THE ETHICS POLICE?: THE STRUGGLE TO MAKE HUMAN RESEARCH SAFE

Robert Klitzman, M.D.
Professor of Psychiatry
Director, Masters of Bioethics Program
Columbia University
Background

• But recently, IRBs/RECs have been increasingly criticized
  • Discrepancies
    • Can impede research
  • Tensions with PIs
  • Are IRBs/RECs broken?
  • Unconstitutional?
Recent Controversies

Since IRBs/RECs were created, research ethics “scandals” and controversies have occurred:

• Kennedy-Kreiger study, involving exposure of lead to children
• Hopkins “checklist” hand-washing study
  • Any need to inform IRBs or patients at 67 institutions?
• SUPPORT Study
  • Randomizing newborns to two levels of oxygen
  • OHRP: consent forms were insufficient
  • Did clinical equipoise exist?
  • Debates continue
• Facebook experiment
  • Have users “signed away” all their rights to be involved in any research Facebook wants to do?
Policy debates

- In US: ANPRM/NPRM:
  - Centralize IRBs more?
  - Exempt certain areas of minimal risk research
  - Let PIs self-determine minimal risk status
  - How to handle biobanks?
- December 2014: NIH
  - CIRBs for all multisite studies?
    - How much should they be centralized, and how might that work?
  - Are other improvements needed, and if so, what?
Yet little empirical data exists

- Very few studies on views and experiences of IRBs/RECs
  - Several quantitative studies
    - Focusing on the form of IRBs/RECs (e.g., structure/process)
    - Not the content of decisions
  - But many questions remain:
    - How do IRBs/RECs make decisions?
    - What challenges do IRBs/RECs feel they face?
    - How do IRBs/RECs view these issues?
QUALITATIVE STUDY OF IRBS
Methods

• Contacted IRB leadership
• Every fourth institution of list of top 240 institutions by amount of NIH funding
• Response rate: 34/60 = 55%
• Asked 50% of these to distribute info to members and administrators
• Semi-structured, in-depth interviews
## Characteristics of Qualitative Sample

<table>
<thead>
<tr>
<th>Type of IRB Staff</th>
<th>Total</th>
<th>% (N=46)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chairs/Co-Chairs</td>
<td>28</td>
<td>60.87%</td>
</tr>
<tr>
<td>Directors</td>
<td>1</td>
<td>2.17%</td>
</tr>
<tr>
<td>Administrators</td>
<td>10</td>
<td>21.74%</td>
</tr>
<tr>
<td>Members</td>
<td>7</td>
<td>15.22%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Gender</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>27</td>
<td>58.70%</td>
</tr>
<tr>
<td>Female</td>
<td>19</td>
<td>41.30%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Institution Rank</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1-50</td>
<td>13</td>
<td>28.26%</td>
</tr>
<tr>
<td>51-100</td>
<td>13</td>
<td>28.26%</td>
</tr>
<tr>
<td>101-150</td>
<td>7</td>
<td>15.22%</td>
</tr>
<tr>
<td>151-200</td>
<td>1</td>
<td>2.17%</td>
</tr>
<tr>
<td>201-250</td>
<td>12</td>
<td>26.09%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>State vs. Private</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>State</td>
<td>19</td>
<td>41.30%</td>
</tr>
<tr>
<td>Private</td>
<td>27</td>
<td>58.70%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Region</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Northeast</td>
<td>21</td>
<td>45.65%</td>
</tr>
<tr>
<td>Midwest</td>
<td>6</td>
<td>13.04%</td>
</tr>
<tr>
<td>West</td>
<td>13</td>
<td>28.26%</td>
</tr>
<tr>
<td>South</td>
<td>6</td>
<td>13.04%</td>
</tr>
</tbody>
</table>

| Total # of Institutions Represented | 34 |
RESULTS
A wide range of issues concerning:

- **Contexts** of decisions
  - Who is on the IRB? How are they chosen?
    - Intra-IRB issues
  - Relationships with feds
  - Relationships with industry
  - Relationships with institutions
- **Contents** of decisions
  - Interpretations of principles and regulations
    - Assessing and weighing risks vs. benefits
    - Undue influence?
    - Is it research?
    - How good does the science need to be?
  - Informed consent
    - Is the form good enough?
- **Relationships with researchers**
  - Research integrity?
- Additional issues in the developing world
Intra-IRB issues

• Very high degrees of commitment and dedication
• Some are “volunteered” for the IRB
Becoming members and chairs

**Before appointment to IRB**

**Institutions vary**
- Appointment may be due to variable reasons
- Individuals vary in prior education and experience:
  - In ethics
    - From some to none
  - In research
    - May have interest
- May be chosen because of complex institutional factors:
  - Assignment “volunteered” by department as routine committee assignment
    - As remedial education/”punishment”
- Turnover of chairs may occur because of:
  - Retirement
  - Scandal
  - Institutional wishes to change IRB
  - Roles may be fluid
Becoming Members and Chairs

Orientations

• Vary from little or none to some
  • “See one, do one”
• Learning “on the job”
  • Can take several months or years
• Often no attendance at national meetings
  • Because of limited resources
“Community” Members

- Finding Community Members
  - Challenges, given needs to understand science
- Retaining Community Members
  - IRBs vary in amount of resources to assist them
- Who They Are
  - Non-affiliated and/or non-scientific?
- What They Do
  - Input on protocols themselves
  - Only assessing consent forms
- Implications
  - Provide more support?
  - Have more then one?
Contexts: Federal Agencies

- IRBs often caught in the middle between the feds and the researchers
- But often “blamed” by PIs as “the messenger”
Amounts of support vary
  - Can increase after a “scandal” or audit, but can then return to prior levels
Differences in how to divide IRBs
  - Initial vs. continuing review
    - e.g., cancer vs. other
    - Separate IRB for normal volunteers?
  - Separate scientific review committees
Compliance offices vs. IRBs
IRBs’ and PIs’ COIs

- Helping PIs
- Competing with PIs

IRB

Recusing vs. Including Co-Investigator
- In discussion
- In vote

- Recusal
- Reminding members about such COIs ("benediction")
COIs (continued)

• Standard:
  • Not having even the appearance of a COI?
  • Direct and indirect financial COIs
  • Rather than financial and non-financial COIs
  • Clearer or more rigorous standards for recusal?
    • Okay to stay in the room for this discussion, if not for the voting?
THE CONTENTS OF DECISIONS:
Assessing and weighing potential risks and benefits of studies not yet conducted: Difficulties

Spectrums of Risk
- From major to minor
- “Significant” or not?
- From likely to unlikely
- From direct to indirect:
  - “Minimal risk”
  - “Minor increase over minimal risk”

Sources of Difficulties in Assessing Risks
- Because of inherent uncertainties of research (i.e., investigating “the unknown”)
- Patients with ongoing, serious disease
- Therapeutic misconception
- Standards:
  - “Truly safe”?
Coercion and Undue Influence: Ambiguities and Dilemmas:

IRBs struggle with dilemmas concerning:

- **Content**
  - How much to give subjects
    - Pay subjects differently based on their income?
    - Will selection bias result?
    - Provision of free care as coercive?
    - What to give subjects (e.g., cash vs. vouchers)
  - Added challenges in several situations:
    - Research on children
    - Research on students
    - Research in the developing world
  - When to compensate subjects
  - Whether, when, and how to inform potential participants about compensation
  - How to define undue influence:
    - Based on “gut feelings” and “common sense”
    - Can be subjective
Process of deciding about undue influence

- IRBs can take time to make these decisions
- Decisions often reflect compromises
- Underlying tensions arise:
  - “Undue inducement” is inherently subjective and difficult to assess in others
  - Questions arise of whether subjects should “volunteer” vs. do it for the money
  - Lack of a consistent standard:
    - Between IRBs
    - Even in one IRB over time
Potential problems with quality of science
- Quality of science can vary
- Quality of science can be:
  - Relatively low
  - Hard to measure
    - Especially possible benefits of eventual findings
  - Not great, but not egregious
  - Low risk, but low benefit
  - Low power
- Separate departmental sign-off can vary in quality
- Particular problems with studies with main goal not research per se:
  - To help industry sales
  - To serve as part of student education

IRB members’ conflicting goals

As IRB members:
- Make science “good enough”
- Minimize risks
- Make risks commensurate with benefits

As scientists:
- Make science “as good as possible”
- Maximize benefits (i.e., social/scientific contribution)

Questions:
- What role to play?
- What standard to use?
  - Whether to make changes if study already approved elsewhere

Tensions:
- PIs may see the IRB as “overstepping” responsibilities
- IRBs may not consider costs to PIs
- RBs may not recognize these issues

Factors
IRB characteristics:
- How “pro research” the committee is
- Members/chairs are PIs

Is the science good enough? Assessing the Quality of Science
Are consent forms legal documents?

**Institutions**
- Often want legal contracts

**Industry Funders**
- Often want legal contracts

**Government Regulators**
- Standards unclear and subjective
  - When is enough enough?

**IRBs**
- Face challenges
  - Are forms legal contracts?
  - Whom do forms protect?
    - What if forms may cause harm?
    - What if forms cannot specify complete study
  - IRBs may feel powerless to improve forms
    - Blame others for long/complex forms
  - IRBs may further change a form over time
  - Whether consent is as a process vs. a form
  - Cost to IRBs increasing length

**Consent Forms**
- Inherent limitations
- Competing IRB goals
  - Reducing length
  - Simplifying language
  - Minimizing changes to avoid antagonizing

**Researchers**
- May minimize risks and maximize benefits to recruit participants
- May not have known patients beforehand

**Subjects**
- Need protection
- May be vulnerable/therapeutic misconceptions
- But may value trust
Variations between IRBs

- IRBs differ in their “colors” and “flavors”
- Vary from “nit-picky” to “user-friendly”
Locations of Variations

• Between IRBs
• Within a single institution
• Within a single IRB
• Within a single member
Causes of Variations

- Occasional perceived differences due to type of community (e.g., rural vs. urban)
  - Related to sexual issues (“other IRBs may be more prudish, and have trouble with HIV prevention studies among gay men, but we don’t”)
  - But very rare
- Differences that arise do not appear to reflect differences in values concerning research ethics
- Differences tend to concern procedural definitions, not community values
Causes of Variations

- Institutional differences
  - Types of studies the IRB has reviewed in the past
  - Past federal audits/“shut downs” of research
  - Differences in research intensiveness/size of institution/reliance on indirect costs

- Individual differences
  - Chairs and members make subjective interpretations
    - Rely on “gut feelings”, “intuition”, “sniff test”
    - Anxiety vs. psychological “comfort” (”peace of mind”)
    - Idiosyncrasies (“temperament”, “pet peeves”, “prudishness”)
    - “Nit-picky” vs. “user-friendly”/”pro-research”
    - “Good catches”: Effects of “many eyes seeing a protocol
Defending Variations

• Justifying differences
  • “Simply interpreting the regulations”
• A few acknowledge “minor differences”
  • As “fine-tuning”
• But differences are often greater
RELATIONSHIPS WITH RESEARCHERS
Do IRBs Have Power?

• Power of chair and the IRB in the institution can vary

• Critical questions:
  • How much power do and should IRBs have?
    • What do these questions mean?
    • Who should decide?
    • Are IRBs the police, judge and jury?
IRB Perceptions of Their Power

• IRBs as having power
  • IRBs may acknowledge that PIs see them as having power
    • But may not acknowledge its full extent
  • IRBs may feel it is legitimate
    • It is based on overriding goals
    • They are trying to help PIs
  • IRBs may see problems but accept these as inevitable
  • IRBs may feel it is small because:
    • It’s based on “the community’s values”
    • But it may be based instead on institutional and/or personality factors.

• IRBs as not having power because:
  • They are “merely following the regulations”
  • They are themselves subject to higher administrative agencies
  • Their process is impersonal and not biased
  • Their process is “open”

IRBs’ Perception of PIs’ Views

• PIs may misperceive IRBs
• PIs may unfairly blame/inappropriately scapegoat IRBs
• IRBs cannot always publically respond to PI accusations
• PI claims that IRBs have power may not be fully valid
“OPEN DOORS”?: IRBS’ RESPONSES TO TENSIONS WITH PIS

FORMS AND CONTENTS OF INTERACTIONS

• Protocol Reviews
  • IRBs vary in reviewer anonymity
  • Anonymity can reduce conflicts but make IRB seem a “faceless bureaucracy”

• IRB Meetings
  • Vary in whether PIs are invited and/or encouraged to attend
  • Presence of PIs can improve PI cooperation, but reduce candor in meetings

• Memos to PIs
  • Range in tone and content (“Using Southern Charm” vs. more bureaucratic).
  • More helpful memos can improve PI cooperation, but take more time
• PI Outreach Education
  • Varies in extent
  • Can improve PI cooperation, but take time and resources

• Toward best practices?
  • More “openness” and accessibility
Added challenges: Emerging economies:

Logistical Challenges

- Developing World
  - IRBs/RECs
    - Quality of IRBs varies
    - Less resources
    - Less training
  - Health system
    - More corruption

- US
  - IRBs’ low knowledge of:
    - Local context
    - Local regulations
    - Standard of care
  - Local views of ethical issues
    - Different views of autonomy
    - Different risks/benefits of daily life
  - But how much such knowledge is enough?
  - IRBs have difficulty knowing when they understand other cultures
Added challenges: Emerging economies: Ethical Dilemmas for US IRBs

- How to interpret principles?
- How much to pay subjects?
- How much sustainability?
- Higher standards?
Added Challenges: Emerging economies

Responses:

**Structural**
- Capacity building of overseas IRBs
- Monitoring IRBs
  - Not always welcome
- Infrastructure changes?
- Communicate more w/ local IRBs?
- Negotiating compromises
- Needs for more communication
  - IRBs communicate poorly in part because they do so via PIs
Possible Federal Changes:
Views of Local IRBs Regarding CIRB Reviews

Perceived Problems and Ambivalence Concerning CIRBs
• General wariness of CIRBs, and support for local IRBs

Perceived Advantages of Local IRBs
• Claims that local IRBs reflect community values
• Local knowledge of subjects
• Local knowledge of PIs
  • “Track records”/reputations
• Protecting “our own” subjects
• “Curbside consults” with PIs
• Desires for local autonomy, authority, and comfort
  • Against “being told what to do”
  • Wariness of centralized, federal bureaucracy
Perceived Problems with CIRBs

• Differences between CIRBs
  • Depends on who are members of the committee
• For-profit CIRBs may have conflicts of interest

Advantages of CIRBs

• Rarely acknowledged
• Streamlining work/Saving Time

Local Members as Biased in Their Views of CIRBs?

Other Possible Solutions

• More regional IRBs?
CONCLUSIONS
Possible changes to improve subject protection:

**Federal level:**

- Centralization?
  - May offer several advantages and disadvantages
- Future of other proposals in the NPRM?
  - Different rules for social science research?
  - Excuse certain minimal risk research?
    - But will PIs have COIs in making these determinations?
Other federal changes:

- More guidance and consensus
  - From OHRP, IOM, and/or others
- More case law/open, published precedents to establish consensus
  - Proprietary information can be redacted
- More consensus concerning areas where difficulties now arise
  - e.g., Is allergy skin testing minimal risk?
- Publishing decisions
  - Minutes or other summaries with proprietary information redacted
  - Similar to case law?
- External appeals process
• More regionalization?
• More external (unaffiliated and non-scientific) members
• Improved informed consent
  • Shorter summary documents to accompany longer forms
  • Yet many details need to be addressed
• Training of IRB personnel, using protocols about which consensus has been reached
  • Is this informed consent “good enough”?
  • Is the quality of the science of this protocol “good enough”?
• Will meet resistance
  • How then to proceed?
Institutional level:

- More resources
  - Compensating members
- Well-trained staff could make independent decisions about key issues
- Providing appropriate compensations to IRB members
Changes needed among BOTH IRBs and PIs

• IRBs and PIs would benefit from more fully understanding:
  • These tensions
  • The underlying causes
IRB Level: Needs for attitudinal changes

• Improving relationships with PIs
  • Better PR
    • Publicizing the benefits of IRBs
  • Some IRBs may misperceive PI complaints
• Increased recognition of:
  • Ambiguous nature of regulations
• Roles of interpretations
  • Acknowledgement of discretionary power?
• Costs of variations
IRB Level:

- More transparency
  - Open doors
- Establishing institutional memory and a body of “case law”
- More and different training
  - Reaching consensus and standardization on definitions, interpretations, and applications of key terms and principles
    - Testing to demonstrate adherence to these standards
- Willingness to be studied
- Sharing “best practices”
  - LISTSERVs
  - National or regional meetings
    - Not always attended
Researcher Level: Needs for change, too

- Changing attitudes
- May misperceive IRBs
- Enhancing understandings Not “blaming the messenger”
- Avoiding inattentive and sloppy submissions to the IRBs
Public level

- Enhancing public education
- Enhancing media understandings
- Larger social/political questions:
  - How much should scientists be overseen?
Future research

• IRBs should be far more open enough to being studied
  • Many IRBs feel that they have nothing to gain
    • But that is incorrect
  • Some IRBs have required informed consent from all members
Broader implications

• How ethical principles get interpreted and applied differently in different settings
• How much of power is in the eyes of the beholder?
• Needs for more humanistic approaches
QUESTIONS?
Robert Klitzman, MD

Professor of Psychiatry
Director, Masters of Bioethics Program
Columbia University

Phone: (646) 774-6912
E-mail: rlk2@cumc.columbia.edu