (column C)

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    - Require certain distribution of events

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  - Common for protocol-level CC/PD plan to provide menu of options
    - Different columns with different types of event
    - Require certain distribution of events
      - » E.g., at least 6 CC events, with at least 2 from column A, 1 from column B, 1 from column C

Community Outreach: Two Components

- Community Consultation (CC)

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Community Consultation (CC)

- What is the community?

Community Outreach: Two Components

Community Consultation (CC)

- What is the community?
  - Geographical aspect = hospital's catchment area
  - At-risk population = people likely to suffer the condition under study
  - Demographic representativeness as *ideal* = strive to reach all groups in geographical area in rough proportion to their prevalence
  - Make efforts to reach vulnerable and under-represented groups

Community Outreach: Two Components

Community Consultation (CC)

- What is the community?
- What is consultation?

Community Outreach: Two Components

Community Consultation (CC)

- What is the community?
- What is consultation?
  - Two-way street: research team informs and listens/learns
    - » Interaction and discussion with the community
  - Chance to hear and document community's perspectives and potential concerns
    - » What is the general feeling among the community toward this research?
    - » What, if any, aspects of the research do they find troubling? What do they like about it?
  - Provide a chance for community members to opt-out of the study
    - » Via bracelet or some other mechanism

Community Outreach: Two Components

Community Consultation (CC)

- What does a strong CC component look like?

Community Outreach: Two Components

Community Consultation (CC)

- What does a strong CC component look like?
  - Meets distribution requirements in protocol-level EFIC plan
    - » Good mix of presentations, discussion groups, interviews with community leaders
  - Strives to reach representative sample of groups
    - » Concerted effort to reach at-risk groups
    - » Concerted efforts to engage minority and vulnerable populations
  - Good-faith effort to listen to community, address questions/concerns, promote understanding
    - » Discuss and provide opt-out mechanism
  - Robust survey administration and documentation of community views
    - » Documented written survey responses versus recording oral responses/impressions
    - » Make surveys widely available at events and/or online

Community Outreach: Two Components

- Public Disclosure (PD)

Community Outreach: Two Components

Public Disclosure (PD)

- Who is the ‘public’ in public disclosure?
  - Same as community for CC: Strive to reach representative audience in catchment area, with particular focus on at-risk and vulnerable groups

Community Outreach: Two Components

Public Disclosure (PD)

- Who is the ‘public’ in public disclosure?

Community Outreach: Two Components

Public Disclosure (PD)

- Who is the ‘public’ in public disclosure?
- What is disclosure?

Community Outreach: Two Components

Public Disclosure (PD)

- Who is the ‘public’ in public disclosure?
- What is disclosure?
  - More of a one-way street than community consultation
    - » Primary aim is to inform the community about the research
  - Disseminate information to the public, via print ads, billboards, flyers, TV and radio, public service announcements
    - » Should contain opportunities for future learning and feedback (links to study website) but no direct interaction

Community Outreach: Two Components

Public Disclosure (PD)

- Who is the ‘public’ in public disclosure?
- What is disclosure?

Community Outreach: Two Components

Public Disclosure (PD)

- What does a strong PD component look like?

Community Outreach: Two Components

Public Disclosure (PD)

- What does a strong PD component look like?
  - Meets EFIC plan requirements for healthy mix of media
    - » Newspaper ads, TV/radio, social media, flyers
  - Should contain concise and informative description of study, and opportunity to learn more (and opt-out)
    - » Links to study website, email contact
  - Like CC, should aspire to reach a representative sample
    - » Efforts to reach all groups represented in catchment area
    - » Efforts to reach at-risk groups
    - » Efforts to reach vulnerable and historically under-served groups
  - Will involve targeting non-English speaking publications and platforms
    - » Translation of ads and materials

Community Feedback After the Community Consultation

- The investigator should provide a report of the community consultation along with an evaluation of the results.
- The report should include details on the following:
  - Type and number of activities
  - Number of community members who participated
  - The level of interaction that occurred between the investigator/research team and the community members (e.g., simply handing out brochures does not fulfill the requirements of a community consultation plan)
  - Demographics of the community members who participated (should be reflective of the community)
- If the community raises concerns and objections about the research, the investigator should address these issues in the report to the IRB.
- Both the investigator and the IRB should consider whether the investigational plan should or could be revised to address community concerns and objections, or whether additional community activities might alleviate these concerns.

Centralized IRB

Advarra EFIC Approach

About Advarra

- EFIC-specific full board panel with members who are experienced in reviewing emergency research
  - Full board meetings twice a month, ad hoc available if need arises
  - Option for advisory review at full board for preliminary, non-binding feedback
- Expedited reviewer team who also specializes in EFIC review
  - In-depth knowledge of 50.24 regulations
  - Helpful for consistency in reviews and common EFIC study deviations

Typical Process

Sponsor/Coordinating Center submits Multisite Protocol to Advarra

Protocol, Product Information, ICFs, Notification Letters, CC/PD Plan, CC/PD Materials

Full Board Review

Master ICF Templates and CC/PD Materials Approved

Individual Sites Submit to Advarra as a Site Submission (SSU)*

Finalized ICF Templates Not Released Until CC/PD Complete and Satisfactory

Site Submission Process – “One Step”

- Structured, well-detailed CC/PD plans from sponsor negate need for pre-review of each site’s activities
- Site begins CC/PD immediately once Advarra has approved the protocol and other materials at initial review
- Once CC/PD complete, site submits their SSU application, including their CC/PD report, which is reviewed at full board
- Once found satisfactory, the board will approve the site/PI, the ICF’s will be released and enrollment via 50.24 can begin

What Does Advarra Look for in a Site Submission?

- Site ability to perform the emergency research
- Investigator qualifications
  - Does not have to have EFIC experience, but human subjects research experience is key
  - Should have expertise in the therapeutic area (emergency medicine, critical care, trauma surgeon, etc)
  - For inexperienced sites/PI, mentorship may be requested by the IRB
- CC/PD report
  - Did you do what you said you were going to do? If not, why, and what did you do to replace that activity?
  - Did you target the correct audiences?

CC/PD Do's and Don'ts

Do

- Follow the CC/PD plan
- Target groups likely to be enrolled
- Target diverse groups where there might be cultural, religious or other factors to take into consideration
- Be clear in communication of what EFIC is to the lay community
- INTERACT with your community!

Don't

- Focus on CC/PD within walls of your institution
- Double-dip on activities (one event counting as two different "menu options")
- Overstate benefit of intervention
- Be afraid to have a boots-on-the-ground approach

Collaboration and Commitment

- EFIC research, and CC/PD in particular, is complicated to do, and review
  - Requires high degree of co-ordination, collaboration, and commitment!
  - Don't be afraid to ask questions!
- Federally funded EFIC research often takes place within a trial network (such as StrokeNet or Siren), each of which has its own lead site and coordinating center
  - Choose/vet sites for adequate qualifications to conduct EFIC research
  - Provide ongoing guidance to sites on how to conduct effective CC/PD
    - May involve putting them in touch with local community groups or resources, such as through PFACs or CTSA
  - Design generic community-facing templates and materials (brochures, text for PD) that are used across sites
  - Vet site CC/PD plans and/or completed reports prior to IRB submission

Questions?

Special Topics

Incidental Enrollment of Vulnerable Populations

- Incidental prisoner, minor and pregnant participant enrollment should be submitted via a prompt reporting event (PRE)
- Subpart C does not apply to 50.24, there is no ability to approve a study under subpart C, even if the likelihood is high prisoner enrollment may occur (trauma studies)
  - Advarra has a pathway where the first time this occurs for a study, the full board may determine that future prisoner enrollment can be review via the expedited pathway