

# Recruitment for Clinical Research

**Ensuring the rights and welfare of participants  
while encouraging research enrollment**

Benjamin S. Wilfond MD

Co-Director, Regulatory Support and Bioethics Core, Institute of Translational Health Sciences

Director, Treuman Katz Center for Pediatric Bioethics, Seattle Children's Hospital

Professor and Head, Division of Bioethics, Department of Pediatrics, University of Washington



UW Medicine  
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Treuman Katz Center  
for Pediatric Bioethics

# The ethical dilemma of clinical research

- Research can unfairly take advantage of research participants
  - The risks of research accrue to
    - Participants
    - Families
    - Communities
  - The benefits of research accrue to
    - Society
    - Future patients
    - Researchers
    - Research sponsor and institutions
- “Informed consent” is a central protection
  - Other considerations are also important
- Recruitment is often overshadowed by informed consent
  - Raises complex questions with ambiguous answers
  - Related to informed consent but distinct

# Smoking cessation during pregnancy

- Randomized study of two behavioral interventions that might help pregnant women quit smoking
  - \$100 for eight week study
- Obstetrician who is PI recommends study to her patients
  - Interested patients speak with study coordinator who reviews study in more detail and then enrolls willing patients
- A patient who declines enrollment with study coordinator
  - Returns for later visit with OB
  - Requests enrollment in the study
- Is it ethically acceptable for the OB to give this patient the consent form, have her sign the form, and enroll her in the study?

# Recruitment

The process of getting people to join a study

- Selecting a population
  - Fairness of population
  - Privacy
- Reaching the population
  - Deciding how to announce the study
    - Letters, phone calls, brochures, in person
  - Deciding who will announce the study
    - Clinician, researcher, study coordinator, family member, community member
- Describing the study
  - Balanced information
- Motivating interest
  - Selecting strategies that promote enrollment
- “Informed consent”

# Ethical questions about recruitment

- Should clinicians recommend that their patients participate in studies?
- Should families and communities encourage participation in studies?
- Should clinicians enroll their patients in their own studies?
- Should study coordinators encourage participation in studies?
- Should research centers be offered incentives to recruit or be penalized for poor recruitment by research sponsors?
- Should research participants be paid to be in studies?

# Yes, but there are ethical concerns about recruitment

- Coercion
- Undue Influences
  - Payment
- Pressures
  - Manipulation and Persuasion
- Exploitation
- Conflict of interest
  - Increases the likelihood of the other ethical concerns

# Decision making about research

## Informed Consent and Recruitment

- Decisional Capacity
- Disclosure
- Comprehension
- Voluntariness

(Faden and Beauchamp 1986)

# Coercion

- “An investigator shall seek such consent only under circumstances that provide the prospective subject or their representatives have sufficient opportunity to consider whether or not to participate and that minimize the possibility of *coercion or undue influence*.”
  - 45 CFR 46, 116
- “Payment to research subjects for participation in studies is not considered a benefit, it is a recruitment incentive... The IRB should review both the amount of payment and the proposed method and timing of disbursement to assure that neither are *coercive or present undue influence*.”
  - FDA Information Sheets, 1998



# Coercion

## Offer vs. Threat

- Offers increase opportunities
- Threats decrease opportunities
- To be coercive, a participant who refuses must be made worse off than if he or she would have been if never asked
  - Lack of coercion is not sufficient for study approach to ethically acceptable
  - Perception of threats are also relevant

# Coercion in Clinical Research

- Patients might perceive that they will lose care by clinician if they do not participate in research
  - Is a clear statement in a consent form enough?
  - Limited data about such perceptions
- IRB review and institutional culture may help reduce this perception
  - However, there are some contexts where participation in research is necessary to receive “care”
- Separating research from clinical activities can help
  - May not always be feasible or even ideal in some contexts
- Concerns about coercion may be about influences

# Influences

- Offers to get people to agree to do things they otherwise might not do
  - Open a bank account and get a toaster
  - Offering overtime pay for extra work
- Influences are routine and only problematic if they are “undue”

# Undue inducements

- “An offer one could not refuse is essentially coercive (or "undue"). Undue inducements may be troublesome because: (1) offers that are too attractive may blind prospective subjects to the risks or impair their ability to exercise proper judgment; and (2) they may prompt subjects to lie or conceal information that, if known, would disqualify them from enrolling -- or continuing -- as participants in a research project.”
  - Office of Human Research Protection. *IRB Guidebook*.
- The concern about undue inducements is about
  - Overestimating the potential for short term gains and discounting long term risks in decision making
    - Risky jobs

# Undue inducement in research

- IRBs can reduce this potential by
  - not approving very risky studies where distorted decisions would be important
  - insuring accurate descriptions of benefits and risks
- Other Inducements
  - Ancillary care to participants
  - Benefits to communities
  - Payment
- Not providing adequate inducements can be exploitive

# Financial inducements

**TABLE 1.** THE THREE MODELS OF REIMBURSEMENT AND THEIR APPLICATIONS TO A HYPOTHETICAL CASE.

VARIABLE	MARKET MODEL	WAGE-PAYMENT MODEL	REIMBURSEMENT MODEL
Justification for payment	Recruitment of subjects is vital to research; monetary incentives help to recruit the needed subject pool.	Participation in research requires little skill but takes time and effort and requires endurance of uncomfortable procedures.	Participation in research should not require financial sacrifice by subjects.
Function of payment	Incentive.	Working wage.	Reimbursement for expenses.
Strategy	Payment is based on supply and demand; completion bonuses and other incentives for completing the study are used.	Payment is based on standard wage for unskilled labor; payment is augmented for particularly uncomfortable procedures.	Payment is determined by subject's expenses and can include payment for lost wages or other expenses incurred.
Components of payment	\$25/hr, \$200 for taking medicine, and \$200 completion bonus.	\$10/hour, \$50 for following the drug schedule, and \$50 for serial blood collection.*	Different for every subject.
Total payment	\$1,125.	\$390.	\$195 (with no wage); \$398 (with student's wage); \$1,645 (with professor's wage).

\*Data are from the Department of Labor, 1998.<sup>18</sup>

Dickert and Grady, NEJM 1999

# Payment

- Payment is less of a concern if risks are not excessive
  - Pediatric regulations further limit risk
- Clearly signals that research is not the same as clinical care
  - Doctors don't pay patients to routine care
- Payment can demonstrate respect

# Manipulation and Persuasion

- Both are approaches to influencing decisions
  - Distinguished by the degree of “pressure” or “control” over the decision
  - Manipulated decision
    - Diminished voluntariness because of “control”
    - Extreme manipulation is “coercion”
- Persuasion is based on reasons and arguments
  - Appealing to altruism
  - As appeals become more emotional, they may be more controlling
  - Advertising that distorts information can reduce comprehension and thus, be controlling

Faden and Beauchamp, 1986



# Exploitation

- Opposite problem of coercion and influence
  - Making an offer that takes advantage of situation so that exchange is not fair
  - Paying too little
- Greater concern in research than coercion
  - Society and researcher benefit
  - Participants may not benefit and can get hurt or just “taken advantage”

# Conflict of Interests

- Primary interest conflicts with secondary interests
  - Financial, academic, relational
  - Can motivate controlling influences or exploitation
- Ubiquitous and not avoidable
  - In clinical medical settings and education
    - Disclosure is necessary but not sufficient
- Requires conscious attention
  - Person may not be aware of potential influence
- Personal and institutional integrity is necessary to manage conflicts

## When does the recruitment approach become more concerning?

- If the study is particularly risky
- If a study is being offered as a “treatment”
- If benefits are overstated or risks are understated
  - When participants have distorted understanding
  - Conflicting interests may result in unintentional distortion of what is presented to participants
- If the research and clinical roles are not distinct

# Primary objectives are different

- Clinical Care
  - Improve patients' health
- Clinical Research
  - Improve scientific knowledge that will benefit society

## Care and Research as a Continuum: Therapeutic Orientation to Clinical Research

“The practice of medicine is in effect the conduct of clinical research...Every practicing physician conducts clinical trials daily as he is seeing patients. The research discipline of the ‘clinical trials’ is the formalization of this daily process”

# Unique ethical constructs have emerged from the therapeutic orientation

- Equipoise
  - A state of genuine uncertainty on the part of the clinical investigator regarding comparative therapeutic approaches (R. Levine 1979)
  - Two key requirements
    - Honest null hypothesis
    - Therapeutic obligation to patient-subject to always recommend superior treatment
- Clinical equipoise
  - A state of genuine uncertainty within the expert medical community (not necessarily individual investigator) about preferred treatment (B. Freedman 1987)
- Therapeutic misconception
  - Patient-subject confuse provision of treatment within randomized trials with patient-centered therapy of standard medical care ( P. Appelbaum 1982)

# Separating Care and Research

## Distinguishing the Ethics of Clinical Research from Ethics of Medical Care

- Therapeutic orientation to clinical trials fosters the therapeutic misconception for both physician and patient-subject
- Miller argues that an ethical justification for research distinct from medical care is necessary (F. Miller 2003)
  - “The good reasons to conduct research without the therapeutic orientation of medical care are not trumped by what physicians owe patient-subjects”
- Emanuel’s eight ethical benchmarks of clinical research can ethically justify clinical research as a separate entity from care
  - Recognizes autonomy of patients to make rational decision about research participation
  - Recognizes importance of furthering generalizable medical knowledge

# 8 Ethical Benchmarks

1. Collaborative Partnership
2. Social Value
3. Scientific Validity
4. Fair Subject Selection
5. Favorable Risk-Benefit Ratio
6. Independent Review
7. Informed Consent
8. Respect for Human Subjects

Emanuel et al. (2000) *JAMA*; (2004) *J Infect Dis*



# Clinicians and researchers

- Clinicians and researchers can be more explicit about their goals when roles are distinct
  - Clinicians can recommend research participation to patients
  - Researchers can encourage study participation
- When the clinician and researcher is the same person this becomes more complex
  - Roles must be balanced
  - Conflicts must be managed

# Dual roles

- Patients may not be clear what “hat” is being worn
- Dual roles most concerning when
  - Research is presented as a therapeutic alternative
  - Condition is serious and/or new
  - Research risks are significant
- Dual roles most necessary when condition is
  - Rare or serious condition
  - Requires specialty care where research is integrated
- Dual-role extends beyond recruitment
  - Can researchers also provide care once in the study?
    - Convenient for participant
    - Researcher obligations to provide care

# Minimizing impact of the dual role

- Study coordinators
- Independent assessment of comprehension and voluntariness

# Study Coordinators

- Study coordinators have multiple obligations
- Balancing advocacies
  - Patient advocacy
  - Subject advocacy
  - Study advocacy

*Davis, Hull, Grady, Wilfond, and Henderson. JLME 2002*

# Advocacies and Relationships

	<b>Patient Advocate</b>	<b>Subject Advocate</b>	<b>Study Advocate</b>
<b>Primary Commitment</b>	Patient welfare	Rights and welfare of research subject	Gather valid clean data via good recruitment and retention
<b>Duration of Relationship</b>	Before, during and after	Before and during	Study specific
<b>Metaphors</b>	“Mothering” “Taking care of”	“Lawyer”	“Policeman of the protocol” “Teacher”

# Representative Quotes

## Patient Advocate

“One of the major roles [in research] is patient advocate, and I don’t think you can divorce yourself from that because you’re doing research...”

## Subject Advocate

“I always approach people from an objective point of view and ...[give] them all the facts and then let them collaborate with us...just being crystal clear ...that there are good and bad points to being in a study...”

## Study Advocate

“Once you make the decision that you like the protocol, you think there is some value here...then you have a commitment to [it]...you need to be in a position to defend it honestly and comfortably.”

# Conclusion

- Be clear about the distinct objectives and ethical framework for research
  - Encourage research participation
- Respect participants
  - Promote comprehension
  - Respect decisions to not participate
- Team approach
  - Can allow staff to “trade roles”
  - Check the mirror to see what hat you are wearing

# ITHS Research Bioethics Consultations

- For researchers, participants, IRBs, others
- Written report can be provided if appropriate
  - [rsbcore@u.washington.edu](mailto:rsbcore@u.washington.edu) or page research bioethicist on call (206) 987-2000 (Six faculty rotate “call”)
- Advisory and Supplemental to IRB
  - Questions that could benefit from in-depth conversation and analysis about ethical issues related clinical and translational research studies

## *Study Development*

Study design  
Recruitment  
Participant selection  
Community engagement  
Informed consent  
Research collaborations

## *Study Implementation*

Informed consent concerns  
decisional capacity  
comprehension  
voluntariness  
Withdrawal from research  
Ancillary care obligations

## *Study Analysis*

Data sharing  
Results disclosure  
Confidentiality in publication  
Collaborative relationships



## ITHS Clinical Research Education Series – Future Talks

- **Tuesday, May 5<sup>th</sup> at 12pm** – *How to Write and Use a Protocol* presented by Carol Wallace, MD, Professor, Pediatric Rheumatology, Seattle Children's
- **Tuesday, June 2<sup>nd</sup> at 12pm** – *The IND/IDE Development Process* presented by Lynne Rose, PhD, Assoc. Professor, Pediatrics, Director, Clinical Operations, Cystic Fibrosis TDN Coordinating Center, Seattle Children's