Workforce and Resource Issues in Organizations Conducting Research involving Vulnerable Participants

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Presentation Overview

Understanding Vulnerable Populations
• Defining Vulnerable Populations
• Barriers to Participation in Research

Engaging Vulnerable Populations in Research
• Ethical Issues
• Personnel Infrastructure and Management
  – Recruitment and Retention
• Organizational Resources and Effectiveness

Examples and Application

Vulnerable Populations

Acc to NIH, RWJ, CDC, etc.
• Children and minors
• Fetuses and neonates
• Pregnant women
• Cognitively impaired persons
• Prisoners
• Homeless
• Uninsured
• Chronically and terminally ill patients
• Elderly and aged patients
• Victims of natural disaster
• Underrepresented minorities
• Other ethnic, cultural, economic, geographic considerations
Defining Vulnerability

Vulnerable Populations Have...

- Lesser Resource Availability
- Greater Relative Risk
- Lower Likelihood of Health-Seeking Behavior

Vulnerability, Vulnerable Populations and Policy (Mary C. Rouf)
National Center for Bioethics Literature
The Joseph and Rose Kennedy Institute of Ethics
Georgetown University

Barriers to Participation of Vulnerable Populations

- Lack of Awareness of Available Research and Community Programs
- Time Demands and Scheduling Conflicts
- Participations Concerns
- Demographic Characteristics

Barriers – Not realizing that they need the service
– Not knowing that the service exists
– Not knowing how to obtain the service
– Not knowing where to obtain the service
– Not knowing how to access affordable services
– Other barriers including how to access transportation, childcare, financial assistance, financial impact (out of pocket costs) information, especially for low-income families.

• Implicit is also a lack of awareness in service providers and researchers

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Barriers to Participation of Vulnerable Populations

Time Demands and Scheduling Conflicts

**Barriers**
- Families across all demographics are busy
- Conflicts with weeknight meeting times
- Conflicts especially difficult for
  - single parents families
  - families working evening shifts or two jobs
  - those with other less traditional caregiver arrangements.
- Long-term planning is difficult for many vulnerable populations

Participations Concerns

**Barriers**
- Lack Interest
- Not sure how their participation or the project will help
- Desire to maintain privacy
- Lack of trust and perceived lack of commitment by researchers
- Previous negative experiences

Demographic and Project Characteristics

**Barriers**
- Inclusion and exclusion criteria too stringent
- Language in recruitment materials create selection bias
- Lack of innovation in research to ensure inclusion
- No considerations for challenges inherent in vulnerable populations
Engaging Vulnerable Populations in Research

- Lesser Resource Availability
  Barriers/Disparities
  - Income
  - Employment
  - Insurance
  - Transportation
  - Childcare
  - Social Networks
  - Technology
  - Etc.

- Greater Relative Risk
  - Health Risks and morbidities depending on condition
  - Etc.

- Lower Likelihood of Health-Seeking Behavior
  - Especially preventative care
  - Related to lack of awareness, access and resources

Ethics in Engaging Vulnerable Populations in Research

Policies and Guidelines
US Regulations and Guidelines
The Common Rule US 45 CFR 46
FDA Regulations US 21 CFR 50 and 56
NIH Policies and Guidelines
CIOMS/WHO International Guidelines
Belmont Report
Ethics in Engaging Vulnerable Populations in Research

*Belmont Report, 1979*

- Respect for Persons/Others
- Beneficence
- Justice

Ethics in Engaging Vulnerable Populations in Research

*Seven principles of an ethical framework*

- Valuable scientific question
- Valuable scientific methodology
- Fair participant methodology
- Fair risk-benefit analysis
- Independent review
- Informed consent
- Respect for enrolled participants


Personal Infrastructure and Management

*Key Components for Training and Management*

- Ensuring Ethics/Sensitivity
- Ensuring Recruitment/Retention
- Planning for Turnover/Continuity
- Maintaining Balance Across Projects
Ensuring Sensitivity and Ethics

**Traditional Approaches**
- Disregard for Input, Engagement
- Disregard for Diversity
- Top Down Approach
- No to Minimal Ethics Training
- No Return of the Results to Target Group/Community
- Narrowly limiting "Expertise" to the Research Team

**Best Practices Approaches**
- Design with Inclusion and Community Engagement
- Diversity a Priority
- Collaborative Approach
- Integrated Ethics Orientation
- Return of the Results to Target Group/Community
- Including member(s) of the target population on the Research Team or Forming an Advisory Board

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Ensuring Recruitment and Retention

**Traditional Approaches**
- One Size Fits All
- Mass Communications
- Corporate/Marketing Approaches
- Text-Heavy
- Research-Centered
- Barriers not Considered
- Vague Timeline and Plan for Retention

**Best Practices Approaches**
- Use Multi-Modal Strategies
- Customize Communications
- Strategies based on data for the target audience
- Simple text; Graphic
- Participant-Centered Barriers Considered
- Clear Timeline and Plan for Retention

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Community Partner Council

- Subcommittees
  - Research
  - Training
  - Health Partnerships

* Bioethics Advisory Board also includes 11 community members

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### Recruitment Strategies

**Most Used**
- Word of Mouth
- Govt/Community Agency Referral
- Flyers/posters in Community
- Community Events
- Information Sharing

**Most Effective**
- Word of mouth
- Elders in the community
- Door to door
- Calling lists/client lists
- Community events

*Honoraria rated by recruiters 4/5 vs. 2/5*

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### Other Suggestions for Successfully Recruiting Vulnerable Populations

- Making participation in research convenient and enjoyable
- Ensure that participants understand and experience the benefits of research
- Build trusting relationships with collaborators and target community
- Offer proper incentives given the demands of the study
- Incentives: flexible hours, benefit others, convenient location, honorarium, meals or snacks, study results, interpreter/multi-lingual materials, meet other families, child care, community referrals, follow up services

### Retention Strategies

**Most Used**
- Recognition
- Snacks/Meal
- Diversity of Staff
- Transportation
- Reminder Phone calls/email
- Convenient location

**Most Effective**
- Convenient location
- Snacks of meals
- Child care
- Reminder call/email
- Transportation or bus tickets

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Other Suggestions for Successfully Retaining Vulnerable Populations

- Create face to face and point of contact opportunities to re-engage the population.
- Using multiple communication strategies (text messaging, web-site locators, multiple phone numbers and addresses).
- Birthday cards, newsletters, etc.
- Consider family-based strategies.

Study Examples: Ensuring Sensitivity, Recruitment and Retention in Research

Strong Study: Multi-Phase Sickle Cell Growth and Nutrition Study

Planning
Communication
Respect for Others

The STRONG Program
Planning and Implementation

Why would families say YES?
- The benefits/incentives outweigh the risks/inconveniences
- Trust the Recruiter and/or Principal Investigator
- They understand the study and feel as though they are giving informed consent
- They think that they can do the study without feeling intimidated
- They are interested in the research question being studied
- They feel as though their participation is important and valuable
- They feel as though their participation and sacrifice will result in some short-term or long-term “good”
- They need the money
Why would families say NO?

- The risks/inconveniences outweigh the benefits/incentives
- Previous bad experiences with research
- They feel as though they do not understand the study or that the “wool is being pulled over their eyes”
- They think that they cannot do the study without feeling intimidated
- They are not interested in the research question being studied
- They are very sensitized to the issue being studied
- They feel as though they do not have anything to add to the study or that nothing meaningful will be done with the information

The STRONG Program: Planning and Implementation

Strategies for overcoming trust/ skepticism barriers:

- Provide detailed information about the STRONG Program (written and verbal).
- Walk families through the informed consent process/ consent form.
- Give hesitant families time to make a decision.
- Respect families’ decision not to participate.
- Create continuity through communication

Strategies for ensuring that participants are not overwhelmed or intimidated:

- Walk them through the procedures during the informed consent and initial visit.
- Give a number/email that they contact call if they have any problems or questions.
- Provide reassurance and support (follow-up phone call).
- Give people permission to get overwhelmed and confused (e.g. tell them the questionnaires can be tricky so if you want to go through them together, word for word, we can do this).
- Allow for a reasonable time window to get valid assessment data
The STRONG Program: Planning and Implementation

Strategies for overcoming a lack of interest:
- Create interest even where there is none through data and education about the problem (nutrition and growth).
- Refer to data (qualitative or quantitative) that this is an important topic and that funding was given to study this issue.
- Validate the fact that there may be a range of experiences (poor growth or normal growth is ok) which is why their participation is needed.

Strategies for Ensuring that they feel as though their participation is important and valuable
- Emphasize the personal aspects of the study (e.g. The first thing we want to do is to talk with everyone in your family about what it is like to be the parent, brother, sister of someone with SCD)
- Emphasize the PI’s goal of getting it right vs. getting it done
- Addressing barriers such as giving out a meal ticket for all day visits and providing a transportation voucher gives the effect of “Rolling out the Red Carpet”
- Ensure closure: Follow-up throughout their participation and send a final “Thank You” or Certificate of Participation

Strategy for ensuring that participants feel as though their participation and sacrifice will result in some short-term or long-term “good”
- Articulate the long-term goal of the study (e.g. to design an intervention addressing these issues) and a personal commitment to see this through.

Strategies for articulating that the money is for reimbursement rather than a handout
- Inform them that they money is payment for their time and inconvenience. Let them know that payments are made in cash, upon completion of each phase of the study.
The STRONG Program: The Communication Plan

Building Strong Relationships with Clinic Staff

- Designing Culturally Relevant and Engaging Recruitment Materials
- Using 2 Versions of the Flyer: Brief and Detailed
- Emphasizing Flexibility and Convenience of the Study (weekend times for DEXA scans)
- Using a Consent Form that Clearly Details Components and Dates of the Study and Associated Honoraria

The STRONG Program: The Communication Plan

- Using Easily Identifiable Folders and Binders
- Giving out Refrigerator Magnets and Business Cards
- Distributing Additional Cards and Flyers to families who may refer another family (word of mouth)
- Keeping Families and Collaborators Updated on Study Progress and Findings
- Maintaining Contact and Providing Support Throughout the Study

The STRONG Program: Respect for People

Underlying assumption that we need participants more than they need us; that we need clinic support more than they need ours; that I need recruiters more than they need me.

- Intrinsic sensitivity to cultural differences and participant challenges.
- Sincere interest and passion for the research that we are conducting.
- Catch All: The Golden Rule.

Design of the study creates opportunities for mutual respect.

Underlying assumption that we need participants more than they need us; that we need clinic support more than they need ours; that I need recruiters more than they need me.
### The STRONG Program: Study Timeline

<table>
<thead>
<tr>
<th>Day</th>
<th>Activity Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Send or Distribute Flyer/ Phone Call</td>
</tr>
<tr>
<td>0</td>
<td>Send Introductory Letter</td>
</tr>
<tr>
<td>1</td>
<td>Initial Phone Call/ Verbal Consent</td>
</tr>
<tr>
<td>3</td>
<td>Send Confirmation for HV 1, Copy of STRONG Study Information/Consent Form</td>
</tr>
<tr>
<td>7</td>
<td>Written Consent/ HV 1- Family Interview</td>
</tr>
<tr>
<td>10</td>
<td>Starting of Diet Diaries/ Questionnaires</td>
</tr>
<tr>
<td>14</td>
<td>Check-In/Support Phone Call</td>
</tr>
<tr>
<td>17</td>
<td>Send Confirmation for HV 2</td>
</tr>
<tr>
<td>21</td>
<td>HV 2 - Review Questionnaire Data and Diet Diaries</td>
</tr>
<tr>
<td>21</td>
<td>Send Confirmation for GCRC Visit + Map</td>
</tr>
<tr>
<td>24-28</td>
<td>GCRC Visit</td>
</tr>
<tr>
<td>30</td>
<td>Send Final Thank You Note</td>
</tr>
</tbody>
</table>

### Ensuring Staff Continuity and Stability

**Create continuity…**

- In the data
- In the details
- In the records/files
- In the communication
- In the relationships
- Through training
- Through trust

### Balancing Personnel Across Multiple Projects

- Defining Priorities Across Projects
- Identifying and Securing Needed Expertise
- Clarifying and Aligning Short-term and Long-term Goals for the PI, Project, and Personnel
- Aligning Personnel Management and Effort with Budgets and Timelines
- Monitoring Timelines, Progress and Goals
Other Projects to Ensure Sensitivity and Recruitment/Retention

- Focus Groups
  - Biobanking
  - Community Child Well-Being
  - Asthma
  - Gene Therapy
  - Stroke
  - Obesity/Nutrition
- Recruitment and Retention for CF, Diabetes, Headache, Obesity
- Research and Education Day

Organizational Effectiveness

- Identify Organizational Priorities, Challenges and Goals
- Identify Root Causes and High Impact Solutions
- Determine Investments and Resources to Address Major Challenges and Ensure Effectiveness

Organizational Effectiveness

**Challenge:**
- Mistrust of Research
- Recruitment and Retention
- Research Collaboration
- Cultural Sensitivity
- Patient and Community
  - Lack of Awareness
- Poor Clinic Attendance

**Goal:**
- Improve clinical effectiveness and research participation through increased awareness and education among patients and families
- Ensure patient and cultural sensitivity and engagement among clinical staff and basic and clinical researchers
Organizational Effectiveness

**Strategy/Action**

- In addition to ongoing meetings, retreats and other efforts to discuss the issues and improve clinical strategies.
- Created a Research and Education Day in 2002 to better engage and educate children and families on various aspects of sickle cell disease care and research.

**SCD Research and Education Day 2011**

In 2011, Cincinnati Children’s Hospital hosted 10th Annual Sickle Cell Research and Education Day.

- Engaged over 80 families in Education, Awareness and Advocacy.
- Youth and families also learned about and participate in research as part of the event.
- Event has been replicated in other pediatric hospitals.
Engaging Youth in Research and Education

SCD Research and Education Day 2011
Engaging Personnel and Volunteers

Community corporations serve as volunteers and provide educational services.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Summary of Event Statistics 2003-2009 (Column 1-6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Event Participation Statistics</td>
<td>Year 1</td>
</tr>
<tr>
<td>Persons with SCD Attending</td>
<td>8</td>
</tr>
<tr>
<td>Number Families Attending</td>
<td>8</td>
</tr>
<tr>
<td>Total Number SCD + Families</td>
<td>14</td>
</tr>
<tr>
<td>Total Number in Attendance</td>
<td>16</td>
</tr>
<tr>
<td>Number of New Volunteers (including Fianles)</td>
<td>-</td>
</tr>
<tr>
<td>Percent Families Contacted (or Attendance)</td>
<td>-</td>
</tr>
<tr>
<td>Number of Workshops Attended (1)</td>
<td>7</td>
</tr>
<tr>
<td>Youth Attending Symposium</td>
<td>-</td>
</tr>
<tr>
<td>Number of Child Programs</td>
<td>8</td>
</tr>
<tr>
<td>Staff/Community Volunteers</td>
<td>3</td>
</tr>
</tbody>
</table>

Note: Not all statistics were available for all years as tracking became more detailed in later years (missing data is marked with a -).

### What do you enjoy about Research and Education Day?

<table>
<thead>
<tr>
<th>Activity</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Food/meal</td>
<td>69.0%</td>
</tr>
<tr>
<td>Meeting other families/kids</td>
<td>76.1%</td>
</tr>
<tr>
<td>Education</td>
<td>80.3%</td>
</tr>
<tr>
<td>Participating in research</td>
<td>66.2%</td>
</tr>
<tr>
<td>Mini-presentations</td>
<td>53.5%</td>
</tr>
<tr>
<td>Childcare/teen symposium</td>
<td>40.8%</td>
</tr>
<tr>
<td>Seeing clinic staff</td>
<td>52.1%</td>
</tr>
<tr>
<td>Learning about research</td>
<td>78.9%</td>
</tr>
<tr>
<td>School supplies</td>
<td>56.3%</td>
</tr>
<tr>
<td>Other</td>
<td>5.5%</td>
</tr>
</tbody>
</table>

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### SCD Research and Education Day 2011

Location of the 1st SCD Research and Education Day In 2001

Research and Education Day 2011

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### On-Line Ethics Resources

http://bioethics.od.nih.gov/academic.html
Albert J. Allen, M.D., Ph.D.
Sr. Med. Fellow, Bioethics &
Pediatric Capabilities
Eli Lilly & Co.

Conducting Clinical Trials
Involving Vulnerable Participants
Worldwide

Disclosures

- Employee & Shareholder, Eli Lilly & Co.
- Member, SACHRP
- Travel support to present at Nov., 2011
  meeting on evaluating abuse potential of
  drugs in development, NIDA/FDA/CPDD

Overview

- Background
- Personal perspective & a bit of corporate
  history
- Global challenges
- Illustrative cases
- Tying things together
Background: Beauchamp & Childress, 2009

- "Vulnerable persons in biomedical contexts are incapable of protecting their own interests because of sickness, debilitation, mental illness, immaturity, cognitive impairment, and the like."
- "Those who are easily susceptible to intimidation, manipulation, coercion, or exploitation are commonly classified among the vulnerable."

Background: Beauchamp & Childress, 2009 (continued)

- "However, this term should be used with caution because it can function to stereotype and overly protect."

Possible Example of “Stereotype” and Consequences

- Patients with a mental illness
  - Group includes those with schizophrenia, autism or a dementia, but...
  - Also includes those with depression (current and in remission), anxiety, ADHD, PTSD, adjustment disorders, etc.
- While some may have “diminished mental capacity” all or most of the time, others may have it infrequently or to a limited extent, and still others may not have it at all.
Possible Example of “Stereotype” and Consequences (continued)

- Identifying patients with a mental illness as “vulnerable,” without considering the specific illness or the patient’s current status, contributes to a stigmatizing stereotype
- In some cases this may prevent or make more difficult research intended to benefit these patients

Possible Example of “Stereotype” and Consequences

- Patients in China
- Western stereotypes of China:
  - Poor, developing country
  - Rural peasants
  - Non-Western civilization, not as “advanced”
  - Totalitarian, communist government
  - Corruption and inefficiency
- Accusations that research in China “exploits” vulnerable population

Possible Example of “Overly Protect” and Consequences (continued)

- Stereotypes and accusations at odds with other aspects of China:
  - One of the world’s oldest and most successful civilizations with its own ethical framework
  - Many academics, including medical and scientific experts, have Western training
  - Rapidly growing economy, 2nd largest in world
  - Large & growing middle/upper classes
  - Health care needs of Chinese population & government efforts to address
Background: Beauchamp & Childress, 2009 (continued)

- Proposed justifications of research practices with a vulnerable population
  - Never allow the practice (regardless of conditions)
  - Always allow the practice (regardless of conditions)
  - Allow the practice only under certain conditions
    - In many cases, bioethics discussion revolves around, “What are the certain conditions?”

Another perspective

Interest 1: Both interests “white,” no disagreement, easy case

Interest 2: Two interests not aligned, disagreement, potentially hard case – shades of grey

Personal Perspective

- Child psychiatrist and pharmacologist
- Training at Univ. of Iowa, NIMH
  - First research ethics training at NIMH in early 1990s
  - Submitted pediatric protocols to NIMH IRB
- Member of UIC IRB in late 1990s
  - Experienced OHRP suspension of IRB
- Unitarian Universalist (whatever that means)
Personal Perspective (continued)

- Since April, 2000 in **global** pharmaceuticals research and development at Eli Lilly
  - Clinical research physician, medical director, senior medical director for primarily pediatric neuroscience product
    - Member of neuroscience protocol review committee (one charge is to consider bioethics)
  - Senior medical fellow chairing/co-chairing Bioethics Advisory and Pediatric Steering Committees

Personal Perspective (continued)

- General observations of industry research
  - Much variability due to differences in drugs, populations, disease state, objectives, etc.
    - Not all research is clinical trials involving drugs!
    - For example, observational studies are common
    - Avoid research with some vulnerable groups (e.g., prisoners)
  - Some trials conducted in only one country, but many trials conducted in multiple countries
    - Sometimes includes US, sometimes not

Personal Perspective (continued)

- General observations of industry trials (continued)
  - Global companies market products globally and respond to global requirements/needs
    - Bigger reason for international trials than cost
  - Industry physicians, others involved in trials generally start out in academia
    - Similar training/values (good and bad)
    - More experienced in drug development and regulatory science than most in academia
A Bit of Corporate History: Lilly Bioethics Program

- Nov., 1996 WSJ article, “Lilly's 'Quick Cash' to Habitues Of Shelters Vanishes Quickly”
  - Vulnerable population: homeless individuals, many alleged to have substance abuse d/o
- Ad hoc committee formed to investigate, composed of both internal and external members
- 1999 Lilly Bioethics Committee established, also included internal and external members

A Bit of Corporate History: Lilly Bioethics Program (continued)

- 2008 Lilly Bioethics Program established
  - Full time staff
  - Bioethics advisory committee (continuation of bioethics committee)

How is all this relevant to “vulnerable” populations?

- Lilly Bioethics Program:
  - Began with questions about research involving a vulnerable population in Indianapolis, IN
  - Has continued and grown, in part, due to:
    - Increased awareness of vulnerable populations
    - Increased research involving vulnerable populations (e.g., pediatrics)
Global Challenges

- “Rules, standards, and practices vary greatly around the globe”…(but)…
- Almost all international codes and national laws and regulations…seem to promote the basic principles of:
  - Respect for persons
  - Beneficence
  - Justice
Global Challenges (continued)

- Almost all international codes and national laws and regulations…agree specifically about certain fundamental requirements, such as:
  - Minimizing risk
  - Obtaining informed consent
  - Requiring independent review of research.

CIOMS International Ethical Guidelines for Biomedical Research Involving Human Subjects (2002)

- "Minimal risk — that is, risk that is no more likely and not greater than that attached to routine medical or psychological examination."
  - What is the context?
    - Healthy individual?
    - General population?
    - Patient with the disease?

US “Minimal Risk” Definition

- From the “Common Rule” [45CFR46.102(i)]:
  - “The probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.”
  - Per NHRPAC: associated with a normal, healthy, average individual (child)
EU “Minimal Risk” Definition

- From the Guide for Ethics Committee Members by the Steering Committee on Bioethics of the Council of Europe
  - “That which, in terms of the nature and scale of the intervention(s), would be expected to result, at most, in a very slight and temporary detrimental impact on the health of the research participant.”

India “Minimal Risk” Definition

- From the Ethical Guidelines for Biomedical Research on Human Participants (Indian Council on Medical Research, 2006)
  - “Minimal risk would be defined as one which may be anticipated as harm or discomfort not greater than that encountered in routine daily life activities of general population or during the performance of routine physical or psychological examinations or tests…”

(continued)

- …However, in some cases like surgery, chemotherapy or radiation therapy, great risk would be inherent in the treatment itself, but this may be within the range of minimal risk for the research participant undergoing these interventions since it would be undertaken as part of current every day life.”
Global Challenges (continued)

- PCSBI Moral Science, 2011
  - Recommendation 9: Promote Community Engagement
- Community engagement – a way to bridge gaps/differences between
  - Researchers in one setting
  - Subjects in a different setting
- Important for all human subjects research, especially with vulnerable subjects

ILLUSTRATIVE CASES

Case 1: Global Pediatric Clinical Trial

- Debilitating primarily pediatric illness with shortened life-span
- Randomized, placebo-controlled as no standard of care approved by regulators
- Regulatory requirements
  - US written request for BPCA & PREA
  - EU required study under PIP
  - Japan agreed to/required by PMDA
- Data safety monitoring board
Case 1: Global Pediatric Clinical Trial (continued)

- Estimated 12,000-14,000 cases globally, but only about 500-700 new pediatric cases per year
  - Trial requires 250 pediatric subjects enrolled over 2 years
- Trial sites proposed: US, Canada, Mexico, UK, Germany, France, Spain, Italy, Sweden, Netherlands, Russia, Poland, Japan, China, Brazil, India

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Case 1: Global Pediatric Clinical Trial (continued)

- Topics that come up:
  - Whose laws, regulations and guidance apply?
  - Country differences re: obtaining child’s assent (Japan, China)
  - Use of placebo control, despite no approved standard of care (almost everywhere, China)
    - Regional variations in existing practices
  - Continued access to trial meds and post-trial access (almost everywhere)

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Case 1: Global Pediatric Clinical Trial (continued)

- What if…
  - Debilitating chronic illness that does not shorten life-span?
  - Debilitating mental illness: for example, schizophrenia, depression, autism or ADHD?
  - Standard of care varies globally, with approved treatments in some countries and different (unapproved) treatments in others?
  - Standard of care based on single, open-label academic trial (and not approved)
Case 2: Global Dementia Clinical Trial

- Add-on to existing therapies
- Randomized, placebo-controlled
- Regulatory requirements
  - Essential part of registration package for US, EU and Japan
    - FDA, EMA and PMDA each require a minimum number of patients from their country/region
    - Due to local regulatory requirements, separate trial will be conducted for/in China

Case 2: Global Dementia Clinical Trial (continued)

- Data safety monitoring board
- Trial requires 9500 subjects
- Trial sites proposed: US, Canada, Mexico, UK, Germany, France, Spain, Italy, Sweden, Netherlands, Russia, Poland, Japan, Australia

Case 2: Global Dementia Clinical Trial (continued)

- Topics that come up:
  - Whose laws, regulations and guidance apply?
  - Regional variations in standard of care, health care systems, etc.
  - Differences re: competence to give consent, mechanisms for surrogate consent (almost everywhere, even within countries)
  - Continued access to trial meds and post-trial access (almost everywhere)
Tying Things Together

- Important to be aware of and seek to protect vulnerable populations…but take care to avoid doing more harm than good
- Vulnerable populations are everywhere…don’t just look for them on the other side of the world
- Global desire to protect human research subjects, including vulnerable groups…but the “devil” is often in the local details

Overview

- Background
- Personal perspective & a bit of corporate history
- Global challenges
- Illustrative cases
- Tying things together

Questions? Allenaj@Lilly.com
Background: Beauchamp & Childress, 2009 (continued)

- “However, this term should be used with caution because it can function to stereotype and overly protect.”
- Proposed justifications of research practices
  - Never allow the practice (regardless of conditions)
  - Always allow the practice (regardless of conditions)
  - Allow the practice only under certain conditions
Assessing Capacity to Consent in Adults with Diminished Capacity

J. Andrew Bertolatus MD
Assoc Professor/IRB Chair
University of Iowa

A potential research subject may have:
- Severely capacity
- Intermediate level of capacity
- No capacity

What if your potential subject is:
- Intubated, on ventilator
- Heavily sedated
- Paralyzed (by drugs)
Scenario presented to our IRB by critical care physician researchers:

- Would like to conduct research on physiology of critical care subjects (and occasionally on interventions that might benefit subjects)
- Most are intubated/ventilated initially (and such subjects are sometimes the focus of the study)

If Intubation/Mechanical Ventilation is an eligibility criterion for study:

- Our IRB usually takes the position that the subject lacks capacity for consent
- Consent will need to come from a surrogate decision maker ("legally authorized representative")

Problem with LARs: 50% of our MICU admits are transferred from other hospitals
Informal survey of several UI MICU researchers

- For ~50% of MICU patients, no potential LAR ever comes to UIHC while patient there
- Even for those who come, it may take 1-2 days or more
- However, when LARs do show up, the percentage who give consent is high for low risk studies (e.g. drawing blood)
- The percentage of LARs who consent is related to actual/perceived risk of intervention.

A MULTICENTER, RANDOMIZED, CONTROLLED CLINICAL TRIAL OF TRANSFUSION REQUIREMENTS IN CRITICAL CARE
NEJM 1999;340:409

Other consent approaches for ICU?

- Phone
  - Probably requires
    - Waiver of consent
    - Waiver of documentation of consent
    - Waiver of HIPAA
- FAX
  - OK, but not many have FAX machines
- E-mail, signed/scanned document?
  - Not very practical
What about: Sec. 50.24 - Exception from informed consent requirements for emergency research?

- Only rarely applied to ICU/critical care research; mostly used in pre-hospital/ER setting
- Onerous procedures
- Has to have possible benefit

Another approach for minimal risk studies

- One of our PIs wanted to look at bacterial DNA in blood of ICU patients
- Needed small amounts of blood, early in MICU stay, before any antibiotics given – couldn't wait for LAR to show up

IRB decided:

- Waiver of consent to:
  - Take small amount of blood at time of clinical blood draw
  - Store for up to 1 week
    - If able to get subject or LAR consent: use sample
    - If no consent in one week: discard sample
What if subject regains capacity?

- In most of our ICU studies, we ask researchers to obtain consent from subject if capacity regained during hospitalization, if consent originally given by LAR.
- Data/samples not used/destroyed if subject wishes
- Researchers tell me: high percentage give consent under this scenario.

In conclusion

- Research in the ICU is difficult due to
  - Very diminished/absent capacity of patients
  - Lack of in-person access to surrogate decision makers
  - Difficult/impossible to get consent at a distance

References

Introduction

- Brief clinical overview Alzheimer Disease (AD)
- Assessment of decision making capacity
- Legally authorized representatives (LAR) and importance of dyad in AD research
- Substituted judgment and best interests
- Recommendations

Alzheimer Disease (AD)

- Alzheimer Disease is a neurodegenerative disorder and is the most common cause of dementia
- Clinical features
  - Memory impairment
  - Language: verbal fluency and anomia
  - Loss of visuospatial skills
  - Reduced insight
  - Apraxia: difficulty learning and performing motor tasks
  - Impaired executive function: planning, poor insight
  - Neuropsychiatric symptoms
Decision-making Capacity and Competency

- Competency is a legal determination, made by a court of law, that a patient has the requisite capacities to make a medical decision.
- This is in contrast to decision-making capacity which is a clinical determination made by the clinician or investigator.

Decision-making Capacity
(VAMCHC Policy Memorandum 512–14/RM)

- 4 components: understanding, appreciating, formulating, communicating.
- The patient needs to understand and appreciate the nature and expected consequences of participation including risk and benefits and alternative to participate.
- The patient must have the ability to formulate a judgment and communicate this decision.

Decisionally Impaired or Incapacitated

- Respect for persons requires special protections for decisionally impaired or incapacitated.
- No specific federal guidelines for assessing capacity.
- 3 categories of individuals whose decision-making capacity is in question:
  - Capacity to provide consent
  - Capacity to provide assent or dissent
  - No capacity to provide assent or dissent where legally authorized representative provides consent.
Age and the Ability to Provide Informed Consent

- The use of age alone as the criterion of ability to consent and therefore participate in research is not valid.
- Studies have shown that education, health status, and inadequate communication about the research rather than age per se contribute to lack of comprehension and recall.

How does one assess decision-making capacity? (1)

- Assessment of cognitive function using Mini-mental status examination (MMSE) (Folstein J Psychiatr Res 1975;12:189)
  - Widely used in routine clinical practice
  - Scores range from 0 to 30, with “normal” 26-30
  - Dementia < 24; adjusted for education < 21
  - Has been criticized for lack of sensitivity in detecting mild cognitive impairment
  - Instrument only tests limited number of cognitive domains

How does one assess decision-making capacity? (2)

- Multiple other instruments to assess cognitive function
  - Montreal cognitive assessment (MOCA), particularly useful for detecting mild cognitive impairment
  - Mini-Cog
  - Mini-CEX
  - It may be necessary to perform disease specific assessments, such as looking for aphasia in stroke patients
How does one assess decision-making capacity? (3)

- MacArthur Competency Assessment tool for Clinical research (MacCAT-CR)
  - MacCAT-CR must be adapted for each research scenario, in keeping with the decision-specific nature of capacity.
- Clinical Dementia Rating (Neurology 1993;43:2412)
- Assess for delirium (fluctuating level of consciousness) using clinical judgment and the confusion assessment method (CAM)

- Reinforcement (multiple sessions) and use of novel procedures (video, story book, simplified CF, etc.) may improve comprehension (empiric evidence supporting this is weak)
Orientation to Person, Place and Time is not Adequate to Determine Capacity to Consent

- Subjects must show that they understand the elements of the research
- Formal assessment of study specific knowledge
  - Can they name the risks, benefits, if participation is voluntary, etc.
  - Based on this test, investigator can propose specific criteria for whether the subject can provide their own informed consent, or whether consent from LAR is required

Problems with Assessment of Capacity

- Mild to moderate inter-rater reliability of assessment of decision making capacity even in experienced psychiatrists based on patient interviews (Kim 2011)
- Use of the MacArthur Competency Assessment Tool for Clinical Research (MacCAT-CR) understanding subscale had moderate-high rate of agreement (Karlawish 2008)
Problems with Assessment of Capacity

- Inherent limitations in the MMSE
- Lack of discriminatory power to identify mild cognitive impairment (MCI)
  - Montreal Cognitive Assessment (MoCA) now more widely used in clinical practice to identify MCI
- MMSE only assess limited number of cognitive domains
- A person’s capacity to perform to perform one function cannot be presumed to be equivalent to his or her capacity to perform other functions.

If There is Evidence of Decisional Impairment or Incapacitation (1)

- PI must provide the IRB with a plan for assessing patient’s ability to assent/dissent
- This is modeled after the approach in children
- General approach in individuals with mild to moderate cognitive impairment (MMSE 16-21) is to obtain their assent
- The threshold for transition to loss of capacity for medical decision making occurs ~MMSE score of 18 to 20 (Pucci, Hirschman)
  - Very mild to mild AD can provide consent (principle of double consent often employed)
  - Mild to moderate AD can provide assent

“Sliding Scale” Approach

- Some advocate that thresholds for “competence” to make decisions about enrolling in a study are a sliding scale, depending in part on the complexity of the study, and risks to subjects
  - The greater the net risk to the subjects, the stricter the requirement for capacity to provide consent
If There is Evidence of Decisional Impairment or Incapacitation (2)

- Family member or other legally authorized representative is asked to make the decision to participate
- Hierarchy of decision making determined by state law (if there is one)
- Federal guidelines for VA studies
- Seek guidance from IRB or institutional legal representatives

Challenges Informed Consent LAR

- Identification of proper LAR
  - Care giver often not LAR
  - State law: If present for decision making in clinical care, does it apply to research?
  - VA handbook 1200.05 hierarchy
- Informed consent from LAR not always an option
  - In a survey of 28 AD Cooperative Study Centers, 14% of the centers reported that their IRB did not allow proxy consent (Kim 2004)

Importance of the Dyad in AD Research

- Caregiver often has to provide information on subject
  - Dyad (Subject with Alzheimer disease and caregiver)
  - In clinical trials caregivers are typically research subjects and also have to provide informed consent.
- Many clinical trials require AD subject-caregiver dyad as part of eligibility criteria
  - Under-representation of demented subjects residing in nursing homes and assisted living facilities in clinical trials of AD drugs in part due to lack of dyad (Hanson 2010)
How do you assure that LAR understands their responsibilities?

- Older caregivers may have subclinical cognitive impaired and difficulty comprehending consent form
  - How do you assure that LAR can provide valid informed consent?
  - Is team obligated to perform assessments of cognitive status of elderly spouse who serves as LAR?
  - What level of documentation is required of informed consent process with LAR?

LAR Challenges in Long-term Studies

- LAR may change during the course of the study
  - Death of spouse (initial LAR)
  - Court appointed guardian, durable power of attorney that may be different than the initial LAR
- How is research team informed of these changes?
- If new information comes to light after the completion of the study that impacts on subjects, who gets notified? Original LAR? “next of kin”?

Options Proposed to Further Protect Rights of Cognitively Impaired

- Capacity to provide informed consent assessed by an individual independent of the research team
- Independent person who obtains informed consent with the focus on whether the patient understands risks and benefits
- Independent participation monitor (GCRC Research Subject Advocate, etc.)
- Prospective authorization
- Periodic re-consenting
Recommendations

- Assessment of capacity to provide informed consent should be tailored to the study population
- Investigators should employ specific assessments relevant to the protocol
  - The subject must demonstrate study specific knowledge, understand and appreciate the nature and expected consequences of participation including risk and benefits and alternative to participate and have the ability to communicate this decision to the team.

Greater the net risk to the subjects:
- Stricter requirement for capacity to provide consent by the subject
- Greater demands and responsibility on the LAR to represent the best interest and or substituted judgment on behalf of the individual with diminished capacity

It may be necessary for the investigator to assess whether the LAR has evidence of impaired decision making capacity, particularly when they are the elderly spouse of the individual.
- The threshold criteria for decision making capacity should take into consideration the nature of the study. The greater the net risk to the subjects, the stricter the requirement for capacity to provide consent.
Consent Capacity and Mental Illness

To respect autonomy is to give weight to autonomous persons' considered opinions and choices...To show lack of respect for an autonomous agent is to repudiate that person's considered judgments, to deny an individual the freedom to act on those considered judgments, or to withhold information necessary to make a considered judgment...

Belmont Report

Assessment of Capacity as a Protection

- When there is concern about a class of prospective subjects
  - Protocol designed to enroll "at-risk" subjects
  - Protocol that may precipitate loss of decisional capacity

- When there is concern about an individual
  - Prior to or at the time of enrollment
  - During study participation
**Fundamental considerations**

- Consent must be **Informed, Understanding, and Voluntary**

- Investigators are responsible for ascertaining that the subject has comprehended the information

- When the risks are more serious, that obligation increases.

---

- What level of understanding and what degree of voluntariness are necessary for a prospective subject to act “autonomously” and make a “free” and “informed” choice to take part in research?

- When does an investigator and an IRB need to confirm that understanding and voluntariness are present and when can it be assumed?

- In what ways does the presence of mental illness affect such considerations?

- How should an IRB address these matters in policy and practice?

---

- Consent capacity is not a “trait”—it is a capacity to make a particular consent decision at a particular point in time.

- Consent capacity therefore will vary depending on the difficulty of the information disclosure, the abilities of the decision-maker, and the complexity of the decision.

- *Enhancing/facilitating* informed consent and *assessing* consent capacity are not distinct.

- Assessment of capacity should focus on elements of consent that are central to the choice at hand.

- The duties of the IRB, investigator, and LAR do not end once the consent form is signed.
Who is likely to have impaired consent capacity?

What is the nature of that impairment?

How and when should capacity be assessed?

An IRB must be familiar with the clinical characteristics of the disorder and sub-population being studied.

The assessment of capacity may then be adapted to the specifics of the study design and nature of anticipated impairment.

Capacity to Consent

- Factual understanding of the information
- Rational manipulation of information
  - Able to appreciate the nature of the situation and its consequences
- Able to evidence a choice
- Depression
- Mania
- Schizophrenia spectrum disorders
- Developmental disorders

IRB Considerations
- Does the consent process meet the needs of the decisionally impaired patient?
- Who “gets” consent?
- Who assesses Capacity? (Training)
- Exactly what does “capacity” mean for the study?
- What methods and thresholds should be applied?
- When to monitor? What to document?

The use of scales and instruments
- Serve to guide the investigator in the assessment of capacity
- Valuable as screening instruments
- Best when tailored to the study
- For example: MacCT-CR, UBACC
UBACC
Arch Gen Psychiatry. 2007;64(8):966-974

1. What is the purpose…?
2. What makes you want to consider participating?
3. Do you believe this is primarily research or primarily treatment?
4. Do you have to be in this study if you don’t want to participate?
5. If you withdraw from this study, will you still be able to receive regular treatment?
6. If you participate, what are some of the things you’ll be asked to do?
7. Please describe some of the risks.
8. Please describe some of the benefits.
9. Is it possible that being in this study will not have any benefit…?
10. Who will pay for your medical care if you are injured…?

Independent Assessment of Capacity

- e.g. Capacity is assessed by the investigator as usual and by a qualified individual who is not a member of the research team and has no reporting relation to the researchers.

- Addresses bias.
Maintaining Data Confidentiality: How IRBs and Investigators Can Avoid the Crisis, and Deal with It Afterward

Outline

- Protecting confidentiality
- Crisis case study
  - Study introduction
  - What occurred
  - Corrective action
  - Consequences
  - Preventive action
- Lessons learned

Protecting Confidentiality
Defining Confidentiality

- Maintenance of the researcher’s agreement with the participant about how the participant’s identifiable private information will be handled, managed, and disseminated.
  - Controls on storage, handling, and sharing of data.
  - Certificates of Confidentiality

Regulatory Requirements

- Responsibility placed on Researchers and IRBs
- 45 CFR 46.111(7) & 21 CFR 56.111(7)
  - When appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.
- No specific guidance from the regulatory agencies on practical implementation

Protecting Confidentiality

- Records should not be used for research purposes without IRB approval
- Protocol should describe appropriate safeguards for protecting confidentiality
  - Consider the data source and method of collection
  - Consider the storage methods
  - Identifiable information should be destroyed as soon as possible
Protecting Confidentiality

- Appropriate safeguards
  - Secure location
    - Locked offices
  - Secure storage and transmission
    - Password protection
    - Encryption of all devices
  - Destruction of data
    - Shredding of paper documents
    - Permanently delete electronic files

Practically...

- Protecting confidentiality is a shared responsibility
  - IRBs: rely on institution to create formal policies and requirements
  - Institution: creates policies for data management and security, often on a departmental basis
  - Investigator: implements the policies for the specific study

Generally...

- Appropriate safeguards are determined by institutional requirements and are not typically imposed by the IRB
  - Institutional and departmental policies
  - IT policies
- Determining specific safeguards can be difficult for IRBs
Shared Responsibility

IRBs require safeguards

Institutions define safeguards

Investigators implement safeguards

Crisis case study:
How do the responsible parties interact when the worst happens?

Study Introduction

- A Prospective Registry of Patients with Severe Acute Pancreatitis
  - Medical/demographic data; per PI:
    - Name / DOB / MRN
    - Date of admission
    - Etiology of disease
    - Grade of disease
    - Gender/race/ethnicity
  - Expedited Category 5
  - Waivers of informed consent and authorization
Study Introduction, Continued

- Data collection
  - Paper
- Data storage
  - Study Manager
    - Secure, web-based database
- Data protection
  - Paper stored in locked office, then shredded
  - Study Manager password-protected

What Occurred

- Laptop computer stolen from a medical resident's car
- Computer contained research subjects' PHI
  - Laptop was not encrypted
  - Laptop was password-protected
  - File containing the PHI was password-protected
What Occurred, Continued

- Failures:
  - Investigators were not IRB-approved to have access to data
    - The medical resident whose laptop was stolen was not listed as a co-investigator in the IRB submission
  - Data were not all stored per IRB submission
    - Stored in a spreadsheet, on flash drives and on hard drives of several computers
  - Data were inclusive of SSNs
    - SSNs not an approved data point in the IRB submission

Corrective Actions

- Reporting
  - Police
  - University Legal Counsel
  - University Research Compliance
  - DHHS
  - State Attorney General
  - Media (>500 records)
  - Individuals
    - Letter to subjects

Corrective Actions, Continued

- Study suspended
  - Immediately by PI
  - By IRB upon notification
- Study amended to improve data confidentiality practices
  - Data immediately entered into REDCap – online, secure database, with no interim record
Corrective Actions, Continued

- IRB review
  - Discussion in numerous IRB meetings (5)
  - PI requested to provide additional justification for waiver requests
  - Suspension was lifted only after all reporting complete, and amendment to update study documents was approved

Consequences

- Letter to subjects
  - Subjects didn’t consent, so weren’t aware that their data were being used for research
  - Not reviewed by IRB prior to being sent to subjects
    - No offer for identity theft coverage initially
  - Written by PI in conjunction with University Legal Counsel

Consequences, Continued

- Impact on subjects
  - What good came from notifying subjects?
  - Could corrective action have caused more stress than the event itself?
Failures

- All three responsible parties failed on a practical level
  - IRB: approved appropriate safeguards but assumed investigator implementation
  - Institution: created appropriate policies but assumed investigator implementation
  - Investigators:
    - failed to understand their responsibility
    - failed to comply with responsibility

Preventive Actions - Investigators

- Education
  - Appropriate safeguards
    - One-on-one
    - Departmental presentations by privacy officer and other research compliance personnel
    - Responsible investigators shared their failure at grand rounds
  - Available resources

Preventive Actions - IRB

- Still determining whether IRB policies are specific enough
- Education to IRB about resources available to investigators
  - Encourage use of those resources in future studies
- Careful review of studies to identify red flags
  - Co-investigators
  - Investigator understanding of requirements
- Careful monitoring of flagged
Preventive Actions - Institution

- Institution provided education to investigators on implementation of policies
- Further development of current policies
- Identification of additional resources
  - Secure study systems: clinical trial management software needed on an institutional level
  - Encryption

Lessons Learned

- Individual failure
  - Investigator
  - Co-investigator
- Institutional failure
  - Appropriate education
  - Not asking the right questions / not asking the questions correctly
  - Scope of work:
    - Keeping 'fences' between studies
    - Allowing investigators to share

Lessons Learned, Continued

- Education
  - Can’t assume level of knowledge
    - MDs/medical professionals
    - PHI
  - Institution- and Department-level understanding is critical
  - Utilize Information Security Officers
Lessons Learned, Continued

- **Technology**
  - No one technological solution to this issue
  - Useless if not utilized correctly
    - Encryption
    - Data transfer (no email, flash drives, etc.)
    - Study codes
    - Keeping the link to the codes separate

- **Rigorous IRB review**
  - Requests for waivers
  - Scrutiny of proposed data collection/maintenance/storage methods
  - Monitoring of studies

Questions?

- **Amy Waltz, JD, CIP**
  - Associate Director
  - Human Subjects Office
  - Office of Research Administration
  - Indiana University
  - acthurst@iu.edu
  - 317.274.8289
  - www.researchadmin.iu.edu
Top Ten Findings from AAHRPP
Step 1 Review of Application Materials and Draft Site Visit Reports

Element by Element Analysis

- Analysis of all reports from organizations which have gone to Council on Accreditation.
- Revised Standards.
- Top 10 elements ranked by concerns found in Step 1 Review of Application Materials upon review by Accreditation Director (Policy and Procedure).
- Top 10 elements ranked by concerns found at the site visit, noted in Draft Site Visit Reports (Practice).

How to Respond

- Step 1 Review of Application Materials: Response is a change to policy and procedure.
- Draft Site Visit Report: Response is a change that can be identified in practice.
  - May need a policy/procedure change.
  - Must include education.
  - Must include monitoring to demonstrate that practice has changed.
1. Element I.5.D. (Non-Compliance)

- 71.4% of Step 1 Review of Application Materials included concerns about this element.
  - 41.1% of Draft Site Visit Reports noted concerns about this element.
  - (This was also the #2 rated concern in Draft Site Visit Reports)

Areas of Concern

- Define.
- Identify.
- Manage.
- Be clear as to who does what, when, and how; also documentation and determination.

#2: Element I.1.A.: Define Research

- 67.9% of Step 1 Review of Application Materials included this element as a concern; only 9.8% found this concern in Draft Site Visit Reports.
- Define systematic investigation; define generalizable knowledge.
- Provide examples for researchers of the kind of research that meets the definition and needs review by the IRB or EC.
#3: Element II.2.C: Conducting Meetings by the Convened IRB

- 67.9% of Step 1 Review of Application Materials have this as a concern; 9.8% of the Draft Site Visit Reports.
- IRB includes a member who represents the general perspective of research participants.
- At least one unaffiliated member is present at convened meetings most of the time.

#4. Element II.3.F. Consent Process

- Process for evaluating and documenting the process for informed consent (Draft Site Visit Reports).
- 63.4% of Step 1 Review of Application Materials; 19.6% of Draft Site Visit Reports.
- Data retention when a subject withdraws.
- Generally, Step 1 Review of Application Materials have a variety of missing parts related to specific requirements for VA, DoD, and the short form.

#5. Element I.4.C. Promoting Involvement of Community Members in Research

- 57% of Step 1 Review of Application Materials do not fully address this element.
- 2.7% of Draft Site Visit Reports note concerns in this area.
- Community based participatory research.
#6. Element II.4.A. Additional Protections (Also #6 for Draft Site Visit Reports)

- 54.5% of Step 1 Review of Application Materials and 26.8% of Draft Site Visit Reports include this element as a concern.
- Problems with Subpart requirements and requirements of other sponsoring agencies.
- Describe additional safeguards, protocol specific findings justifying the determinations.
- Documentation.

#7: Element I.7.A. Test Articles

- 54.5% of Step 1 Review of Application Materials; 13.4% of Draft Site Visit Reports include this concern.
- Regulatory requirements, details (Step 1 Review of Application Materials).
- Draft Site Visit Reports: Verifying the IND, IDE.

#8: Element II.3.C: Equitable Selection

- Step 1 Review of Application Materials: 54.5%.
- Draft Site Visit Reports: 12.5%.
- Advertisements, Recruitment, Payment Arrangements.
#9: Element I.5.B. Quality, Efficiency, Effectiveness (#9 on Draft Site Visit Reports)

- 53.6% Step 1 Review of Application Materials; 25.9% in Draft Site Visit Reports.
- One goal, one objective, one measure.

#10: Element II.2.G. Suspension and Termination of Research

- 53.6% of Step 1 Review of Application Materials; 21.4% at Draft Site Visit Reports.
- Determining and Documenting and Reporting.
- Timeframes for reporting.

Draft Site Visit Reports #1 Finding: Element II.1.B.

- Evaluating IRB members and providing individual feedback.
- 33.9% in Step 1 Review of Application Materials; 50.9% in Draft Site Visit Reports.
Draft Site Visit Reports # 3: Element I.8.E.

- 35.7% Draft Site Visit Reports.
- Sponsor notifies organizations of safety concerns after the study has ended.

Draft Site Visit Reports # 4: Element I.4.B.

- Community outreach: evaluation of outreach activities.
- 29.5%

#5: Element II.5.B. Documentation

- 28.6% in Draft Site Visit Reports.
- Minutes.
- Protocol specific findings.
#7: Element I.6.B. Conflict of Interest
- Define, Disclose, Educate, Manage, Report.

#8: Element II.2.D. Convened IRB Review
- 26.8%.
- Substantive modifications return to convened IRB for review.
- Flagging of records.
- Criteria for approval.

#10: Element I.8.C. Contracts
- Data and safety monitoring plans in contracts.
- 25.9% in Draft Site Visit Reports.
Implications of the New PHS Conflict of Interest Requirements

What’s the issue?

- “A conflict of interest is a set of conditions in which professional judgment concerning a primary interest (such as a patient's welfare or the validity of research) tends to be unduly influenced by a secondary interest (such as financial gain).”  NEJM 1993;329(8): 573-576
- Perceived COI: Perception may be because of misinterpretation of facts, incomplete information, poor communication, or past experiences
- Real COI: Must meet established criteria

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Prevalence Of Academic-industry Relationships Among Academic Research Faculty

Health Affairs 2009; 28:1814-1825.
Relation Between Industry Sponsorship and Study Outcome in Original Research Studies

RCT indicates randomized controlled trial.

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<td>Yaffe et al., 2001</td>
<td>RCT</td>
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<td>Kypragos and Xie-Norton, 2002</td>
<td>RCT</td>
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<td>Fisker et al., 1999</td>
<td>Economic Analysis</td>
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<td>Cho and Shark, 1999</td>
<td>Original Research</td>
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<td>Turner and Spitholtz, 1997</td>
<td>Original Research</td>
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<td>Swan and Mejias, 1999</td>
<td>Retrospective Cohort</td>
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<td>Overall</td>
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Impact of Disclosing Financial Ties

- Systematic review of 20 original, quantitative studies of patients', research participants', or journal readers' views about financial ties (FTs) to pharmaceutical and medical device companies.
- Acceptability of FTs (8 studies)
  - Patients were more likely to view personal gifts to physicians as unacceptable, compared with professional gifts
- Importance of Disclosure (10 studies)
  - Most patients and research participants believed FTs should be disclosed
- Impact of Disclosure on Willingness to Participate in Research (7 studies)
  - One-quarter of participants reported less willingness after disclosure of FTs

Arch Intern Med 2010;170:675

What’s the element?

- Element I.6.B. The Organization has and follows written policies and procedures to identify, manage, and minimize or eliminate individual financial conflicts of interest of Researchers and Research Staff that could influence the conduct of the research or the integrity of the Human Research Protection Program. The Organization works with the IRB or EC in ensuring that financial conflicts of interest are managed and minimized, when appropriate.
What’s the element?

- Element II.1.D. The IRB or EC has and follows written policies and procedures so that members and consultants do not participate in the review of research protocols or plans in which they have a conflict of interest, except to provide information requested by the IRB or EC.

What’s the element?

- Element III.1.B. Researchers and Research Staff identify and disclose financial interests according to organizational policies and regulatory requirements and, with the Organization, manage, minimize, or eliminate financial conflicts of interest.

What might you consider?

- What regulations apply to your organization
- Who must disclose
- What must be disclosed
- What is the disclosure process
- How are disclosures evaluated and managed
- What is the role of the IRB or EC
- How are COI evaluations and management plans communicated
What material will be looked for?

- Disclosure forms
- Policy and procedures
- Reviewer checklists
- Minutes
- Consent forms

2011 Revised FCOI Regulation

- Promoting Objectivity in Research: 42 CFR Part 50 Subpart F
- Published in Federal Register on August 25, 2011
- Implementation by August 24, 2012
- Applies to each Notice of Award issued subsequent to compliance dates of final rule
- Institutions that implement the regulation prior to August 24, 2012 signify their compliance by making the institutional FCOI policy publicly accessible.

Major Changes to the 1995 Regulations

- Lower financial disclosure thresholds
- New conflict of interest training
- New public accessibility requirements
- Increased transparency for travel reimbursement
**Investigator**

- **Investigator** = Any other person, regardless of title or position, who is responsible for:
  - The design, conduct, or reporting of research funded by the PHS, or
  - Proposed for such funding, including persons who are sub-grantees, contractors, collaborators, or consultants

- **Discloses**
  - Significant Financial Interests (SFI)
  - No later than the time of application for PHS-funded research
  - Travel

- **Updates**

**Significant Financial Interest (SFI)**

- **Defined as a financial interest (FI):**
  - If a **publicly-traded company**, if the value of past 12 months (can be defined as the last calendar year) remuneration + value of current equity >$5,000 (on the day of disclosure)
  - If a **non-publicly-traded company** (e.g., startup) if the value of past year’s remuneration >$5,000 OR…
  - If the investigator holds **any equity interest**
  - Intellectual property rights (e.g., patents, copyrights), royalties from such rights, and agreements to share in royalties related to such rights

- That reasonably appear to be related to the Investigator’s institutional responsibilities

**Institutional Responsibilities**

- Investigator’s professional responsibilities on behalf of the Institution including, but not limited to activities such as:
  - Research
  - Research consultation
  - Teaching
  - Professional practice
  - Institutional committee memberships
  - Service on panels such as Institutional Review Boards or Data and Safety Monitoring Boards.
Exclusions

- Income from seminars, lectures, or teaching, and service on advisory or review panels for government agencies, institutions of higher education, academic teaching hospitals, medical centers, or research institutes affiliated with an Institution of higher education
- Income from investment vehicles, such as mutual funds and retirement accounts, as long as the Investigator does not directly control the investment decisions made in these vehicles

Travel

- Any reimbursed or sponsored travel
  - Paid on behalf of the investigator and not reimbursed to the investigator so the exact monetary value is known
  - Related to institutional responsibilities
- Report
  - Purpose
  - Sponsor/organizer
  - Destination
  - Duration
- Does not apply if sponsored by a federal, state, or local government agency; institution of higher education; academic teaching hospital/medical center/research institute affiliated with an institution of higher education

Updates

- At least annually
- Within 30 days of
  - Discovering or acquiring a new SFI
  - Joining a project
Institution

- Any domestic or foreign, public or private, entity or organization that is applying for, or receives, PHS research funding
- Responsibilities
  - Determines
  - Manages and monitors
  - Reports
  - Mitigates noncompliance
  - Trains
  - Makes available

Determines

- Institution determines relatedness
  - Determination made by designated institutional official(s)
  - Not investigator
- Is SFI related to PHS funded research?
  - The SFI could be affected by the PHS funded research or is an entity whose financial interest could be affected by the research
- If Yes, is the SFI a financial conflict of interest (FCOI)?
  - A FCOI exists when a SFI could directly and significantly affect the design, conduct or reporting of the PHS funded research

Subrecipients

- Requires prime awardee to take reasonable steps to ensure subrecipients comply with rule
- Accomplished by establishing as part of subaward agreement
  - The subrecipient will comply with its own FCOI policy or policy of the prime awardee
  - Include time periods to meet SFI disclosure, if applicable, and FCOI reporting requirements
- Subrecipients who rely on prime awardee must identify FCOIs in sufficient time to allow awardee institution to report FCOI
Manages

- If FCOI exists then the institution develops and implements a management plan
- Manage means to take action to address a FCOI, which includes reducing or eliminating the financial conflict of interest, to ensure that the design, conduct, or reporting of research is free from bias or the appearance of bias.
- Key management plan elements
  - Role and principal duties of the conflicted investigator
  - Conditions of the plan
  - How the plan is designed to safeguard objectivity in the research project
  - Confirmation of the investigator’s agreement to the plan
  - How the plan will be monitored to ensure compliance

Potential Management Plan Examples

- Public disclosure when presenting or publishing the research
- Disclosing in informed consent
- Appointing an independent monitor
- Modification of the research plan
- Change of personnel or personnel responsibilities or disqualification of personnel
- Reduce or eliminate FCOI
- Severance of relationship

Reports

- Provide initial and ongoing FCOI reports
- Initial – prior to expenditure of funds
- Ongoing – within 60 days of identifying a new FCOI
- Ongoing – annually
  - Status of FCOI and any changes to management plan
  - Due when grantee submits annual progress report or at time of extension
Elements of an FCOI Report

- Grant number
- PD/PI or contact PD/PI
- Name of Investigator with the FCOI
- Name of the entity with which the Investigator has an FCOI
- Nature of FCOI (e.g., equity, consulting fees, travel reimbursement, honoraria)
- Value of the financial interest (by range) or a statement that a value cannot be readily determined
- A description how the financial interest relates to NIH-funded research and the basis for the Institution’s determination that the financial interest conflicts with such research
- Key elements of the Institution’s management plan

Mitigate Noncompliance

- Whenever an SFI that was not disclosed, identified, reviewed or managed in a timely manner is identified, the institution has 60 days to make the determination of an FCOI and report the FCOI, if it exists.
- If an FCOI exists, complete and document a Retrospective Review within 120 days of determination of noncompliance and implement, on at least an interim basis, a management plan.
- If applicable, update existing FCOI report to specify the actions that have been, and will be, taken to manage the FCOI going forward.
- After retrospective review report promptly if bias is found and submit a Mitigation Report.
- Submit annual FCOI report thereafter.

Mitigate Noncompliance

- If can’t mitigate bias or can’t manage may result in imposition of special award conditions, suspension of funding or other enforcement actions.
- Institution responsible for establishing adequate enforcement mechanisms and provide for employee sanctions or other administrative actions to ensure investigator compliance.
Train

Institutions must require that each Investigator complete FCOI training
- Prior to engaging in research related to any NIH funded project
- At least every four years, and
- Immediately when any of the following circumstances apply
  - Institution revises its policy in a manner that affects the investigator
  - When an investigator is new to the institution or
  - When the institution finds an Investigator is not in compliance with the Institution’s policy or management plan

Make Available

- Make information concerning FCOIs held by senior/key personnel publicly accessible
  - Provide written response within five business days of a request or
  - Web site
    • Update the website annually and within 60 days of identifying any new FCOIs

Information to be made publically available

- Investigator's name
- Investigator's title and role with respect to the research project
- Name of the entity in which the SFI is held
- Nature of the SFI
- Approximate dollar value of the SFI (dollar ranges are permissible) or a statement that the interest is one whose value cannot be readily determined through references to public prices or other reasonable measures of fair market value
COI: FDA Regulations

- Applies to investigators and sponsors – requires Sponsor to disclose or certify no COI for participating investigators
- Provides additional information to allow FDA to assess the reliability of clinical data
- Investigator = listed or identified investigator or sub-investigator directly involved in the treatment or evaluation of research subjects
- Reporting Requirements
  » Equity interest that exceeds $50,000 during the study plus one year
  » Financial arrangements between the sponsor and the investigator whereby the value of the investigator's compensation could be influenced by the outcome of the trial
  » Any proprietary interest in the product studied held by the investigator
  » Significant payments of other sorts of $25,000 beyond the cost of the study

Physician Sunshine Act

- Section 6002 of the Affordable Care Act
- As of January 2012, pharmaceutical and device manufacturers must report all gifts and payments to physicians and teaching hospitals to a federal database
- Threshold is $10 per item, or $100 per year
- Results will be published in 2013 in a web based, searchable format

Steps to Take

- Review and Revise Policies
  – Who is required to disclose?
  – Which activities require disclosure?
  – What amounts require disclosure?
  – What is the timing around disclosure?
- Review Processes
  – Structured of management plans
  – Reporting requirements
  – Time lines
  – Subrecipients
- How will public disclosure be addressed?
- Education
### Summary of Major Changes to the 1995 Regulations

#### Table: Important Financial Interests (SFI) threshold
- **1995 Regulations**: No minimum threshold of $5,000 for disclosure generally applies to payments or equity interests. Arn threshold of $5,000 for disclosure generally applies to payments for services and equity interests. Include any equity interest in non-publicly traded entities.
- **2011 Final Rule**: Arn threshold of $5,000 for disclosure generally applies to payments for services and equity interests. Include any equity interest in non-publicly traded entities.

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<td>Arn threshold of $5,000 for disclosure generally applies to payments or equity interests. Arn threshold of $5,000 for disclosure generally applies to payments for services and equity interests. Include any equity interest in non-publicly traded entities.</td>
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#### Table: Institutions/Investigators and Reporting of Identified FCOIs
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| FCOI training                | no requirement    | Each Investigator must complete training prior to engaging in research related to any PHS-funded grant or contract and at least every four years, and immediately under the designated circumstances:  
  - Institutional FCOI policies change in a manner that affects Investigator requirements  
  - An Investigator is new to an Institution  
  - An Institution finds an Investigator noncompliant with Institution’s FCOI policy or management plan. |
| Retrospective Review         | not mentioned     | Institution is required to conduct a retrospective review in those cases of non-compliance with the regulation but is not required to report the review to the PHS Awarding Component. The Institution will be required to notify the PHS Awarding Component promptly and submit a report to the PHS Awarding Component only in cases where bias is found. The report will address the impact of the bias on the research project and the actions the Institution has taken, or will take, to eliminate or mitigate the effect of the bias. |