Protection, Over-Protection, and Pseudo Protection

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May, 2012

Disclaimer

- The views expressed in this talk are my own. They do not necessarily – in fact they probably do not – represent the views of the National Institutes of Health or the Department of Health and Human Services
- Some of these views are based on work with Frank Miller

Background

- Current approach to research regulation and research ethics in the U.S. took shape between 1966 and 1981.
- In 1966, NIH began to require independent review and written informed consent
- Major impetus was series of examples of abusive clinical research
Background

• These reforms have played central role in protecting rights and well-being of subjects
• We actually don’t know how much abusive research is prevented or deterred by this system or whether the benefits justify the costs
• Will bracket such issues

But

• The institutional structure of independent review committees
• And cadre of professionals who compose, staff, and provide ethical guidance for these committees
• Has led to what I call protectionism

Protectionism

• Judgments or policy guidance that restricts design or conduct of human research that are motivated by the aim of protecting research subjects but which:
  – Goes beyond what is necessary for legitimate protection (over-protection)
  – Or, perversely, are contrary to interests of research subjects (pseudo-protection)
Over-Protection
• When IRBs prevent people from participating in scientifically valid and socially valuable research that involves some net risks
• But where prospective subjects might reasonably consent to participate for altruistic or other reasons

Pseudo-Protection
• IRBs prevent prospective subjects from participating in research when participation would actually advance their well-being, all things considered, because subjects receive medical or financial benefits that more than compensate them for the medical risks

Three Aims
• Define and illustrate distinction between legitimate protection, over-protection, and pseudo-protection (the latter will be more fully explored in next talk)
• Offer some hypotheses as to what gives rise to and sustains over-protection and pseudo-protection
• Hope that this will help in discouraging IRBs from endorsing positions that restrict socially valuable research for reasons not grounded in legitimate subject protection
Legitimate Protection

- Two central features of current approach are:
- (1) Before subjects can be asked to consent, there must be a prior determination that "risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result" 45CFR46
- (2) valid informed consent

After all

- We can ask: why not leave things to investigators and subjects (perhaps with monitoring of consent process)?
- Simply insisting on valid informed consent would have prevented most or all of the standard examples of abusive research
- Seems most consistent with respect for autonomy

And . . .

- IRB review exercises power over prospective subjects by deciding which protocols they can enter
- Is that not a violation of autonomy and a failure to respect persons?
- Isn’t that paternalism?
Autonomy

• “An autonomous person is an individual capable of deliberation about personal goals...”
• “To respect autonomy is to give weight to autonomous persons' considered opinions and choices...” (Belmont Report)

Consent and Assent

• Just as pediatric research requires informed consent of parent and assent of child
• Research with adults requires informed consent of IRB and functional equivalent of assent of subject
• The relationship is structurally identical

My position

• Prior review is paternalistic at its core
• Deal with it
• Such paternalism is often justifiable
Why the avoidance?

• Paternalism is negatively valenced in the United States
• We do not want to confront the obvious tension between the avowed respect for autonomy and support for a system that might be thought to convey a lack of respect for the judgment of prospective subjects.
• Autonomy is one of the core canonical values of bioethics and research ethics

The Concept of Paternalism

• We needn’t get too precise
• Apparent violation of a moral norm to promote agent’s interests
• Usually but not always involves interference
  – Requiring someone to do something
  – Preventing someone from doing something
  – Deception
  – Withholding information

Some Distinctions

• Direct and Indirect
• Soft and Hard
• Individual and Group
Direct and Indirect Paternalism

- Direct Paternalism
  - Seat Belts, Helmets
- Indirect Paternalism (Not permitting consensual agreements)
- In other words, foreclosing opportunities
  - Habitability Statutes, FDA
- FDA restricts manufacturers for the benefit of consumers

Soft and Hard

- Soft paternalism: restricting the freedom of persons whose decision-making is defective
- Hard paternalism involves restricting the freedom of persons who are substantially autonomous and whose decision-making is not defective.
- Soft paternalism: decision-maker’s understanding and appreciation of facts
- Hard paternalism: decision-maker’s values

Soft and Hard

- It is easier to justify soft paternalism
  - Doesn’t violate autonomy
- Some think that hard paternalism is never justifiable
  - Climbing Mt Everest
  - Refusing blood transfusion
Varieties of Soft Paternalism

- Status Soft Paternalism
  - Children, demented
- Decisional Soft Paternalism: Competent Adults
  - Mill’s Bridge Example
  - Psychotherapy
  - Subjects with insufficient expertise

Defects in Decision Making

- mistaken (or inadequate) factual beliefs (e.g., what one thinks is sugar is actually poison)
- inadequate information
- substantially impaired cognitive functioning
- impulsiveness
- lack of self-control or weakness of will
- distortions of judgment or appreciation relating to risks of harm
- vulnerability to power or authority.

Individual and Group

- Individual soft paternalism: interference is targeted at specific individual
- Group soft paternalism (GSP): policies targeted at groups, some of whom are not impaired
  - Prescription drugs
  - Some can safely self-medicate
  - Not feasible to distinguish those who can from those who can’t
  - So we restrict all
IRBs and GSP

- Interventions by IRBs are of low visibility
- In some cases protocols are disapproved or modified
- In other cases, protocols are never proposed
- Limitations on financial benefit
- Potential subjects may never know that their options have been limited by IRBs

IRBs and GSP

- Structure and operation of research regulation system is best understood as GSP
- Not claiming that IRB members should be consciously motivated by paternalism
- Rather, the reasonable risk criterion that IRBs are asked to apply is rooted in group soft paternalism
- May also apply to intense screening of consent process
- This is legitimate subject protection

But
Over-Protection

• IRBs engage in over-protection when they prevent people from participating in scientifically valid and socially valuable research that involves net risks
• But where prospective subjects might reasonably consent to participate for altruistic or other reasons

Over-Protection

• Common Rule places NO de jure limits on the level of risks so long as they are reasonable in relation to anticipated benefits and so long as subjects give valid consent
• De facto, it is likely that many IRBs go beyond this and put sharp limits on net risks that subjects may be asked to accept

Over-Protection

• Possible such limits may be ethically justified even if not required by law
• But they may give insufficient moral weight to value of research
• And may fail to respect autonomy of prospective subjects, i.e. hard paternalism
Examples of Over-Protection

– Excessively low tolerance for research risks
– Prohibiting net risks in treatment or control interventions in RCTs
– Applying standards of oversight appropriate to medical research to quality improvement, observational data collection
– Requiring lengthy consent documents
– Mandating a plethora of consent options for future use of stored samples
– Excessive rigor with respect to social and behavioral research that poses minimal risks

Over-Protection and Non-Events

• Very difficult to observe costs of over-protection
• Research that is never submitted or contemplated because researchers (or prospective researchers) believe their proposals will be rejected or because they decide that it’s not worth the hassle

Equipoise

• Standard ethical guidance for RCTs requires state of uncertainty in the professional clinical community about relative merits of treatment and control intervention
  – “The benefits, risk, burdens, and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods” (Declaration of Helsinki)
Equipoise

- Receives support from applying model of medical care to research: no patient-subject should be randomized to treatment believed to be inferior
- Rules out placebo-controlled trials whenever proven effective treatments are available

Equipoise

- Needlessly prohibits socially valuable RCTs that expose participants to net risks
  - Depression
  - Anxiety
  - Arthritis
  - Low back pain

Equipoise

- Placebo controlled trials are valuable to obtain rigorous efficacy in conditions with subjective outcomes and high rates of placebo response
- Active controled equivalence or non-inferiority studies suffer from serious methodological problems
Equipoise

• No general ethical requirement to protect subjects from known net risks of harm
• Even proponents of equipoise accept exposing patient-subjects to nontherapeutic procedures, e.g. biopsies, blood draws, lumbar punctures

Equipoise

• View that net risks are legitimate for non-therapeutic procedures but illegitimate for control interventions is incoherent
• No reason to prohibit treatment or control interventions that carry net risks if
  – (1) risks are not excessive
  – (2) justified by potential value of knowledge
  – (3) subjects could reasonably consent to accept those risks

Equipoise

• Why would a patient-subject would consent to participate in a net-risk study when they could assure themselves of standard of care without research-related procedures?
  – Altruism
  – Access to experimental treatment not otherwise available
  – Post-trial benefits
  – Payment
Equipoise

- If subjects would join a non-equipoise study only if they were making mistaken judgments about risks and benefits of participation, then soft-paternalistic rationale would kick in.
- But if subjects could reasonably choose to participate, then IRBs should approve such research so long as there is a process for obtaining valid consent.

From Over-Protection to Pseudo-Protection

Pseudo-Protection

- When IRBs are motivated by the aim of protecting subjects from harm but when they disallow studies in which subjects would actually benefit from participation.
- Prospective subjects may reasonably believe there are compensating benefits to them such as access to medical care, medical screening, or payment.
Pseudo-Protection

• Where a substantial proportion of the population lacks health insurance, some patients may be motivated to enroll in placebo-controlled trials or non-equipoise trials in order to get access to treatment that would not otherwise be available.
• Such objections confuse justifiable concerns about the background conditions that makes it reasonable for people to participate in research as a means of getting medical care with objections to allowing them to do so.

Pseudo-Protection

• IRBs seem to exhibit an ethical worry that offers of payment are coercive or constitute undue influence.
• Anecdotal evidence suggests that IRBs frequently accept (and, we assume, sometimes apply) mistaken interpretations of these concepts to the detriment of prospective subjects
• Now we have data

Pseudo-Protection

• Will say more in panel to follow about these misconceptions
• Will assert for now that offers of payment are never coercive and constitute undue influence only if they distort subject’s evaluation of risks and benefits
• IRBs adopt conceptions of coercion and undue influence that are not used in other contexts, e.g. employment
Sources of Protectionism

- Over-protection and pseudo-protection is natural although undesirable outgrowth of institutional system developed for the regulation of human subjects research
- Because pseudo-protection is not protection at all, I set it aside

Sources of Protectionism

- IRBs and ethical guidance can err in two different ways (1) under-protection of subjects and (2) over-protection of subjects.
- The institutional “logic” of IRBs promotes much greater concern for the former error than for the latter.
  - better that ten worthy and non-dangerous protocols be disapproved or amended than that one subject not be adequately protected.

Sources of Protectionism

- False positives (where IRBs approve studies that should be rejected) produce visible signs of failure to protect identifiable subjects that result in public attention to research harms
- By contrast, when studies are inappropriately disapproved or modified (false negatives), the negative consequences for statistical lives in foregone scientific research are relatively invisible
Sources of Protectionism

• The “March of Dimes Phenomenon.”
• March of Dimes Foundation was formed to support treatment and research for polio.
• When Foundation-supported research led to a vaccine that effectively eliminated its raison d’être, the organization did not declare victory and disband.
• Rather, the Foundation changed its focus from polio to birth defects.

Sources of Protectionism

• So long as the organization continued to do important and necessary work, there is nothing untoward about the change of mission.
• But if organizational survival depends on an excessively expansionary view of the organization’s mission, then we have something to worry about.
• IRBs should be prepared to recognize that – as with all organizations – they, too, are vulnerable to expansionary tendencies.

Sources of Protectionism

• The organizational imperative of IRBs is reinforced by the imperatives of organizations, such as Public Responsibility in Medicine and Research (PRIM&R) that provide education, training, and certification for IRB members and administrators.
• These organizations understandably stress the importance and complexity of IRB activity and are constantly on the lookout for new problems and forms of research that require the protection of subjects.
Sources of Protectionism

• Bioethicists are in the business of detecting ethical problems in research and are prone to discover or declare more problems with research than to declare that the process is working reasonably well to prevent and deter abusive research.

Sources of Protectionism

• We should all recognize that our positions and decisions often reflect our desire to signal our concerns to others.
• Bumper stickers
• The Toyota Prius and the Honda Civic Hybrid
• IRB members may sometimes engage in over-protection or pseudo-protection to signal their moral concerns for the well-being of research subjects even when such restrictions actually work to the detriment of subjects or fails to respect their autonomy.

Conclusion

• Independent review and oversight of clinical research is a vital component of research ethics and regulation because prospective research subjects as a class are sometimes not well positioned to protect their interests solely by means of consent.
• Nonetheless, this process brings with it the potential for protectionism—restrictions on research aimed at subject protection but which are not justified by subject protection.
Conclusion

• In service of permitting ethical clinical research, IRBs should strive to avoid over-protection and pseudo-protection.
• IRBs should stand back from their important and hard work to reflect on the organizational and personal motivations that lead them to err on the side of protectionism.