Regulatory considerations in natural history studies

Jonathan M Green, MD MBA

Director, OHSRP

February 3, 2022

NIH Office of Intramural Research
Office of Human Subjects Research Protections

Agenda

- Overview including terminology
- Distinction between research and the practice of medicine
- What should be in the protocol and consent
- AE/SAE tracking
- Taking a family hx, who is a research participant?

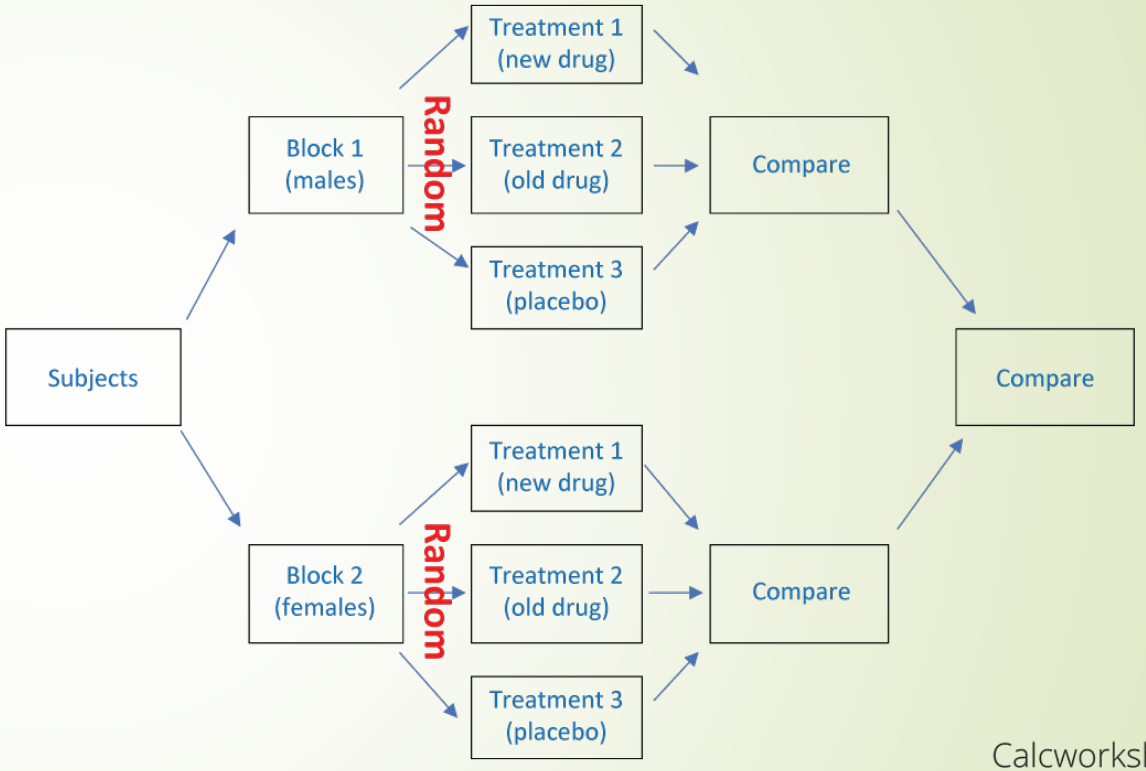
What is a natural history study?

What is a natural history study?

"a preplanned observational study intended to track the course of the disease. Its purpose is to identify demographic, genetic, environmental, and other variables (e.g., treatment modalities, concomitant medications) that correlate with the disease's development and outcomes. Natural history studies are likely to include patients receiving the current standard of care and/or emergent care, which may alter some manifestations of the disease. Disease registries are a frequent platform to acquire the data for natural history studies."

- https://www.fda.gov/media/122425/download

What is not a natural history study?



Calcworkshop.com

Natural history studies

- Follow cohorts of people with a condition over time
- Gather data to determine the course of a disease/condition
- Generate ideas to be tested in other studies
- Do ***not*** test interventions either as part of the initial study, substudy or amendment.

Research vs Practice

- Research is a class of activities designed to test a 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.

Research vs. Practice of Medicine

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) as partly because notable departures from standard practice are often called "experimental" when the terms "experimental" and "research" are not carefully defined.

- Belmont report

The clinical-research conundrum in natural history studies

Research vs Practice

Research

- Systematic
  - Protocol driven
  - All or some subjects based on protocol specified criteria
- Primary intent is generalizable knowledge (though subject may benefit)
- Secondary data collection from clinical care

Practice of medicine

- Individualized
- Not systematic or protocol driven
- Primary intent is to benefit individual patient (though knowledge may be gained)
- Cannot include investigational drugs/devices except for expanded access

Kinds of research interventions

Systematic research interventions

- Protocol specified
- Time or event driven
- All subjects or a specific cohort
- Enable uniform data collection
- Examples:
  - yearly MRI on all subjects in a MS study, or when a subject experiences a prespecified change in functional status
  - q 3 month CBC on immunodeficiency study,

Data collection during clinical care

- Medical record data extracted from the clinical record during the course of clinical care
  - Exam findings, lab work, imaging data
  - From NIH or non-NIH sources (be cognizant of HIPAA please)

Mixed clinical/research interventions

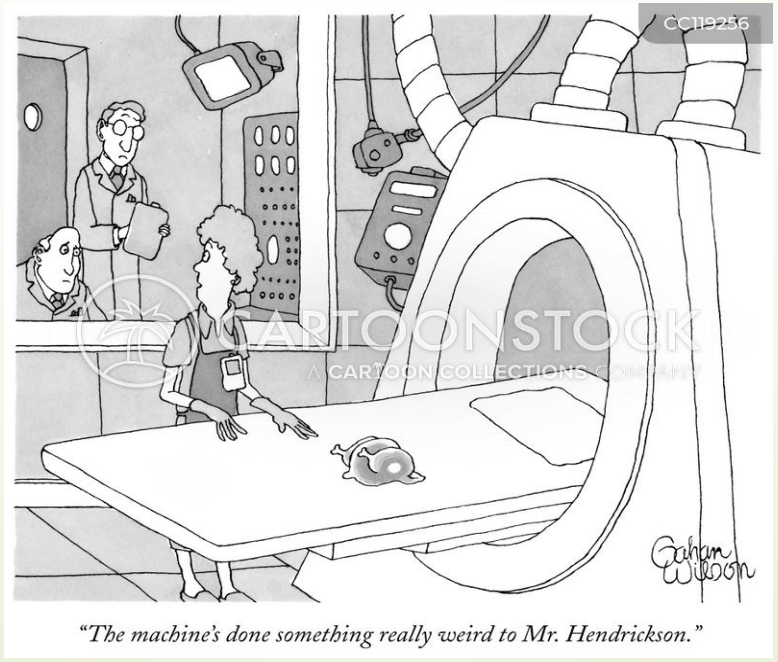
- When a research procedure is inextricably linked to a clinical intervention
  - Extra biopsies when a clinically indicated diagnostic procedure is performed
- Protocol should describe the clinical procedure sufficiently for the IRB to understand what is being done
  - Describe the incremental risks which are those of the research procedure, not of the clinical procedure itself

Clinical care vs standard of care

- Just because something ***is not*** the same as what is done outside of NIH doesn't mean its research.
  - Designed and intended to benefit an individual patient based upon their specific condition at that time and known to have a reasonable chance of success.
  - May or may not be the same as what is done at a doctors office or non-research hospital.
  - Different imaging machines, special assays, off-label use of approved drugs all can be clinical but not necessarily SOC.

Standard of care vs clinical care

- Just because something ***is*** the same as what is done outside of NIH, doesn't mean its not research
  - Same lab assay, same imaging as what is used clinically, when protocolized is considered a research intervention (e.g., imaging to assess and document disease progression)



"The machine's done something really weird to Mr. Hendrickson."

What should be in the protocol and consent?

- All interventions done for research purposes must be fully described in the protocol and consent.
- Those activities that are done solely for non-research purposes should not be in the protocol and consent.

What is research?

- ***Research*** means a systematic investigation, including research development, testing, and evaluation, designed to develop or contribute to generalizable knowledge. Activities that meet this definition constitute research for purposes of this policy, whether or not they are conducted or supported under a program that is considered research for other purposes. (45CFR46.102(l))

How can I tell if it is research?

- Is the intervention systematic?
  - Done based on a protocol specified criteria
    - Yearly brain MRIs on all subjects enrolled in a natural history study of multiple sclerosis
    - Brain MRIs when subjects enrolled in a natural history study of MS experience a pre-specified change in functional status
    - Pulmonary function tests every 6 months on all patients enrolled on a natural history study of pulmonary hypertension
    - Complete blood counts every 3 months on all patients enrolled on a natural history study of immunodeficiency diseases.
    - Bone marrow biopsies on patients enrolled in a natural history study of myelodysplastic syndrome when the white blood cell count exceeds a pre-specified threshold.

How can I tell if it's research?

- Is it being done primarily to contribute to generalizable knowledge?
  - Data will used in endpoint analysis
  - Plan to report on it
  - Primary intent is to learn about a specific condition (even if it may clinically benefit an individual)

Research or clinical?

- A researcher follows subjects with immunodeficiency syndromes in a natural history study. The protocol specifies that subjects will have blood work performed every 6 months and a CT of the chest performed annually to assess the extent of bronchiectasis. Subjects are also seen on an as-needed basis if there is clinical deterioration, and the investigator orders additional diagnostic procedures or provides therapies as clinically indicated. The data from the clinical interventions will be collected and analyzed for research purposes.
- What is research?
  - Blood work
  - CT scan
  - Secondary analysis of clinical data
- What is not research?
  - Diagnostic procedures and therapies done on individual subjects that experience a clinical deterioration.

Use of clinical data for research

- Suggested Protocol language
  - *If subjects undergo diagnostic testing or treatment for clinical purposes, the medical record data will be collected and analyzed for research purposes so that we may gain a full characterization of the disease. This includes all laboratory and imaging data from the NIH Clinical Center*
- Consent
  - *We may also use information such as laboratory or imaging results collected from you during any clinical treatment provided at the NIH Clinical Center, for research purposes. This is so that we can gain a complete understanding of your condition.*
- Risks
  - Breach of confidentiality

Is it research or clinical?

- A protocol enrolls persons with unusual phenotypic feature that are suspected of having a genetic basis. Individuals are brought to the NIH Clinical Center and undergo a large battery of tests that vary depending upon the presentation of their condition. Because of the unique nature of each person's condition, the specific tests may vary considerably from person to person.
- Is it research?
  - Is it systematic?
  - Is the primary intent to contribute to generalizable knowledge?

Can I provide medical treatment to patients enrolled in a natural history study

- Natural history study to follow patients with primary immune-deficiency diseases. Protocol requires subjects to come in every 6 months for blood work and imaging for research purposes. Subjects also come in when symptoms of infection develop. At that time, protocol specified labs and imaging are performed.
- If a subject comes in with signs and symptoms of an infection, can I order additional non-research testing to diagnose this patient's condition, and provide them with appropriate antimicrobial therapy?

YES

IRBs do not regulate the practice of medicine

Can I do this in my natural history study?

- The postdoctoral fellow working with me notices that over the past 6 months, she has seen more infections with a certain fungus. She wants to look back over the past 2 years records of all subjects enrolled in the study to determine the incidence of infections with this pathogen. Can she do this?

Maybe and only if….

The protocol and consent describe accessing the clinical medical record for research purposes AND it falls within the scope of the IRB approved protocol.

Can I do this in my natural history study? – example 2

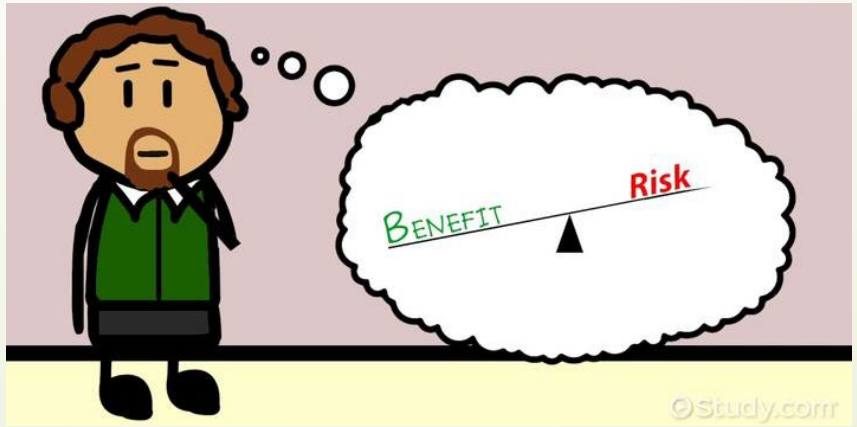
- My postdoctoral fellow does the retrospective analysis and thinks that it is possible that subjects treated with one antifungal drug did better than some with a different drug. However, the data is not great and not controlled. She wants to prospectively test the 2 drugs in subjects enrolled in the natural history study using a randomized study design. Can she do this under the existing natural history study?

NO

This is a new interventional trial. A new protocol and submission to the IRB is required.

Is there benefit in a natural history study

- 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). (45 CFR 46.111(a)(2))



What flavor of benefit?

- Direct
  - Arising from the research intervention
- Inclusional/ancillary/collateral
  - Arising from the other aspects of the protocol
- Aspirational
  - Social value of the scientific knowledge

Benefit

- IRB will only assess the benefit of the research interventions
  - Not the benefit of incidental clinical care
- Potential benefit should be clearly described in the protocol
  - Potential therapeutic benefit of a research intervention
    - Not typically part of a natural history study
  - Monitoring or detection of a condition that might permit earlier or more effective therapeutic intervention
    - In this case, the monitoring procedure must be part of the research itself.

Enrolling children – Subpart D

- Minimal Risk
- Greater than minimal risk with a prospect of direct benefit
- Greater than minimal risk without a prospect of direct benefit if the risk is no more than a minor increase over minimal, and intervention will contribute to generalizable knowledge about the subject's condition.
- None of the above, but Secretary of HHS approves.

Enrolling children – Subpart D 46.404/50.51

Healthy Kids

- Minimal Risk
- Greater than minimal risk with a prospect of direct benefit
- Greater than minimal risk without a prospect of direct benefit if the risk is no more than a minor increase over minimal, and intervention will contribute to generalizable knowledge about the subject's condition.
- None of the above, but Secretary of HHS approves.

Enrolling children – Subpart D 46.405/50.52

- Minimal Risk
- Greater than minimal risk with a **prospect of direct benefit**
- Greater than minimal risk without a prospect of direct benefit if the risk is no more than a minor increase over minimal, and intervention will contribute to generalizable knowledge about the subject's condition.
- None of the above, but Secretary of HHS approves.

Direct benefit

- A benefit is direct if:
  - It accrues to the individual research participant
  - Is a result from the specific research intervention or procedure, and not from ancillary benefits.
- Tangible, positive outcome that may be experienced by the individual

Enrolling children – Subpart D 46.406/50.53

- Minimal Risk
- Greater than minimal risk with a prospect of direct benefit
- Greater than minimal risk **without a prospect of direct benefit** if the risk is no more than a **minor increase over minimal**, and intervention will contribute to **generalizable knowledge about the subject's condition**.
- None of the above, but Secretary of HHS approves.

No Healthy Kids

Reporting requirements

- Same as for any other studies per policy 801
- AE/SAE tracking
  - Track those related to the research (not the underlying condition)
  - Describe in protocol
    - common, expected low grade AEs may not need to be tracked
  - *AEs and SAEs that are related to the research procedures described in this protocol will be recorded, except for Grade 1 or 2 AEs that are expected. AEs and SAEs that in the investigators' judgment are not at least possibly related to research procedures, for example, those that are due to the natural course of the disease, will not be recorded as AEs/SAEs in the research database*

Statistical analysis plan

- More limited than interventional clinical trial
- Relevant endpoints and analysis should be described
- Descriptive statistics at a minimum

Family members – Collecting a family history

- Is the family member a subject?
  - Collecting identifiable private information about the family member
  - Must submit the family history questionnaire for review
- If yes…either consent (with or w/o a waiver of documentation) or a waiver of consent required.
- Best practices
  - Collect w/o identifiers if scientifically feasible
  - Collect minimum amount of data that is scientifically necessary, especially if under a waiver.

Family members - enrolling

- Significant privacy concerns around recruitment and contact.
- Best practices
  - Proband should contact family member first, can provide IRB approved information sheet
  - If not feasible, detailed plan for contact must be described in protocol
    - Verbal/written scripts provided
    - Only minimum amount of essential information collected prior to consent (may require waiver)

Resources

- Revised protocol template
- OHSRP Guidance document
- FDA guidance document
- Presentation by Dr Christine Grady on Benefits In Research (videocast here)