Outcome Unknown:

The Ethics and Mechanics of Informed Consent in Research Involving Genomics, Questionable Pre-clinical Results, and the Risk of Death

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Agenda

- The Current and Revised Common Rule framework for obtaining Informed Consent
- Ethics of obtaining informed consent for research that involves the unknown and currently unknowable, including genomic research, future undefined research, significant risk studies involving death as a risk
- Case study: When a healthy volunteer died in a European clinical trial for a new FAAH Inhibitor pain and mood disorder medication, the Temporary Specialist Scientific Committee's call for further clarification regarding use of healthy volunteers in light of troubling animal study results

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Background

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Hippocratic Oath

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- "I will come for the benefit of the sick"
- "I will keep them from harm and injustice"
- Note: "Above all, do no harm" is not in the actual "Oath" but in a later Hippocratic document

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Nuremberg Trial

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Nuremberg Code

- Consent of the human subject is absolutely essential; free from force…with sufficient knowledge and understanding
- The degree of risk should never exceed that determined by the humanitarian importance of the problem to be researched
- Results sought must be unprocurable by other…means
- All unnecessary physical and mental suffering and injury should be avoided

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Nuremberg Code

- Designed on the basis of animal experimentation
- Conducted only by scientifically qualified persons.
- The human subject can withdraw at any time
- Researchers should be prepared to terminate the study if…continuation is likely to result in injury, disability, or death

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Tuskegee

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- Observed but did not “treat” syphilis
- Not even after 1947 with the advent of penicillin

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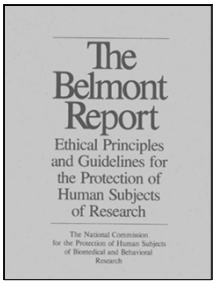
The Belmont Report (1979)



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Belmont Report

- Respect for Persons
- Beneficence (maximize possible benefits, minimize possible harms; proceed only with a “favorable risk/benefit ratio”)
- Justice (several different precepts to consider)
- Non-Maleficence implicit?

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World Medical Association's Declaration of Helsinki

- Ethical Principles for Clinical Research with Human Beings
- Revisions: 1964, 1975…. 2013 (7th)
- Recent revisions concern: use of placebo, post-trial access

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Beauchamp & Childress, Principles of Biomedical Ethics

- Revised: 1979, 1989, 1994…2013
- Emphasizes four principles (Autonomy, Non-Maleficence, Beneficence, Justice)
- Four Principles approach may not be the last word
- But provides a provisional set of moral sign-posts that may then be refined and/or extended

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But conduct may be ethically unacceptable without being contrary to all four considerations at the same time. For example—

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A simple research dilemma:

- A doctor, interested in research, has a patient with a serious, though treatable, condition. But instead of helping the patient, the doctor decides to let the condition "naturally progress" to a more advanced stage.
- The patient trusts the doctor and believes that the doctor must be doing what is necessary to promote the patient's health.
- The doctor knows that the patient believes this. But the doctor says nothing to explain the true nature of what he is doing.

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The Common Rule

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The Common Rule

The Federal Policy for Protection of Human Subjects

- Original – 1991, adopted by 15 federal agencies/departments
- Built upon 1981 HHS regulations
- Followed the Nuremberg Code (Nuremberg trials after WWII), the Declaration of Helsinki (World Medical Association 1964), and the Belmont Report (U.S. 1979)

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Purpose of the Common Rule

To promote uniformity, understanding, and compliance with human subject protections and to create a uniform body of regulations across the federal departments and agencies

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Final Rule

Federal Policy for Protection of Human Subjects ("Final Rule") published in the Federal Register on January 19, 2017

- https://www.federalregister.gov/documents/2017/01/19/2017-01058/federal-policy-for-the-protection-of-human-subjects
- Changes take effect on July 19, 2018 (with some exceptions)

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Changes to Informed Consent

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Impact on Ethics of Research

What if the Changes to Informed Consent had been in effect…

when Premature infants were enrolled in the SUPPORT study?

at the beginning of the Tuskegee Syphilis Study?

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What Changed?

New requirements for the process and the documentation and new elements

- Meant to enhance the understanding of prospective subjects and their legally authorized representatives

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What Changed?

But the underlying principle is the same.

- Informed consent forms must still present and organize information with enough detail and in a way that facilitates a potential subject's understanding of why/why not he/she may want to participate in the clinical trial.
- In a large part, what is required will depend upon the nature of the research (potentially controversial research will require more).

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New Requirements

__.116(a)(4): The prospective subject or his/her legally authorized representative must be given:

1. the information that a "reasonable person" would want to have in order to make an informed decision whether to participate and
2. an opportunity to discuss that information (must have enough time and opportunity to ask questions and get answers).

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New Requirements

__.116(a)(5): requirements for the content, organization, and presentation of information

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New Requirements

__.116(a)(5)(i):

- Must begin with "a concise and focused presentation of the key information that is most likely to assist a prospective subject or legally authorized representative in understanding why one might or might not want to participate in the research" that is
- "organized and presented in a way that facilitates comprehension"

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New Requirements

__.116(a)(5)(ii): "Informed consent as a whole must present information in sufficient detail relating to the research, and must be organized and presented in a way that does not merely provide lists of isolated facts, but rather facilitates the prospective subject's or legally authorized representative's understanding of the reasons why one might or might not want to participate."

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New Requirements

Provide a brief description of 5 "factors" at the beginning of the process and template:

1. Consent is being sought and participation is voluntary;
2. The purposes of the research, expected duration of participation, and procedures to be followed;
3. The reasonably foreseeable risks and discomforts;
4. The benefits to the prospective subject/others may be reasonably expected from the research; and
5. Appropriate alternative procedures or courses of treatment that might be advantageous to the prospective subject.

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Elements of Informed Consent

Required Elements remain the same [__.116(b)(1)-(8)]:

1. A statement that the study involves research, an explanation of the research and its duration, a description of the procedures involved, and identification of which of those procedures are experimental;
2. A description of the reasonably foreseeable risks and discomforts;
3. A description of the potential benefits to the subject or others reasonably expected from the research;
4. A disclosure of the appropriate alternative procedures or courses of treatment;

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Elements of Informed Consent

5. Information concerning the confidentiality of subject records, compensation, and whether treatment for injuries will be provided;
6. Compensation or treatment in the event of a research related injury (adverse event);
7. Relevant contact information; and
8. Participation is voluntary and the participant may withdraw at any time without penalty/loss of benefits.

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Elements of Informed Consent

Situational Elements also remain the same [__.116(c)(1)-(6)]:

1. The procedure/treatment may involve risks that are currently unforeseeable to the subject, embryo, or fetus;
2. When the investigator may terminate the subject's enrollment;
3. The costs to the participant;

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The Elements of Informed Consent

4. The consequences for withdrawing and procedures for terminating participation;
5. Significant findings may arise that impact a subject's willingness to continue participating and these findings will be shared with the subject; and
6. The approximate number of subjects.

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New Elements

The Final Rule adds ***four additional elements regarding biospecimens*** when appropriate.

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New Elements

1. __.116(b)(9): a statement of either:
   - "that identifiers might be removed from the identifiable private information or identifiable biospecimens and that, after such removal, the information or biospecimens could be used for future research studies or distributed to another investigator for future research studies without additional informed consent from the subject or the legally authorized representative, if this might be a possibility"; OR
   - "that the subject's information or biospecimens collected as part of the research, even if identifiers are removed, will not be used or distributed for future research studies."

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New Elements

2. __.116(c)(7): a statement "[t]hat the subject's biospecimens (even if identifiers are removed) may be used for commercial profit and whether the subject will or will not share in this commercial profit"

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The Elements of Informed Consent

3. __.116(c)(8): a statement "[w]hether clinically relevant research results, including individual research results, will be disclosed to subjects, and if so, under what conditions"

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The Elements of Informed Consent

4. __.116(c)(9): a statement "whether the research will (if known) or might include whole genome sequencing (i.e., sequencing of a human genome or somatic specimen with the intent to generate the genome or exome sequence of that specimen"

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Impact on Ethics of Research Going Forward

Will the Changes to Informed Consent…

Expand Access to Research for Under-Served Communities?

Encourage More People of all Demographics to Enter Clinical Trials?

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Broad Consent

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Impact of Ethics on Research

What if Broad Consent had been in effect when…

Henrietta Lacks was diagnosed with cervical cancer?

When John Moore underwent treatment for hairy-cell leukemia at the Medical Center of the University of California at Los Angeles?

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Broad Consent for Secondary Research

The Final Rule gives researchers the option of obtaining ***broad consent*** from subjects to store, maintain, and use ***identifiable*** private information and biospecimens for unspecified future studies.

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Optional

Broad consent is ***never*** required.

- It is simply an option available.
- Researchers can still use nonidentified biospecimens, get consent, or get an IRB waiver for the specific study.

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All or Nothing

If a subject ***declines*** to give broad consent, then informed consent is required for ***every*** study using the subject's ***identifiable*** private information or ***identifiable*** biospecimens. It is not possible to get a waiver from the consent requirement if the subject declines to give broad consent. [__.116(f)(1)]

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What Is Covered?

Identifiable Biospecimen = "a biospecimen for which the identify of the subject is or may readily be ascertained by the investigator or associated with the biospecimen"

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What Is Covered?

Identifiable Private Information = "private information for which the identify of the subject is or may readily be ascertained by the investigator or associated with the information"

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Requirements

- Must meet general requirements for consent [__.116(a)(1)-(4) and (6)]:
  - legally effective consent;
  - sought under circumstances that provide "sufficient opportunity to discuss and consider whether or not to participate and "minimize the possibility of coercion or undue influence";
  - in language understandable to the subject/legally authorized representative;
  - provide "information that a reasonable person would want to have in order to make an informed decision whether to participate" and "an opportunity to discuss that information"; and
  - cannot include exculpatory language in which the subject/legally authorized representative waives or appears to waive any legal rights

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Requirements

- This means:
  - The consent should contain a description of the information and biospecimens that might be used and the types of institutions and individuals that might perform the research.
  - If the subjects are not told about the specifics of a future study, they must be told that their specimens may be used for research for which they have not provided consent.
  - If the proposed secondary research is objectionable or controversial, the description needs to be more detailed to meet the reasonable person standard.

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Plus Elements of Broad Consent

Instead of the elements of normal informed consent, there are different elements for broad consent [new subsection ___.116(d)]:

1. A description of any reasonably foreseeable risks or discomforts to the subject [(b)(2)];
2. A description of any benefits to the subject or others that may reasonably be expected from the research [(b)(3)];
3. A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained [(b)(5)];

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Elements

4. A statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled [(b)(8)];
5. If applicable, a statement that the subject's biospecimens (even if identifiers are removed) may be used for commercial profit and whether the subject may share in the commercial profit [(c)(7)];
6. If the research involves biospecimens, whether the research will (if known) or might include whole genome sequencing [(c)(9)];

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Elements

7. A general description of the types of research that may be conducted with sufficient detail to allow a reasonable person to decide whether to consent [(d)(2)];
8. A description of the identifiable private information or biospecimens that might be used, whether that information or biospecimen may be shared with other researchers, and the types of intuitions or investigators who may use the information or biospecimen [(d)(3)];
9. The length of time the information or biospecimens will be stored, used for research purposes, and maintained (can be indefinite) [(d)(4)];

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Elements

10. If it applies, a statement that the subjects will not be informed or specific research studies using the information or biospecimens, including a statement that the subjects may not have chosen to participate had they known the use [(d)(5)];
11. To the extent it applies, a statement that clinically relevant results will not be shared with subjects [(d)(6)]; and
12. Whom to contact concerning questions about the subjects' rights or harms from the research [(d)(7)].

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Then What?

Once broad consent is obtained, researchers can conduct secondary research using the identifiable private information or identifiable biospecimens if the IRB determines the proposed secondary research fits within the scope of the broad consent and is exempt.

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Exemptions

1. __.104(d)(7): exemption for storage and maintenance of identifiable private information or identifiable biospecimens for potential secondary research use IF the IRB conducts a limited IRB review and determines (from __.111(a)(8)):
   a. Broad consent was obtained in accordance with __.116(a)(1)-(4), (a)(6), and (d);
   b. Broad consent is appropriately documented or waiver of documentation is appropriate; and
   c. If there is a change made for research purposes in the way the identifiable private information or identifiable biospecimens are stored/maintained, there are adequate provisions to protect the subjects' privacy and to maintain the confidentiality of the data

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Exemptions

2. __.0104(d)(8): exemption for research involving the use of identifiable private information or identifiable biospecimens for secondary research use if:
   a. Broad consent that meets the requirements of __.116(a)(1)-(4), (a)(6), and (d);
   b. Documentation of informed consent or waiver of documentation;
   c. The IRB conducts a limited IRB review as required by __.111(a)(7) and determines that the research to be conducted is within the scope of the broad consent; and
   d. The investigator does not include returning individual results to subjects as part of the study plan

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Impact on Ethics of Research Going Forward

Will Broad Consent…

Expand Access to Research for Under-Served Communities?

Discourage Potential Subjects from Participating in Research?

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NOW Exempt

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What Changed?

The Final Rule adds four new categories of exempt activities that are not considered "research" for purposes of the Common Rule based upon the perceived risk.

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EXEMPT: Secondary Research Using Identifiable Private Information or Identifiable Biospecimens when:

a. The identifiable private information/identifiable biospecimens are publicly available;

b. The information is recorded by the investigator in a way that the identity of the subject cannot be readily ascertained directly or through identifiers, the investigator does not contact the subjects, and the investigator does not re-identify the subjects;

c. The research involves the collection and analysis of identifiable health information regulated by HIPAA for the purposes of health care operations, research, or public health activities and purposes as those terms are defined by HIPAA; and/or

d. The research is conduct by or on behalf of a federal department or agency using government-generated or –collected information obtained for nonresearch activities subject to federal privacy protections

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New Categories of Exempt Activities

3. Storage and maintenance for secondary research for which broad consent is required [__.104(d)(7)]

4. Secondary research for which broad consent is required [__.104(d)(8)]

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Impact of Ethics on Research Going Forward

Will the Exemption…

Undermine Confidence in the Research Community?

Lead to Medical Advances that Enhance the Perception of Clinical Research?

61

Beyond the Common Rule:
The Import of Basic Bioethical Considerations in Achieving Compliance in Human Subject Research

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Elements in an Ethical Decision-Making Process

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- Can clarify important features of research practice
- Highlight several challenges
- Respect for autonomy:
  - Calls for "informed consent"
  - Lay persons may have difficulty:
    - Understanding the research design
    - Fully appreciating the risks

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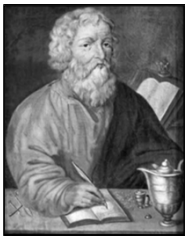
- Important to:
  - Benefit people
  - Avoid causing harm
    - Since Hippocrates (c. 460 – c. 370 BC):
      - "First, do no harm"
    - "Iatrogenic" harms can occur
      - Should be avoided



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- Experimental treatments may be risker than established therapies:
- With research:
  - Participants may not benefit
  - We must distinguish between research

  On the sick vs. the healthy
- But some research:
  - May be costlier in developing countries

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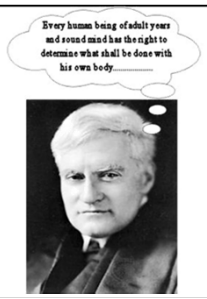
Law and Bioethics

Ethical concerns and principles have been codified into laws, and vice-versa:



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Law and Bioethics

- Ethical concerns and principles have been codified into laws, and visa-versa:
- Cardozo actually wrote:

- In the case at hand, the wrong complained of is not merely negligence. It is trespass. Every human being of adult years and sound mind has a right to determine what shall be done with his own body; and a surgeon who performs an operation without his patient's consent commits an assault, for which he is liable in damages.

- *Schloendorff v. Soc'y of N.Y. Hosp.*, 211 N.Y. 125, 129–30, 105 N.E. 92, 93 (1914)

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BUT WHAT DOES THIS HAVE TO DO WITH RESEARCH COMPLIANCE?

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Nuremberg Trial

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Law and Bioethics

- Ethical concerns and principles have been codified into laws
  - Federal Law: "The Common Rule" 45 C.F.R. 46
- Other, state laws regarding human subject protection
  - FDA regulations
  - Accreditation standards for hospitals
  - Professional Society Ethical Standards

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Law and Bioethics

- Laws must be followed
  - Rules based on utility vs. principle
- But often, they do not provide full guidance
  - Laws tell us what we legally must do, or must not do.
- Duty to rescue as an example
  - How should researchers manage situations that laws can not specifically address?

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How should researchers manage situations that laws can not specifically address?

- The law says researchers must inform participants about adverse events,
- But not what qualifies as an adverse event.
- Ethical rules guide conduct when the law is in conflict:
  - NIH rules vs. FDA rules
  - Consider the case of Jesse Gelsinger

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Ethical Challenges in R & D

- Therapeutic Misconception (TM)
- Equipoise / Standard of Care
- Fair Compensation / Undue Inducement

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Therapeutic Misconception (TM)

- Questions regarding TM:
  - What is TM?
  - Why is TM a problem?
  - What can be done about TM?

75

What is tm?

- Participants inaccurately attribute therapeutic intent and individualized care to research

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Why is tm a problem?:

- Failure to appreciate the risks:
  - Can lead to post-participation regret
  - Can lead to requests for "compassionate" use:
    - And/or post-trial access when efficacy and/or safety are not yet well-established
- Basic respect for the person as an autonomous agent requires dispelling such misconceptions

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Participants should

- Know and understand what is involved:
  - With false beliefs and/or misconceptions
    - Participants won't really know what one is doing

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The Quest for Equipoise

- Reflects the demands of beneficence, non-maleficence, and justice:
  - Obtained when there is a state of "genuine uncertainty within the medical community"* about two arms in a research study
- *Freedman, NEJM 1987

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Challenges

- Determination of equipoise
  - Level of uncertainty
- Equipoise can change over the course of a study as new data becomes available
- Patients may not want to be randomized, especially to placebo

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Reimbursement vs. Compensation

- Ethical considerations for how much to pay participants
  - Reimbursement
    - For time, travel, etc.
  - Compensation
    - Generically to refer to any form of payment
    - Differing types of compensation
    - Payment for assumption of risk?

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Concerns About Undue Inducement

- What is inducement?
- When and why is inducement ever "undue"?
- Debates on this

82

Compromise of autonomy:

Offering prospective enrollees payments they perceive to be very large can compromise a person's better judgment

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…and thus unduly influence the individual to ignore or under-appreciate the extent to which participation in the study actually risks harms and/or the loss of health benefits otherwise obtainable

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Non-maleficence

A payment offer might be so large as to tempt would-be recipients into concealing relevant information (that would have excluded them from the study); as a result, the study may carry an un-necessarily greater risk of producing harmful effects.

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Beneficence

The presence of such participants (who should have been excluded) can compromise the scientific validity of the research and thus reduce the likelihood that it will make a reliable contribution to the progress of biomedical science.

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Justice

- If payment goes beyond basic compensation in order to "incentivize" participation
- Then burdens and risks of research may be disproportionately born by poorer people, while the benefits of the research are disproportionately enjoyed by wealthier persons

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Complications

- When is it rational for a person to say, "I do understand the risks but I value the money still more."
- A payment 'large enough' to incentivize people of modest means would not be large enough to incentivize wealthy people.
- To what extent can the process of enrolling people in a research study be treated as a purely commercial transaction and to what extent must it be constrained by the ethical commitments of the profession?

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Does compensation to encourage participation through the end of a study discourage participants from reporting disqualifying clinical symptoms or developments?

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- AND THEN,
- THEORY MEETS PRACTICE. . .
- BADLY.

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A Case Study: the FAAH Inhibitor Case

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THE FAAH Inhibitor Case:

- The Phase 1 Bial study conducted by Biotrial "recruited 128 healthy volunteers aged 18–55, who were paid €1,900 (US$2,060) each." (*Nature*)
- "Ninety people received different doses of the drug [BIA 10-2474], and the remainder a placebo." (*Nature*)
- Timetable of Events – as reported by *Nature*
  - Between July 2015 and December 2015, the trial tested escalating single doses of the drug without observing any serious adverse side effects.
  - In January 2016, six participants fell ill. They were the first to receive repeat higher doses [(50 mg) of the compound] over the course of several days.
  - The first participant to fall ill experienced adverse symptoms on January 10 and was declared brain dead.
  - On January 11, Biotrial administered the drug to 4 additional patients, and then halted the trial. Five patients were hospitalized in the days that followed.
  - One of the patients was discharged, and the condition of the other four was judged to be serious but stable.
  - Authorities contacted the 84 other people who received the drug at lower doses to arrange medical check-ups; none of the 18 given neurological check-ups showed any of the symptoms seen in the hospitalized people.
- *Source: *Nature*, January 2016: http://www.nature.com/news/scientists-in-the-dark-after-french-clinical-trial-proves-fatal-1.19184

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- BUT FIRST,
- WHAT IS **FAAH**?

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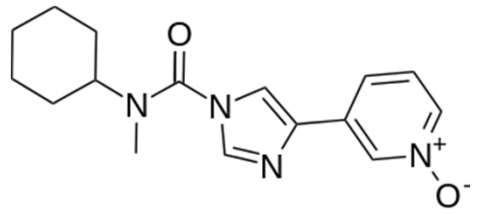

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- **F**atty
- **A**cid
- **A**mide
- **H**ydrolase

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Why Do We Care About FAAH?

Studies in cells and animals and genetic studies in humans have shown that inhibiting FAAH may be a useful strategy to treat ANXIETY DISORDERS.

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Questions:

- Knowing only these facts, are there any ethical concerns with this study?
  - If so, what?
- What, if anything, should the researchers do now?
- Is there any other information you would like to know to address these questions?

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Further Developments

- In February 2016, the journal *Science*, reported the following :
  - January 10 was the first day the first participant fell ill. That patient died January 17
  - The situation was not reported to the French **National Agency for Medicines and Health Products Safety** (ANSM) until January 14, 3 days after Biotrial stopped the study.
  - Biotrial had promised in an informed consent form: 'You will be informed about any new significant information that could affect your willingness to continue the trial." In a December 2016 "Open Letter" in *The Lancet* , researchers not affiliated with the study * requested the French authorities to release data surrounding the compound for pharmacokinetic and pharmacodynamics analysis. As of June 2017, this information has not been provided.

*Clinical pharmacology experts Kim Brosen, Christian Funck-Brentano, Heyo K. Kroemer, Munir Pirmohamed, and Matthias Schwab
(Source: *The Lancet*, December 9, 2016. http://www.thelancet.com/pdfs/journals/lancet/PIIS0140-6736(16)32515-6.pdf)

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Further Developments

- In March 2016, a panel of experts selected by the National Agency for Drug Safety:
  - Concluded adverse reactions were a direct result of the compound and high dosage of the compound;
  - Questioned the company's seemingly over-exhaustive animal studies on a variety of animals, raising suspicion that the company had knowledge of potential toxicity; and
  - According to *The Guardian* (March 2016), the experts noted "that the drug test volunteers were relatively old (aged up to 49) and some presented various risk factors 'vis-a-vis certain adverse drug reactions.'"**

**Source: *The Guardian*, March 7, 2016. https://www.theguardian.com/science/2016/mar/07/french-drug-trial-man-dead-expert-report-unprecidented-reaction
CenterWatch, June 1, 2017: http://www.centerwatch.com/news-online/2017/06/01/disclosures-bring-continued-focus-biail-trial/

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Further Developments

- In April 2016, ANSM's **Temporary Specialist Scientific Committee** (TSSC) called for further clarification regarding:
- "The reasons for using four different species for the toxicology studies."
- "The circumstances of death by bronchopulmonary disease in dogs."
- "The circumstances of death during studies on primates at high doses."
- "The results of any microscopic examinations of the brains of deceased primates."
- "The reasons for down-titration in the 13-week study in dogs."
- "The reasons for the apparent lack of preclinical pharmacology studies for confirming, before transfer to humans, the analgesic effect of BIA 10-2474, especially compared to benchmark analgesics."
- *Source: *Regulatory Affairs Professionals Society*, March 2016. http://www.raps.org/Regulatory-Focus/News/2016/03/30/24519/ANSM-Committee-Delves-Into-Nitty-Gritty-of-Fatal-French-Phase-I-Trial/

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TSSC Recommendations

- New best practices for human trials:
- "Demonstration of pharmacological activity…should be a requirement in the future before in-human administration or even before continuing toxicology studies can be envisaged. Preclinical pharmacology studies should be conducted as early as possible, on an adequate dose range (dose-effect curves) and should be designed so as to be reasonably predictive of real-life, future therapeutic efficacy."
- "A neuropsychological assessment with clinical interview and cognitive tests should be…part of…volunteer screening…in Phase 1 trial for drugs with central nervous system" activity.**
- Detailed and well-supported arguments for the choice of maximum dose to be tested in volunteers"
  - E.g., "…it appears unjustified to…test a dose (100 mg) 80 times higher than that presumed to induce complete and prolonged FAAH inhibition (claimed mechanism of action of the drug tested)."
- "A large-scale consensus process should cover Phase I dose-escalation strategies to establish recommendations for more reasonable and careful practices than those applied."
- "Pharmacokinetic parameter variability and extremes, and not only the mean, should be taken into account for setting the next dose level."
- *Source: *Regulatory Affairs Professionals Society*, March 2016. http://www.raps.org/Regulatory-Focus/News/2016/03/30/24519/ANSM-Committee-Delves-Into-Nitty-Gritty-of-Fatal-French-Phase-I-Trial/
- **Trial participants in this study were up to 49 years old, and some presented various risk factors "vis-à-vis adverse drug reactions" (*The Guardian*, March 7, 2016. https://www.theguardian.com/science/2016/mar/07/french-drug-trial-man-dies-6-expert-report-unprecedented-reaction)

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Healthy Volunteers

- Patients, rather than healthy volunteers, are used to various kinds of chemotherapy trials.
- Based on what researchers knew at the beginning of the study, should they have used healthy volunteers, rather than patients?
  - If so, under what circumstances?
  - Do you have any questions about the use of these participants?

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Healthy Volunteers

- Regulations change periodically change, due to various factors. Regardless of what the regulations may say currently,
  - What if animal studies suggest that the study entails more than minimal risks of serious adverse events?
  - Should that change your considerations?
- What if you have a friend dying of AIDS?

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- What if the study potentially has a greater social benefit than the FAAH study discussed earlier?
  - E.g., if animal studies suggest that a drug might reduce the risk of Stroke by 80%?
  - Would that change your considerations?

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Final Wrap Up

- Use what you have learned today and you **ensure better compliance**.
- Underlying ethical principles may seem simple but can pose complex dilemmas.
- Ethical dilemmas often involve conflicts between ethical principles. Hence, there may be more than one reasonable answer. First identify and eliminate the less reasonable answers.
- Right answers are often subtle and/or complex - using the framework will enable you to reason your way to one or more proper solutions.
- Carefully examine the reliability of the facts upon which you are basing your analysis.
- Double check for biases.
- Moral intuitions (gut feelings) are important starting points for ethical analyses, but in the end, when significantly affecting other people's lives, you need to be able to articulate the reasoned basis for your conclusions.

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