Research vs Practice: Separating church from state in NIH protocols

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Objectives

Understand the conceptual, ethical and regulatory basis for the distinction between research and clinical practice

Apply this knowledge in the context of NIH protocols including clinical trials as well as those for screening, natural history protocols and training protocols

Identify the unique issues posed by screening protocols and how screening meets the regulatory definition of human subjects research

Research vs Practice

Research is a class of activities designed to test an hypothesis, permit conclusions to be drawn and thereby to develop or contribute to generalizable knowledge.

Practice is a class of activities designed solely to enhance the well being of an individual patient, and that have a reasonable expectation of success.

Clinical Practice v Research

It is important to distinguish between biomedical and behavioral research, on the one hand, and the practice of accepted therapy on the other, in order to know what activities ought to undergo review for the protection of human subjects of research. The distinction between research and practice is blurred partly because both often occur together (as in research designed to evaluate a therapy) and partly because notable departures from standard practice are often called "experimental" when the terms "experimental" and "research" are not carefully defined.

- Belmont report

Researchers vs Practitioners

Researcher

- Role is to conduct research.
- Primary obligation is to collect scientifically valid data.

Practitioner

- Role is to provide care to their patient.
- Primary obligation is to act in the individual patients best interest.

Researchers vs Practitioners

Conflicts in roles

- Physician
- Investigator

Competing obligations

- Obligations to the patient
- Obligations to science

Physician:Patient Relationship

Fiduciary Relationship

- Recognition that patients are vulnerable
- Imbalance of knowledge and power
- Greater obligation placed on the physician to promote the welfare of the patient

Based on trust

- Trust that the physician is knowledgeable.
- Trust that the physician will use that knowledge for the best interest of the patient.
- Trust that the physician will place his or her own self interest behind that of the patient.

Roles and obligations

Physician

- Obligated to act in her best interest.
- Provide her with the best medical care you can, tailored to her disease and social context.
- The Duty of Personal Care

Patient

- Participate in the shared decision making process by providing information on goals, values and helping decide what treatment options best meet those.

Obligations of Researchers

Scientific Duty

- The duty to conduct any trial for which they are responsible so as to produce scientifically valid results in a timely manner, lest the participation of human subjects be in vain.

Protective Duty

- The duty to protect human subjects' well being in the face of medical burdens and risks of research participation.

What happens when roles are confused?

Therapeutic Misconception

Therapeutic Misdirection

Therapeutic Misconception

- Patients belief that their physician would not offer non-efficacious therapy, even in the context of a research study.
  - Unjustified expectation of personal benefit from participation in the study.
  - Fail to understand essential concepts such as randomization
- If a patient-subject harbors a therapeutic misconception, is consent truly informed?

Therapeutic Misdirection

Inappropriate decision making on the part of the physician-investigator based on the belief that research is therapy.

- Decisions to “finesse” the eligibility requirements in order to enroll a subject that the physician perceives might benefit (or converse).
- Keeping a patient in a trial when they should be withdrawn due to a toxicity (or converse).

Why therapeutic misconception?

Clinical trial brand names:

- AFFIRM
- ALIVE
- APLAUSE
- ASSRT
- AVERT
- BEST
- BETTER
- BRAVO
- BRILLIANT
- CHAMP
- CONVINCE
- COURAGE
- DEFINITE
- EXCEL
- FASTER
- GREAT
- GUSTO
- HER0
- HOPE
- MAGIC
- MIRACL

What do consents say?

You are invited to participate in a research study testing the safety and effectiveness of a new medication X. This medicine is not approved by the FDA, but we believe it may be promising for the treatment of your condition.

You are invited to be part of an experiment. We would like to determine how much of this new drug we can give to patients before they experience severe side effects. We do not know if this experimental drug works, or exactly what the side effects will be. In all likelihood, you will receive a dose too small to be effective on your tumor, and you may receive a dose that makes you sick.

What happens when activities are confused

The patient/subject cannot accurately distinguish whether what is being done to them is for research or clinical purposes.

The physician-investigator fails to recognize what activities are covered by regulation

The IRB reviews activities that are outside its jurisdiction and for which IRB review is inappropriate

The IRB makes incorrect regulatory determinations

Research vs Practice

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Clinical vs Research

CLINICAL

Individual decisions

Not protocol driven

Best interest of the individual patient

Does not include the use of unapproved drugs/devices

- May include off label use of approved drugs/devices
- Exception: expanded access

Does not include doing assays/tests/procedures purely for the purposes of research

RESEARCH

Decisions not tailored to individual

Driven by protocol

Not necessarily in best interest of individual patient

May include unapproved drugs/devices

- May also include approved drugs/devices

Often includes assays/tests/procedures purely for research

What do IRBs do?

§46.111 Criteria for IRB approval of research.

(a) In order to approve research covered by this policy the IRB shall determine that all of the following requirements are satisfied:

(2) 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. In evaluating risks and benefits, the IRB should consider only those risks and benefits that may result from the research (as distinguished from risks and benefits of therapies subjects would receive even if not participating in the research). The IRB should not consider possible long-range effects of applying knowledge gained in the research (*e.g.,* the possible effects of the research on public policy) as among those research risks that fall within the purview of its responsibility.

Regulatory definition of HSR

You are doing human subjects research, if for research purposes, with a living individual, you either

- Interact or intervene with the person
- Collect, analyze…..identifiable private information or identifiable biospecimens

The bottom line

If a test/procedure/intervention is specified in the protocol the IRB will consider it research

- Fully described in the protocol and consent

If a test/procedure/intervention is dictated solely by the clinical needs of the individual patient, then its clinical.

- will likely vary from patient to patient
- SHOULD NOT BE IN THE RESEARCH PROTOCOL OR CONSENT

What…you have to be kidding!

Wait a minute…..I am a pulmonologist and I study the biology and treatment of severe asthma and am developing a new therapeutic agent for the treatment of this devastating disease. As part of that I see a lot of patients enrolled in my trials and in addition I manage their asthma. Are you telling me that I can't include any of the data collected during their treatment in my research?

What part is the research?

Analysis of data &/or samples that were collected for clinical purposes is the research activity

- The research is the secondary review and analysis of data that have been, or will be, collected for non-research purposes.

Protocol and consent should describe this aspect.

What do I put tell the IRB?

Protocol should say:

- Standard clinical care will be provided to patients with XYZ disease. Clinical interventions and procedures will be based upon the specific needs of the individual patient. Routine clinical consents will be obtained per standard clinical practice
- Clinical data and excess biospecimens collected as part of clinical care will be analyzed research purposes.
- Consent and protocol should NOT describe the risks of the clinical procedures.
- Consent should describe breach of confidentiality risk

Can I mix it up a little?

What if I want to do a few research tests?

- Describe in protocol and consent
- When you will do them, to whom, what the risks and potential benefits are….
- IRB has to be able to assess this against the HHS regulatory criteria for approval, FDA regs and NIH policies

Clinical Care protocols

Origin: Everyone seen at the NIH has to be enrolled on a protocol

Intent is to provide routine clinical care to patients

- Pool of potential subjects
- Training
- Keeping up clinical skills

Collection of clinical data and excess clinically collected biospecimens should be the research the activity.

- Protocol and consent should describe this as the research.

Remember:

- Unapproved drugs/devices are always research (unless expanded access)
- Don’t sneak in extra tests/scans etc because you want the data for research

Natural history protocols

Goal: follow patients with specific conditions over time to determine the natural course of the disease.

If there are protocol driven events, these are research interventions

- Describe in protocol and consent.

If providing actual clinical care and collecting the data

- Describe this in protocol and consent similar to SOC protocol

Screening is research

Goal: determine eligibility for a trial

Definition of HSR:

- Interacting or intervening with a living individual
- Collecting or analyzing identifiable private information or biospecimens

2 flavors of screening

Review existing data

- Clinical or research

Collect new data and/or biospecimens

Screening is research

Review of data that was previously collected (clinical or research)

- Describe in protocol, waiver of consent (pre-2108 CR) by IRB
- No waiver needed for 2018 common rule or under FDA regs

Interventions done for the purposes of determining eligibility for a trial are research interventions

- Activities must be described in the protocol
- Risks must be described in protocol and consent
- IRB must weigh risk of intervention against potential benefit of the protocol being reviewed (45 CFR 46.111(a)(2))

Screening

General principle: Screening should include the fewest and least risky interventions necessary to determine eligibility into a trial.

Goal: Minimize exposure to potential harm for those that screen fail.

Screening protocols

Stand alone, used to determine eligibility into a multitude of trials

Problems:

- No benefit associated with the screening, as benefit is associated with the downstream trial
- Subjects may have more done to them then necessary to determine specific eligibility thereby exposing to unnecessary risk

Screening – 2 options

Describe all screening activities as part of the trial

- Screen fails are fine and expected!
- Account for in accrual ceiling

If a separate screening protocol:

- Activities must be no more than low risk for adult
  - Single CT scan, needle biopsy of a peripheral LN, BM bx
- No more than minimal risk for a child due to subpart D regs

All activities must be described in protocol and consent

- No carte blanche

Training protocols

Training is necessary but training is not research

Trainees can (and should) learn by participating in research

Examples: Training protocol

Design: Clinical physiologic, neuropharmacologic, and neurochemical testing will be performed during outpatient clinic visits or during inpatient admissions, depending on the individual testing schedule. Inpatient testing may be done in conjunction with other Protocols (Most of the testing under this Protocol can be completed in a single outpatient visit over the course of a workday. Testing procedures under this Protocol will be performed as needed for adequate Fellow training. In addition to autonomic medical history and physical examination, clinical testing procedures may include (A) monitoring of hemodynamics, sweating, and other physiologic parameters associated with the Valsalva maneuver, orthostasis, or external temperature manipulation; (B) venous blood sampling for assays of levels of catecholamines and related neurochemicals; (C) administration of autonomic test drugs; (D) skin biopsies; (E) pupillometry; (F) gastrointestinal phonography; (G) urinary bladder ultrasound; and (H) neurobehavioral rating scales.

Outcome measures: The main outcome measure is competency in clinical and laboratory evaluation of autonomic disorders, based on assessment of the Fellow by the Principal Investigator at approximately 6-month intervals. A secondary outcome measure is results obtained under this Protocol, which may be analyzed and reported as research data along with data from other Protocols

Study Objectives: The main objective of this Protocol is to train Fellows in evaluating and testing patients with known or suspected disturbances of autonomic function. A secondary objective is to include results of evaluations and testing with those from other Protocols, for future data analyses.

This is not a research Protocol. No hypotheses will be evaluated.

Screening Protocol (1)

OBJECTIVES

To evaluate patient's, transplant donors', or healthy volunteer's eligibility for participation in ABC IC research protocols.

To collect results of screening test for use on subsequent research protocols as baseline (e.g., pretreatment) values.

Screening Protocol (1)

Inclusion Criteria

Subjects will be entered on this protocol at the time of their first visit to the NIH Clinical Center outpatient clinic or inpatient service if:

- The subject carries the diagnosis of a disorder for which the ABC IC has an active research protocol, and based on information received from an outside physician, he/she appears to meet at least preliminary eligibility criteria for that protocol **OR**
- The subject is a donor for a subject for whom the ABC IC has an active stem cell transplant protocol and based on information received from an outside physician, he/she appears to meet preliminary eligibility as a donor **OR**
- The subject is a normal volunteer for whom the ABC IC has an active study recruiting healthy normal volunteers and he/she appears to meet preliminary eligibility as a normal volunteer
- Age $\geq$ 2 and Weight >12 kg (healthy volunteers age $\geq$8)

Screening Protocol

Patients and healthy volunteers who are enrolled on this protocol will be evaluated by Intramural ABC IC physicians, research nurses and clinical associates to determine their eligibility for one or more of the Intramural ABC IC primary research protocols. Screening tests and procedures that are required by these primary research protocols will be conducted in order to establish eligibility for these protocols. **These procedures may include, but are not limited to, tests on blood, CSF, urine, tumor tissue or other specimens; pulmonary function tests; TB skin tests; subspecialty consultations; molecular diagnostics on blood, bone marrow, or tumor tissues including next generation sequencing (NGS); radiographic and nuclear medicine studies, which may require the administration of contrast or a radioisotope tracer; and needle or open biopsies for the determination of diagnosis, stage or prognosis.**

No treatments will be administered to subjects as part of their participation in this protocol, other than medications or treatments necessary for performance of screening tests, for example bronchodilators for pulmonary function tests, contrast for imaging studies, or analgesia for bone marrow aspiration and biopsy. Separate informed consent will be obtained prior to anesthesia, conscious sedation and/or invasive procedures, when applicable.

Screening Protocol

Background:

• Patients and healthy volunteers who are being evaluated for NIH Intramural Research Program (IRP) protocols must be screened to determine whether they meet the eligibility criteria prior to enrollment.

Objectives:

• Evaluate patient or healthy volunteer eligibility for participation in NIH IRP research protocols.

Eligibility:

• Patients and healthy volunteers who are being evaluated for and treated on protocols within the NIH IRP

Design:

• This protocol is not a research study

• Screening tests and procedures that are required by the primary research protocols are conducted in order to establish eligibility for these protocols.

Screening Protocol

3.1 STUDY DESIGN

Patients and healthy volunteers who are enrolled on this protocol will be evaluated by NIH IRP physicians, research nurses and clinical associates to determine their eligibility for one or more of the NIH IRP's primary research protocols. Screening tests and procedures that are required by these primary research protocols will be conducted in order to establish eligibility for these protocols. **These procedures may include, but are not limited to, tests on blood, CSF, urine, tumor tissue or other specimens; pulmonary function tests; TB skin tests; subspecialty consultations; molecular diagnostics on tumor tissues; radiographic and nuclear medicine studies, which may require the administration of contrast or a radioisotope tracer; and needle or open biopsies for the determination of diagnosis**, stage or prognosis. Germ line genetic testing will not be performed on this protocol. In some cases, specific research samples required for the primary research protocol may be collected during the screening process in order to prevent us from having to subject the patient to a painful procedure on multiple occasions (e.g., bone marrow aspirations). These research specimens will be discarded or stored for future research purposes with the consent of the patient or his/her parent or guardian, if the patient is not eligible for or elects not to enroll on the primary research protocol.

The bottom line

IRBs review research not clinical care

IRBs have to know exactly what is being done to whom and why

IRBs evaluate all the criteria for approval for an individual protocol in front of them.

The bottom line

If its specified in the protocol, its research

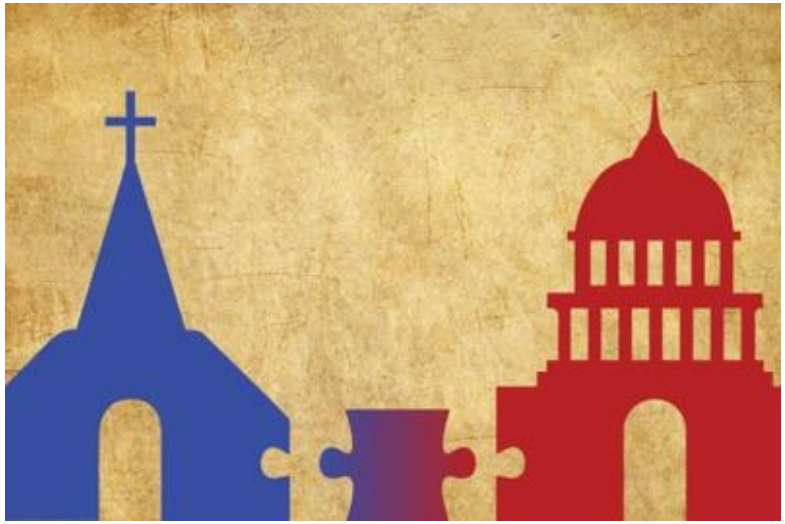
- Don’t list out clinical care in the protocol

If the risks are in the consent, they are research risks

- Don’t discuss risks of clinical care in consent

Review of existing identifiable clinical (or research) data for new research is OK

- Needs IRB approval
- Primary risk is breach of confidentiality



Screening is research (always)

If an intervention is being done for the purposes of determining eligibility into a research protocol, its research

- Describe fully in protocol and consent

Looking at existing medical records to determine eligibility is research

- Risk is breach

Screening activities should always be the fewest and lowest risk procedures needed

Stand alone screening must be low risk for adult, minimal risk for minors

- There is no benefit that the IRB can balance against risk with a free standing screening protocol