

Exception from Informed Consent in Pediatric Trials

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Naynesh R. Kamani, MD

James Chamberlain, MD

Jill M. Baren, MD, MBE, FACEP, FAAP

Moderator: Susan McHenry, EMS Specialist

Exception from Informed Consent - An IRB perspective

Naynesh R. Kamani, MD

Professor of Pediatrics, Professor of Microbiology, Immunology and
Tropical Medicine

Chair, Institutional Review Board,
Children's National Medical Center,
Washington, D.C.

Protocol # 3969 : Use of Lorazepam for the Treatment of Pediatric Status Epilepticus: A Randomized Double-Blinded Trial of Lorazepam and Diazepam

- This was the **first clinical trial** being conducted **in children** with Exception From Informed Consent (EFIC) in an emergency research setting using the 21 CFR 50.24 FDA regulations
- Allow an EFIC from subject or LAR for studies involving:
 - A requirement for an IND/IDE
 - Human subjects with life-threatening medical conditions with unproven/unsatisfactory treatments
 - Subjects who cannot give consent
 - Intervention must be given prior to IC being feasible

EFIC Studies

- Additional requirements in order to protect this maximally vulnerable population that lacks autonomy but has unmet medical needs and needs to benefit from new therapies
 - Community consultation with representatives of community(ies) in which research will take place and subjects are drawn from
 - Public disclosure of information before start of study and at completion
 - Commitment by PI to make efforts to contact family member
 - Establishment of an independent DMC

IRB Responsibilities When Approving EFIC Studies

- Life threatening condition, unproven/ unsatisfactory treatments for condition, and collection of valid scientific evidence necessary
- Obtaining IC not feasible: due to nature of medical condition, time constraint and no way to prospectively identify participants
- Prospect of direct benefit demonstrable
- Study not practicable without waiver of IC
- Research plan define length of potential therapeutic window and investigator commits to attempts to contact LAR
- IRB reviews and approves ICD's (used when advance IC feasible and allows participants to opt out of study)
- Additional protections of rights/welfare of research subjects: community consultation, public disclosure before study and after study completion, establishment of independent DMC, attempts to contact family member (not LAR) to determine participation

Challenges for the IRB

- First EFIC study in children; IRB staff/membership had no prior experience with review and approval of EFIC studies
- Additional training was needed for IRB membership to enable them to review additional procedures needed to give approval
- Need for IRB member participation in meetings with community members
- Definition of community consultation and public disclosure phases is a challenge

Community Consultation

- Defined as Consultation by PI and research team (and, if necessary IRB) with representatives of community in which clinical investigation is conducted and from which subjects are drawn

IRB Review of CC/PD Component of Study

- IRB requested that PI provide IRB with draft plan for CC and PD
- Required PI to provide IRB with quarterly progress reports on progress of CC
- During review process, IRB requested that PI provide communications from other centers on their plans for CC
- Reviewed and recommended changes to slide presentation to be used for meetings with community
- Requested that PI develop an information sheet for participants and CC

IRB Review of CC Plan

- At each quarterly review:
 - Summary of all activities
 - Summary of all survey data from CC meetings
 - Letter/meeting minutes of Community Advisory Board meetings
 - Summary of any community feedback
- IRB members' role:
 - Has community been sufficiently consulted about study?
 - Does feedback necessitate revisions to CC/PD plan or protocol?

Challenges in Community Consultation

- Definition of Community is not clear in regulations
 - Is it the community at large?
 - Is it the population seen in the ED/neurology clinics?
- Process for conducting CC is not specified in regulations
 - Community advisory boards
 - Telephone/paper surveys
 - In-person meetings
 - Meetings w/community representatives/leaders

CC Efforts by PI and Research Team

- In-person meetings with parents
 - In neurology clinic;
 - In hospital emergency department
 - At parent/community meetings held at CNMC or in community settings
- Communications w/community-based organizations, churches, parent support groups
- Apprising the CAB of study and CC progress
- Challenges research team faced:
 - Overall poor attendance at meetings
 - Lack of participation by non-affected community members
 - 1/17 non-epilepsy community parent support groups, 0/17 church groups and 0/8 other groups responded following contact;

Public Disclosure

- Brochures/posters/flyers in ED & Neurology clinics
- Information regarding the seizure study included in Children's annual Check-up flyer that goes home with ~65K DC school children
- Ads placed in Washington Parent, Washington Informer and The City Paper
- National Website for parents/physicians
- 24 hour hotline
- Print media provided with website info

Public Disclosure

- Statement that IC will not be obtained from most patients
- Information about test articles/risks and benefits
- Synopsis of research protocol/study design
- How will potential subjects be identified?
- Participating sites/institutions
- Descriptions of attempts to contact LAR
- Suggestions for how to “opt out” of study

Community Consultation

- How much CC is sufficient prior to IRB approval for trial to move forward?
- IRB approval granted after:
 - Detailed review of summary report on all activities conducted as part of CC/PD
 - Determination that research team had conducted a good faith effort/due diligence to consult with the community

Timeline for IRB Approval

- Initial submission to IRB: 12/1/2006
- Protocol discussed at IRB meeting: 1/4/2007
- Approval given to start community consultation piece:
3/1/2007 Quarterly review of CC activities
- Approval given to start public disclosure: 12/20/2007
- Final approval given to start subject enrollment:
5/1/2008
- Enrollment of 1st patient: 9/15/2008

Use Of Lorazepam For The Treatment Of Pediatric Status Epilepticus: A Randomized Double Blinded Trial Of Lorazepam And Diazepam

Meeting the Requirements for the Exception from Informed Consent

James Chamberlain, MD
PI, Pediatric Seizure Study

Learning Objectives:

- Understand the lorazepam trial
- Understand the justification for using EFIC
- Understand where institutions and IRBs might have difficulty with EFIC

Overview of the Lorazepam Trial

- Randomized, double blind trial comparing IV lorazepam to IV diazepam.
- Eligible patients are those that present to the Emergency Department (ED) with SE.
- Drug administration within 5 minutes of ED arrival.
- Efficacy and safety data collected over 48 hours.
- Adverse event tracking for 30 days.

Requirements for EFIC

- Life threatening condition
- Informed consent not feasible within the therapeutic window
- Available treatments *unproven* or *unsatisfactory*

Life Threatening Condition

- Etiology of SE:
 - known patients with epilepsy (32% to 47%);
 - acute neurological conditions such as meningitis, trauma, tumors, stroke or encephalitis (23% to 44%);
 - atypical febrile seizures (14% to 24%). *
- Approximate mortality from SE is 4%* and depends on the etiology
- Etiology unknown when patient arrives to ED

* *Maytal J, Shinnar S, Moshe SL, Alvarez LA. Low Morbidity and Mortality of Status Epilepticus in Children. Pediatrics 1989; 83:323-331*

Life Threatening Condition

- Resultant morbidity from adverse neurologic sequelae (epilepsy, motor deficits, learning difficulties and behavior problems) is age-dependent;
 - ~29% in those who experience SE in infancy
 - ~6% in those who experience SE at an age over 3 years.
 - Increasing recognition of
- There is also increasing scientific recognition of
 - Kindling and need to stop convulsions emergently
 - early damage to brain if convulsions are not stopped

Informed Consent Not Possible Within Therapeutic Window

- Termination of seizure activity with pharmacologic treatment may result in immediate benefit through improved maintenance of vital functions and long term benefit through a decrease in neurologic sequelae.
- Experts agree that the initiation of treatment should be early to avoid the potential for neuronal damage secondary to prolonged seizure activity

Manno, EM. New Management Strategies in the Treatment of Status Epilepticus. Mayo Clinic Proceedings. Vol 78. 2003. p508-518.

Informed Consent Within Therapeutic Window

- Therapeutic window typically defined within 5 minutes to maintain vital functions and avoid neurologic sequelae

Fleisher, Ludwig et al. Textbook of Pediatric Emergency Medicine. Chapter 83: Neurological Emergencies. 5th Edition. 2006. p.763

Current Treatment Unsatisfactory

What is unsatisfactory?

Current Treatment Unsatisfactory

- Benzodiazepines considered most effective agents for initial treatment of SE, achieving lasting control in 80% of patients
- However, respiratory depression is a common and serious side effect of benzodiazepines.

De Negri M, Baglietto MG. Treatment of Status Epilepticus in Children. Pediatric Drugs 2001;3(6):411-420.

Treiman DM. The role of benzodiazepines in the management of status epilepticus. Neurology 1990; 40(5 Suppl 2):32-42.

Current Treatment Unsatisfactory

- Potential advantages of lorazepam over diazepam
 - Increased duration of action,
 - Increased effectiveness in terminating SE,
 - Lower incidence of respiratory depression

Current Treatment Unsatisfactory

- Potential disadvantages of lorazepam over diazepam
 - Not FDA approved for children for SE treatment
 - Limited data available on safety and efficacy in children
 - Study 1 is the first attempt to collect pharmacokinetic data for Lorazepam use in pediatric SE.
 - Needs to be refrigerated
 - a concern for prehospital providers

Current Treatment Unsatisfactory

- Currently most textbooks and guides recommend both drugs for use in SE.
- There are no large studies for EITHER drug.
 - Studies too small to achieve statistical significance
- Limited data shows trend toward lorazepam superiority in efficacy and safety
- Lorazepam may have some pharmacological advantages
- Individual physician choice dictates use of lorazepam versus diazepam.

Community Consultation: FDA Guidance

- Definition of Community
 - “community in which research will take place”
 - Geographic area where hospital or study site is located
 - “community from which subjects will be drawn”
 - Group of patients who share a particular characteristics (i.e. patients with the disease of interest)

Opportunity to Object: Pre-enrollment

- A toll free phone number will be provided during community consultation and public disclosure activities
- Continuous website availability
- When approached in neurology clinic
- Wrist bands will be given to participants who object (refuse).
- There will also be a list of object (refused) patients in the ED.

Specific Institutional Concerns

- Public relations
- EFIC and children
- Community “consent”
- Delays in therapy because of study procedures

Exception from Informed Consent in the Pediatric Seizure Study: Pearls from the Planning Process

Jill M. Baren, MD, MBE, FACEP, FAAP
Professor of Emergency Medicine and Pediatrics
University of Pennsylvania School of Medicine
Human Subjects PI, Pediatric Seizure Study

Recognition of Possible Need to Conduct Trial Without Consent

- Significant logistical barriers identified during preliminary study
 - Patient recruitment outside the ED
 - Slow enrollment (multiple study extensions)
 - Protocol violations
- Federal regulations for research without consent exist and could be applicable
- Pediatric seizure study group investigators provided collective expertise that study was not feasible with prospective informed consent

Plan - Application of 21 CFR 50.24

- FDA regulated trial
- All criteria must be satisfied and accepted by
 - FDA as part of IND application
 - Local IRBs of participating sites
- Sponsor must inform other investigators at all sites and the FDA if protocol was not approved by any single site

Conditions

- Subjects are in a *life threatening condition*, available treatments *unproven* or *unsatisfactory*, collection of valid scientific evidence is necessary to determine safety and effectiveness of intervention
- *Informed consent not feasible* within the therapeutic window
- Participation holds *prospect of direct benefit*
- Study *cannot be practicably carried out* without the waiver
- Appropriate *attempts to contact LAR or family member* are made within the therapeutic window
- IRB has *reviewed and approved* the consent procedures

Additional Protections

- Community Consultation
- Public Disclosure before the trial
 - Establish opportunity to object procedures
 - (opt-out or refusal)
- Public Disclosure after the trial
- Independent Data Monitoring Committee
- Process to contact and obtain informed consent from Legally Authorized Representative

Process

- Discussion with ethicists and experts in pediatric clinical research
- Initiated IRB dialogue early in planning stage
- Prepared IRB resource binder
- Developed a centralized detailed operational plan for the additional human subjects protections required
 - Developed materials and tested content of messages
 - Developed a menu of community consultation methods
 - Developed a menu of public disclosure methods
 - Developed an opt-out plan presented during CC/PD events
 - Developed plan for contact of LAR during enrollment

Defining Community for the CC/PD Process

- Described the catchment area surrounding the hospitals where the study was being conducted
- Considered factors such as social influences, regional health services, and health profiles
- Sought assistance from public affairs and/or community relations departments in hospitals and universities

Challenge

- Academic centers and regional hospitals typically serve a large geographic area due to the specialty nature of their services
- May not be feasible to define the community solely on geography for such centers
- Instead, focused on disease-based community definitions and/or other features of a community such as cultural/ethnic/linguistic characteristics

Disease Specific Community

- Search of patients from emergency department administrative data
 - Repeat visits to the ED for seizures
- List of neurology patients diagnosed with epilepsy and regularly followed at the hospital

Community Consultation - Methods

- 4 broad categories
 - In-depth qualitative methods (Focus groups)
 - Open forums (Public meetings)
 - Surveys/Interviews (Individual)
 - IRB enhanced/initiated activities (Appointed members, liaisons)

Community Consultation

- Did not expect sites to engage in all of these activities
- Together, the sponsor (NICHD), PI, local IRB, and site investigators chose activities that are most feasible, cost-effective, and which in their best estimation would provide the most adequate information about the community

Public Disclosure - Methods

- **Public media**
 - Newspaper, television, radio (including foreign language)
- **In-hospital resources**
 - Posters, flyers, newsletters, brochures, letters to providers and patients
- **Electronic media/postal service/telephone hotlines**
 - National website geared toward lay public and medical and research personnel (linked with local websites and foundations/organizations)
 - Downloadable materials/templates
 - Link to opt-out procedures
 - 24 hour advertised hotline with recorded message

Plan: Opt-out Procedures

- **Prospective Informed consent**
 - Parents/patients with known seizure disorder approached for consent/assent in neurology clinics and other clinical areas before status epilepticus event
 - Prior experience showed that we would only reach few eligible patients this way

Opportunity to Object: Pre-Enrollment

- Toll free phone number or website link provided during community consultation and public disclosure activities
- Continuous availability
- Identification of subjects who wish to opt out:
 - Wrist bands will be given to those who object
 - Wrist bands will be given to those who provide informed consent
- List of opt-out patients in the ED
 - Linked to electronic tracking, registration, or clinical procedures

Opportunity to Object: After Enrollment

- Informed consent sought from the LAR when feasible
 - After medical and emotional stability achieved
 - After clinician has effective dialogue with LAR
- Can refuse further study procedures
- Attempts to contact LAR or family member continues throughout hospitalization
- Age appropriate assent per local IRB

Progress - IRB Communications

- All sites had early dialogue with IRB
- All IRBs showed willingness to work with investigators
- Many had scheduled educational sessions for IRB members at their site
 - Requirements of 21 CFR 50.24
 - Examples of CC/PD activities from other trials
 - FDA 2006 Draft Guidance on Exception from Informed Consent Regulations
 - IRB Resource Binder

Prior Experience With EFIC

- Several sites conducted prior trials under EFIC
 - 2 site IRBs had recommendations for investigator
 - 1 site had a pre-meeting with IRB to review plan in place for requesting review of EFIC studies
 - 1 site had recently approved 2 studies using EFIC
- Other sites had pre-established IRB policies and instructions for a potential protocol that fell under 21 CFR 50.24

IRB Plan for Review of EFIC

- IRB Liaison assigned to investigator
 - Several sites
 - Liaisons attended community consultation activities
- Special IRB subcommittee/section
 - One site which had previously refused to review studies which fell under 21 CFR 50.24
- Incorporate EFIC activities within existing community advisory boards
 - 3 sites

Challenges

- One IRB persistently viewed community consultation results as indicative of community consent for study to take place
 - Determined a “threshold level” of agreement
- Several IRBs had concerns about identification procedures for patients who wanted to “opt out”
- Investigators had differing opinions on methods of obtaining informed consent

Challenges

- Various definitions of community
 - Seizures are relatively rare in general population
 - Messages may not have been well received
- Public disclosure
 - Potential for enormous expense with little effectiveness
 - TV and radio ads could cost thousands alone
 - Not sure how to get the message to interested public

Progress

- Sites came up with a site specific plan for meeting requirements of EFIC
 - Customized CC/PD activities
- Executed stepwise IRB submission and roll-out of community consultation
 - More experienced sites first
 - Potential to share information with positive or negative implications

Study Management

- Co-PI structure at national level
 - Coordinating scientific investigator
 - Protocol development
 - Coordinating human subjects investigator
 - Develop and implement all aspects of regulatory process and human subjects protections
 - Create an overall centralized EFIC plan
 - Opportunity to carefully examine all aspects of the process
- Joint activities
 - Steering committee leadership
 - Interface with sponsor
 - Trial preparation and conduct

Lessons learned: Focus Groups

- Participants generally in favor of research being performed without consent
- Common themes:
 - Concerns about side effects
 - Community awareness of study
 - How to “opt-out”
- Concerns diminished after further discussion
- Adolescents expressed willingness to participate
 - 91% parents expressed willingness to enroll their child in study
- Several parents completed opt-out forms for clinical reasons

Focus Group Strengths and Weaknesses

- In-depth qualitative method that generated detailed and rich information
- Dedicated time to examine the attitudes of a small group of individuals
 - Selected for interested parties who were more likely to provide meaningful input
 - Potential for greater interaction among the participants
 - Generated conversation directed by the group participants
- Information obtained was of high quality and useful in IRB deliberations
 - Diversity of information was dictated by composition of groups
- Cost depended on the number conducted
 - Minimal to moderate in relation to overall study costs (~\$1000/group)

IRB Communications

- Interim reports sent to IRB chair after each focus group
- IRB liaison provided progress report during full committee meetings
- Asked to conduct one additional focus group involving parents and teens without seizure disorder
- Summaries and individual transcripts made available for IRB deliberations
- Protocol fully approved for conduct under 21 CFR 50.24 after community consultation results reviewed

Lessons Learned: Survey Methods

- Adults accompanying a child in the ED or neurology clinic
- No requirement for complaint related to seizure in ED
 - Cost-effective way to capture group that may represent first time seizure patients
- Process linked to opt-out or possible prospective consent

Survey Results

- Hundreds of surveys completed
 - 80% of participants felt study was important and would allow their child to participate
- Common themes
 - Concerns about side effects
 - Concerns about consent process
 - Concerns that Lorazepam not FDA approved for children
- High agreement that medical research and “experiments” in emergency care are important but expressed concern about enrolling without consent
 - 65% felt that emergency research without consent was acceptable within their communities

Survey Strengths and Weaknesses

- Controllable way to disseminate information
 - One on one technique allowed for greater interaction between the investigator and participant and avoided group bias
 - Time consuming and can be costly depending on personnel
- Potential for influence on the part of the survey administrator
- Information was of moderate to high quality and informed IRB deliberations

Pearls:

- Conducting a trial under EFIC is not a random process; it takes a lot of thought and time
- Don't assume that IRBs are more educated about the regulations than you are
- Do not take a “one size fits all” approach
 - IRBs, investigators AND communities are characterized by local customs and practices
- There are a huge number of misconceptions about the regulations that you must correct
- Do not assume that your materials are getting the right message across

Successful Strategies

- Develop a plan and a strategy for global administration of the human research protections aspects of the trial
 - Appoint a “human subjects czar”
 - Early appointment of DSMB to review EFIC plan
- Investigator initiated IRB guidance through the process is essential
- Investigator-IRB communication is the cornerstone of the process
- Correcting misconceptions about the regulations
 - e.g. community consultation ≠ community consent
- Pilot material and be willing to make changes based on community input

Q & A Session



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