How to Conduct Research under an Exception from Informed Consent (EFIC)
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Agenda

• At the completion of this didactic, participants will be able to:
  – Understand the reasons for performing EFIC research
  – Describe the advantages and disadvantages of EFIC
  – Appreciate how EFIC studies differ from other forms of EM research
  – Identify pitfalls in the IRB approval process for EFIC
Agenda

• At the completion of this didactic, participants will be able to:
  – Participate in meaningful research targeting often neglected ED patient populations
“The systematic examination of patient care that is expected to be continuously available to diverse populations presenting with undifferentiated symptoms of acute illness, injury, or acutely decompensated chronic illness, and whose outcomes depend on timely diagnosis and treatment.”

Emergent Care Research

- Common conditions including:
  - Cardiac arrest
  - Major trauma
  - Stroke
  - Seizure

- Generally, conditions characterized by **altered level of consciousness** and inability of the subject to provide informed consent at the time of enrollment
Human Subjects Protection in ECR

• Principles of the *Belmont Report* (1979):
  – Respect for Persons (“Autonomy”)
  – Beneficence (“Secure Well-Being”)
  – Justice (“Fairness in Distribution”)

• Applications of these principles include:
  – Informed consent
    • Information, Comprehension, Voluntariness
  – Risk/Benefit assessment
  – Selection of subjects

Challenges in ECR

• Patients are often **incapacitated**
• A legally authorized representative (LAR) may not be available within the therapeutic window
• How do we achieve “respect for persons” when informed consent is not feasible?
The Final Rule

- **Federal Regulations**
  - 21 CFR 50.24 (FDA) – Exception from Informed Consent (EFIC)
  - 45 CFR 46 (DHHS, “Common Rule”) – Waiver of Informed Consent (WIC)
- Collectively known as “The Final Rule”
Institutional Review Board (IRB)

• Local institutional body that approves the conduct of research
  – Focused primarily on representing the **rights** of participants
  – Balances the rights of participants against the **need for research** that includes them

• Membership includes researchers, community representatives
Institutional Review Board (IRB)

• Under the “Common Rule” (45 CFR 46), IRBs may approve an informed consent process that:
  – Waives the requirement to **obtain** informed consent; or,
  – **Alters** some or all of the elements of informed consent; or,
  – Waives the requirement to **document** informed consent (i.e., to obtain a signature)
EFIC Requirements

• The research involves no more than minimal risk to subjects;

• The research could not be carried out practicably without the waiver or alteration;

• The waiver or alteration will not adversely affect the rights and welfare of the subjects; and,

• Where appropriate, subjects will be provided with additional information about their participation.
Indications for EFIC

- Life-threatening condition
- Available treatments are *unproven* or *unsatisfactory*
- Research is needed to determine the safety and effectiveness of interventions
- Informed consent is not feasible within the therapeutic window
- Research carries the prospect of direct benefit to subjects
Additional Human Subject Protections

• Community Consultation
• Public Disclosure before / after the trial
• Independent Data Monitoring Committee
• Process to contact and obtain informed consent from Legally Authorized Representative (LAR), as feasible
• Establish Opportunity to Object to Procedures
“There is no single acceptable way to accomplish or fulfill the community consultation requirements, nor will all studies require the same amount, type, or extent of community consultation activities.”

- **Options**
  - In-depth qualitative methods (e.g., focus groups)
  - Open public forums
  - Surveys / interviews
  - IRB enhanced / initiated activities
Who/What Is “The Community”? 

• FDA Guidance: “population in which investigation will be conducted, and from which subjects will be drawn”
  – Geographic area where hospital or study site is located
  – Group of patients who share particular characteristics (e.g. patients with disease of interest)
    • Consultation is NOT recruitment of subjects
    • Consultation is NOT consent
  – Different in emergency medicine
    • Patients may not choose when or where they go
    • Communities overlap
Features of Community Consultation

• Provide opportunities for broad community **discussion**
• Ensure that community involved in the research **participates** in the consultation process
• Present information so that community **understands** the proposed research including risks, benefits, etc.
• Ensure that relevant communities **have input** into IRB’s decision-making process before the research study is initiated
Presenting Information to Communities

• Progression from general to specific:
  – Clinical research design / concepts
  – Exception From Informed Consent (EFIC) research
  – Trial-specific information

• Ideally:
  – Knowledge of the trial and the challenges of emergency research leads to a general acceptance of the value of research
  – Community members are generally supportive of the research and come to the conclusion that the only way to conduct these trials is under EFIC
Community Consultation

• Problems & Pitfalls:
  – How much consultation is enough?
  – Budgets & investigator time are limited
  – Planned events may be canceled or rescheduled
  – Difficult to be “noticed” in large volume of “stuff” on the web, in the media
Public Disclosure

• **Before** the study begins
  – To “provide sufficient information to allow a reasonable assumption that the broader community is aware of the plans for the investigation, its risks and expected benefits [...], and the fact that the study will be conducted without obtaining informed consent from most study subjects.”
  – If applicable, an opt-out mechanism should also be discussed
  – May include targeted mailings, advertisements, or community meetings

• **After** the study ends
  – “Ensure that the communities, the public, and scientific researchers are aware of the study’s results”
  – May include journal articles, news articles, and community meetings
Consent/Assent for Enrollment

• Before enrollment:
  – “The investigator must obtain informed consent from the LAR within the therapeutic window, if feasible” or else, if feasible, provide the LAR an opportunity to object to participation in the research.

• After enrollment:
  – “Consent is not required for continued participation in the study,” but “the IRB may nevertheless decide that developing an informed consent form to be used for continuation in the study would be appropriate.”
Consent/Assent for Enrollment

• Regulations require that the LAR / subject “be provided [with information about enrollment] at the earliest feasible opportunity” while understanding there exists a “balance between prompt notice and consideration for the LAR or family member’s emotional state”

• Notification of enrollment is required even if subject expires

• Subject /LAR may always withdraw their enrollment

Glitch Detection

- Researchers view protocols scientifically and pragmatically, but try to consider other points of view:
  - ProTECT III study drug is progesterone, a neurosteroid that is generally known as a female sex hormone – a potential concern for males
  - ProTECT III study drug is dissolved in ethanol - a potential concern for Muslims and others who practice the abstinence of alcohol consumption

- But there may be ethical considerations or concerns that the investigators have not yet considered
EFIC Case Studies
Early EFIC Studies

- Diaspirin Cross-linked Hemoglobin Study
- Multicenter Vest Cardiopulmonary Resuscitation Study
- Feasibility of a Proposed Method of Performing Community Consultation (RCT of phenytoin vs. placebo for posttraumatic seizures in children with head injury)
- The Prehospital Treatment of Status Epilepticus Trial (PHTSE)
- Public Access Defibrillation (PAD) Trial
- Views on Informed Consent in Emergency Situations (VOICES) Study
- Brain Cooling after In-hospital Pediatric Cardiac Arrest
- Effectiveness of an Innovative Emergency Department Procedure for the Initial Management of Brain Trauma Compared with Standard Procedure
- L-Arginine Trial
- The PolyHeme Trial
Controversial clinical trial in which hundreds of people were unknowingly injected with an experimental blood substitute.

- Primarily took place in cities with a disproportionate number of minority citizens.
- 13/20 cities had higher minority populations than the national average.
- Minority subjects accounted for 15/16 people enrolled in one Detroit hospital.
- Minority community felt they were treated like ‘guinea pigs’.
PolyHeme

• Use of a blood substitute in the resuscitation of trauma patients with hemorrhagic shock

• Community Consultation:
  – Community Council:
    • Key members of the high-volume trauma communities, identified by community relations staff.
    • Attended by research team (presenters), IRB member, hospital public relations coordinator, community relations coordinator, and 12 council members.
  – Public meetings – 83 attendees
  – Talk radio program on local station – 5 callers
  – 24-hour hotline set up to facilitate feedback – 16 callers

• Public disclosure
  – Flyers, in-house publications, newspapers, radio PSAs
PolyHeme

- Community Consultation consisted of 4 poorly-attended information sessions: 1 at a Rotary club, 2 at a shopping mall, 1 at a baseball game

- Inadequate Community Consultation
  - A private citizen expressed concerns regarding the adequacy of consultation to the county commissioners, who subsequently approved the study and appeared not to address community concerns
  - Requests to perform community consultation at two African-American churches were declined. An important minority population did not weigh into the protocol, despite the fact that the population served by the study site includes many African-Americans who would be potential study subjects
PolyHeme - Community Consultation

• Feedback:
  – General acknowledgment of the need for study
  – General skepticism about risks, motives, and potential profit
  – African American community very sensitive to the issue of “shouldering a large proportion of the research burden”

• This concern was highlighted by concurrent media coverage of President Clinton’s apology to the victims of the 1932 Public Health Service (PHS) syphilis study
Randomization continued up to 12 hours after study entry, even after the patient was admitted to the hospital, when blood would be available.

- Some ethicists suggested that trial could be designed to seek consent once out-of-hospital phase using EFIC was completed.

Inconsistency of IRB Review

- Some IRBs found serious concerns and disapproved it, while others approved the same protocols with no recognition or, at the least, little discussion on the problematic areas.

Investigators were not informed of adverse events reported by other sites.
Emergency care research networks are paving the way for investigator-initiated EFIC trials
Recent EFIC Trials

- PECARN
  - Pediatric Seizure Study
- NETT
  - RAMPART
  - ProTECT
- Out-of-Network Trials
  - Outpatient CPAP trial (Vancouver)
  - Vasopressin rescue for in-pediatric intensive care unit cardiopulmonary arrest refractory to initial epinephrine dosing: a prospective feasibility pilot trial (CHOP, Philadelphia)
  - AVERT Shock: Arginine Vasopressin During the Early Resuscitation of Traumatic Shock (UPenn, Philadelphia)
PECARN Seizure Study

Efficacy and Safety Study Comparing Lorazepam and Diazepam for Children in the Emergency Department With Seizures

- First federally-funded multi-institutional research network in pediatric emergency medicine
- 6 nodes, 18 ED affiliates
- Data Coordinating Center (University of Utah)
- Academic, community, urban, rural, general, and children's hospitals
- Network serves approximately 800,000 acutely ill and injured children/year
PECARN Seizure Study

• Two-part study funded by NICHD
• Lorazepam identified as highest priority drug for study to obtain FDA label
• Study 1: Pharmacokinetics
  – 11 sites; 65 subjects; dose established at 0.1 mg/kg
  – Significant consent and enrollment barriers identified
• Study 2: Randomized controlled trial of lorazepam vs. diazepam for pediatric status epilepticus
  – Efficacy and safety study
PECARN - Regulatory History

- Negotiation with FDA/NICHD on consent issues
- 18 months pre-trial activity seeking EFIC
  - Included national panel on “Emergency Research in Children: Ethical, Regulatory, and Clinical Challenges”
- IND approved July 2007 using 21 CFR 50.24 regulations
- Community consultation and public disclosure required as additional human subject protections
  - Activities at all (12) study sites
  - Drop out of one site due to administrative denial of trial
- Full IRB-approval at all 12 sites
- Patient enrollment: January 2008 – March 2012 = 310 pts enrolled
Community Consultation

• How did we define our “community”?  
  – Catchment area surrounding the hospital study sites  
    • Challenge: Academic centers and regional hospitals typically serve a large geographic area due to the specialty nature of their services  
  – Individuals with particular social / medical characteristics  
    • Search of patients from emergency department administrative data (e.g. Repeat visits to the ED for seizures, list of neurology patients diagnosed with epilepsy and regularly followed at the hospital)

• Methodology  
  – Focus Groups  
  – Surveys
PECARN - Focus Groups

- 69 parents and patients recruited from ED, neurology clinic and inpatient floors; 22 (31%) participated
- Trained facilitator participated in development of a topic guide
- IRB liaison present at 3/4 focus groups
- Study representative available to answer technical questions
- Linked to an opt-out registry or possible prospective consent
  - 2 parents (9%) completed opt-out forms for clinical reasons
- Discussion recorded and transcribed
- Participants generally in favor of research being performed without consent
- Concerns about side effects, community awareness and opt-out diminished after further discussion
- 91% parents expressed willingness to enroll their child in study
PECARN - Surveys

• Adults accompanying a child in ED or neurology clinic: 170 surveys completed
• No requirement for complaint related to seizure in ED
  – Aimed to capture population where the clinical investigation will be conducted, and from which the subjects will be drawn
  – Cost-effective way to capture group that may represent first-time seizure patients
• Process linked to opt-out or possible prospective consent: 17 participants (10%) completed opt-out forms
• Common concerns: Side effects, consent process, Lorazepam not FDA-approved for children
• High agreement that medical research and “experiments” in emergency care are important, but expressed concerns about enrolling without consent: only 65% felt that emergency research without consent was acceptable within their community
Important Lessons Learned

• Not a random process and it took a lot of thought and time
• Learned that IRB was not more educated about the regulations than the study team
  – Corrected misconceptions about the regulations
• Did not take a “one-size-fits-all” approach
  – IRBs, investigators AND communities are characterized by local customs and practices
• Need for flexibility to make sure that materials got the right message across
  – Piloted material and be willing to make changes based on community input ("glitch detection")
### Feasibility of “Pre-consent”

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<th>Pre-consent</th>
<th>Standard IC</th>
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<td><strong>1330</strong></td>
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<tr>
<td><strong>10</strong></td>
<td><strong>37</strong></td>
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- **Screened**
- **Eligible**
- **Approached**
- **Consented**
- **Enrolled**
# Cost Effectiveness of “Pre-Consent”

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<th>Pre-C</th>
<th>Standard IC</th>
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</thead>
<tbody>
<tr>
<td>Hours Screening</td>
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<td>303</td>
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<tr>
<td>Hours spent approaching patients for consent</td>
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<td>46</td>
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<tr>
<td>Hours spent obtaining informed consent</td>
<td>51</td>
<td>19</td>
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<tr>
<td>Cost per patient enrolled</td>
<td>$1,271</td>
<td>$186</td>
</tr>
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Would save $1,085/pt using standard IC
Conclusions

• EFIC is an essential methodology for emergency care research

• Allows us to study subjects that could not be otherwise studied in prospective trials

• Beware of pitfalls!

• EFIC is do-able, but requires:
  – Patience
  – Persistence
  – Positive attitude