

# *Exception from Informed Consent for Emergency Research*

## *Brief Highlights*

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Part 15 Hearing

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# Overview

- History
- Focused Content of § 50.24
  - Beneficence and Respect for Persons
- Experience
  - FDA
- HHS Secretarial Waiver
  - OHRP
- Issues to be addressed
- Next Steps



# History



# History of 21 CFR 50.24

- Recognized unmet need for treatment options in the emergency setting
- Recognized need for explicit regulations to promote research to validate emergency treatment options
- FDA sought input from the public, including representatives of patient advocacy organizations and the research community
  - FDA was advised that without alternative informed consent procedures emergency research could not be conducted. Therefore, the safety and effectiveness of emergency treatment options could not be determined.



# History of 21 CFR 50.24

## ■ Significant public input:

- 1994 Congressional Hearing addressed problems encountered in securing informed consent of subjects
- 1994 Coalition Conference of Acute Resuscitation and Critical Care Researchers resulting in a consensus document offering recommendations
- 1995 FDA and NIH co-sponsored a public forum on emergency research during which
  - Many participants expressed concern that the current regulations value individual autonomy and the right to informed consent at the expense of the principles of beneficence and justice
  - The majority of participants supported new regulations to clearly permit the waiver of informed consent for acute care research if certain defined conditions and safeguards are met



# History of 21 CFR 50.24

## ■ Regulations

- 1996 Adoption of FDA regulation § 50.24
- 1996 Announcement of HHS Secretarial Emergency Research Consent Waiver

## ■ Guidance

- 2000 Draft issued
- 2006 Updated draft issued
  - Interim source of information
  - Provides additional context for today's discussions



# Beneficence

Belmont Report, 1979

- *“Persons are treated in an ethical manner not only by respecting their decisions and protecting them from harm, but also by making efforts to secure their well-being*
  - *The problem posed by the imperatives is to decide when it is justifiable to seek certain benefits despite the risks involved, and when the benefits should be foregone because of the risks”*



# Respect for Persons

Belmont Report, 1979

- *“Incorporates at least two ethical convictions:*
  - *Individuals should be treated as autonomous agents*
  - *Persons with diminished autonomy are entitled to protections”*



# Tension between Beneficence and Respect for Persons in § 50.24



How should the principles of beneficence and respect for persons be ethically balanced?



# Focused Content of § 50.24



- ❖ Given that informed consent is unobtainable, § 50.24 requires additional protections to further safeguard patients
- ❖ IRBs, clinical investigators, sponsors, and FDA have increased responsibility for implementation of these additional protections



# Beneficence

- Life-threatening situation
- Available treatments are unproven or unsatisfactory
- Evidence supports prospect of direct benefit to the subjects



# Beneficence

- Risks associated with the intervention are reasonable in relation to risks and benefits associated with:
  - Subject's medical condition
  - Standard therapy (if any)
  - Proposed intervention or activity
- Mandatory establishment of an independent data monitoring committee



# Respect for Persons

- The investigator has committed to attempting to contact:
  - a legally authorized representative (LAR) for each subject, or,
  - the subject's family member and providing the opportunity to object (if a LAR is not reasonably available)
- The IRB reviewed and approved procedures for:
  - Obtaining and documenting informed consent (subject or LAR)
  - Providing an opportunity for a family member to object to a subject's participation
  - Informing subject/LAR/family member of a subject's inclusion in the clinical investigation and the right to discontinue participation



# Respect for Persons

## Efforts to inform

- Consultation 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 . . . prior to the intervention
- Public disclosure of sufficient information following completion of the clinical investigation to apprise the community and researchers of the study



# Experience



# Number of Submissions to FDA Since Inception of 21 CFR 50.24

- In 10 years since it became effective:
  - 56 total requests to use the Rule in CDER, CDRH, and CBER
  - 21 studies were conducted, are currently being conducted, or are about to enroll
  - Some reasons for studies not being conducted:
    - Do not meet requirements of § 50.24
    - Do not meet requirements of IND/IDE regulations
    - Not approved by IRB
    - Sponsor withdrawal
- FDA carefully scrutinizes these submissions to verify that they meet the regulatory requirements



# Usefulness of the Rule

Majority of studies still ongoing

- Allowed the conduct of research in a number of critical areas that could not otherwise have been done, such as:
  - improving brain recovery after cardiac arrest or head injury
  - treatment of acute liver failure
  - treatment of traumatic hemorrhagic shock
  - treatment of hypovolemic shock following blunt trauma
  - public access automated defibrillation post cardiac arrest
- Contributed to peer-reviewed literature
  - on informed consent in emergency research
  - on medical knowledge about emergency interventions
- Approval of treatment intervention, e.g., Concentric Retrieval System for retrieval of thrombus from neurovasculature post ischemic stroke, Automated External Defibrillators for public access



# HHS Secretarial Waiver of Informed Consent in Certain Emergency Research

## Background

- Under 45 CFR 46.101(i) the HHS Secretary may waive the applicability of some or all of the provisions of 45 CFR part 46.
- On October 2, 1996, HHS published a Federal Register notice announcing a waiver of the following requirements for certain emergency research:
  - obtaining informed consent (under 45 CFR 46.116 and 45 CFR 46.408); and
  - documenting informed consent (under 46.117).
- The waiver applies to research conducted or supported by HHS.

# Key Differences Between Secretarial Waiver and 21 CFR 50.24

- The Secretarial waiver for emergency research is not applicable to research involving pregnant women or fetuses, or prisoners.
- If (i) the waiver applies, and (ii) the research is conducted or supported by HHS and regulated by FDA, the provisions of 21 CFR 50.24 must be satisfied.
- If the research is not subject to FDA regulations at 21 CFR 50.24, the IRB must find, document and report to OHRP that specified conditions (comparable to the conditions in 21 CFR 50.24) have been met.

# Next Steps for OHRP

- OHRP plans to seek public comment on the current Secretarial waiver of informed consent for certain emergency research.
- OHRP will work closely with FDA to ensure FDA's rule and the Secretarial waiver remain consistent.

# Issues to be Addressed



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Need additional input

- We hope to learn more about the challenges of conducting clinical emergency research, and possible solutions to those challenges.
- Adequacy of human subject protections under § 50.24
  - **Interpretation of particular terminology in § 50.24**
    - “unsatisfactory or unproven”
    - “practicably”
    - “prospect of direct benefit”
- **Clarification of responsibilities**
  - IRBs
  - Clinical investigators
  - Sponsors



# Issues to be Addressed

## Need additional input

### ■ Community consultation

- Costs, benefits, feasibility, effectiveness
- Minimum requirements
- Use of information obtained during the process
- Documentation, public disclosure of community consultation activities

### ■ Public Disclosure

- Minimum requirements
- Submission of public disclosure information
- Public disclosure of research results

### ■ Opt-out mechanisms

- Necessity and feasibility

### ■ Other types of public discussion before study is initiated

- Is it needed? If so, in what circumstances? If so, what is the best venue for these discussions?



# Next Steps

- Review written comments submitted to FDA docket (2006D-0331) on questions found in Federal Register Notice for Part 15 Hearing published on 8/28/06
- Review comments submitted to FDA docket (2006D-0331) on draft guidance
- Review submitted presentations associated with public input from Part 15 Hearing
- Evaluate possible options that respond to received feedback

