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ICTR Lunch & Learn

July 9, 2024

50 Years of Human Research Protections- Reflecting on our Past to Prepare for the Present

Megan Kasimatis Singleton, JD, MBE, CIP

Associate Dean, Human Research Protections & Director of the Johns Hopkins Medicine Human Research Protection Program

OHRP Virtual Event

National Research Act 50th Anniversary

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Feedback

Watch Event

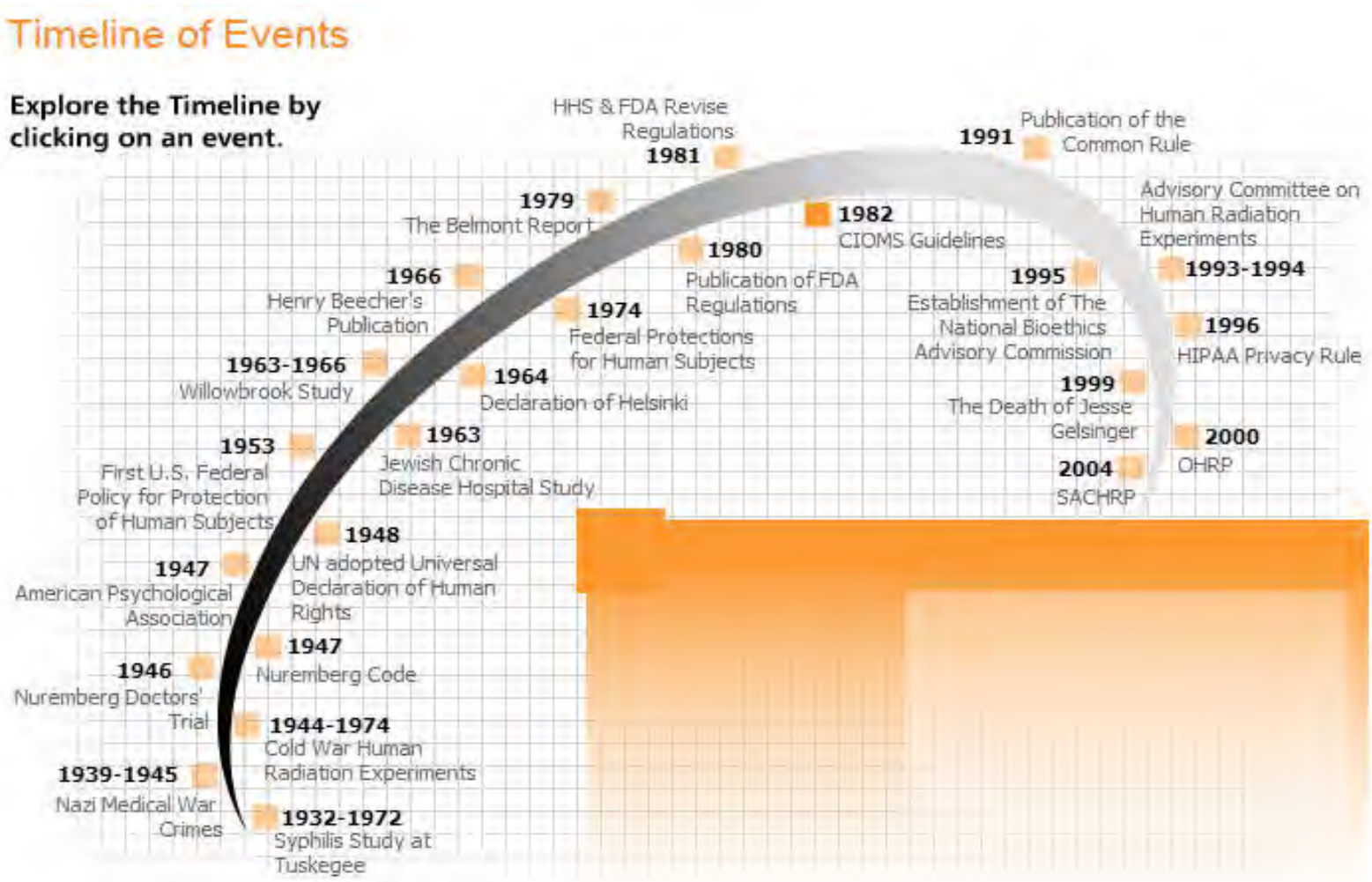
Agenda - PDF

Livestream on Friday, July 12, 2024
12:00 pm to 2:30 pm ET
No Registration Required

National Research Act 50th Anniversary | HHS.gov

Johns Hopkins Institute for Clinical & Translational Research

Timeline of Events



Historical Background

- Nazi Experiments: Systematic experimentation on concentration camp detainees for the purpose of German military development & race differentiation
  - Nuremberg Code
  - Declaration of Helsinki
- Henry Beecher (1966) : NEJM article –identified 22 cases of published research that involved unethical practices in research

Study of Untreated Syphilis

Study of Untreated Syphilis (1937-1972):

- Aimed to evaluate the natural progression of syphilis
- Funded by the Public Health Service
- The study initially involved 600 Black men – 399 with syphilis, 201 who did not have the disease.
- Informed consent was not obtained
- Researchers told the men they were being treated for "bad blood," a local term used to describe several ailments, including syphilis, anemia, and fatigue.
- In 1940s Penicillin became the treatment of choice for syphilis but men in the study were not treated
- In 1972 Associated Press Reporter Jean Heller first released a story about the study

Public Health Service Study of Untreated Syphilis at Tuskegee and Macon County, AL - Timeline - CDC – OS

AP WAS THERE: Black men untreated in Tuskegee Syphilis Study | AP News

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Ad Hoc Advisory Committee Panel Charge

- Determine whether the study was justified in 1932 and whether it should have been continued when penicillin became generally available.
- Recommend whether the study should be continued at this point in time, and if not, how it should be terminated in a way consistent with the rights and health needs of its remaining participants.
- Determine whether existing policies to protect the rights of patients participating in health research conducted or supported by the Department of Health, Education, and Welfare are adequate and effective and to recommend improvements in these policies, if needed.

Panel concluded that the study was not ethically justified and the study was stopped

Important Reflections of the Ad Hoc Committee

"The problem of ethical experimentation is the product of the unresolved conflict between two strongly held values: the dignity and integrity of the individual and the freedom of scientific inquiry"

"We have, as will be seen, made far-reaching recommendations for change. We do not propose these changes lightly. But throughout, in accordance with our mandate, our concern has not been just to define the ethical issues, but also to **examine the structures and policies** thus far **devised to deal with those issues**. In urging greater societal involvement in the research enterprise, we believe that the goal of scientific progress can be harmonized with the need to assure the protection of human subjects."

FINAL REPORT of the Tuskegee Syphilis Study Ad Hoc Advisory Panel (1973) (lsu.edu)

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The Committee cites Philosopher Hans Jonas

“ A slower progress in the conquest of disease would not threaten society, grievous as it is to those who have to deplore that their particular disease be not yet conquered, but that society would indeed be threatened by the erosion of those moral values whose loss, possibly caused by too ruthless a pursuit of scientific progress, would make its most dazzling triumphs not worth having.”

Jonas, "Philosophical Reflections on Experimenting with Human Subjects," 98 Daedalus 219, 245 (1969) .

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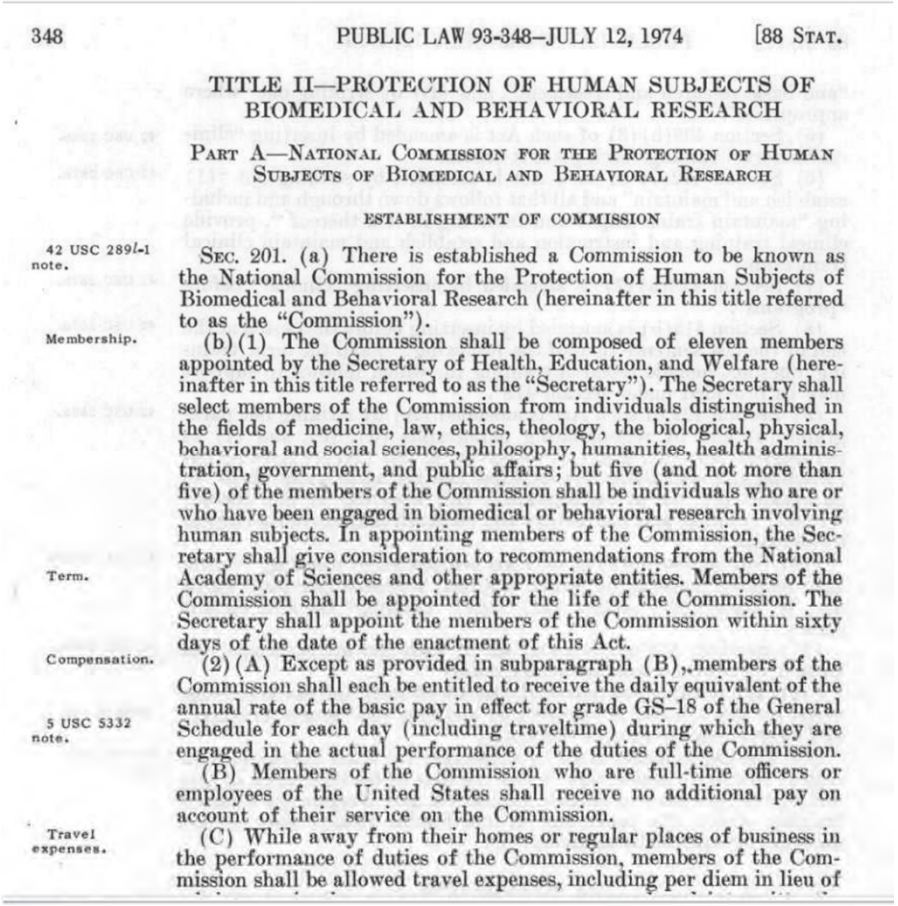
National Research Act

Published July 12, 1974

Established the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (1974-1978)



348 PUBLIC LAW 93-348—JULY 12, 1974 [88 STAT.

TITLE II—PROTECTION OF HUMAN SUBJECTS OF BIOMEDICAL AND BEHAVIORAL RESEARCH

PART A—NATIONAL COMMISSION FOR THE PROTECTION OF HUMAN SUBJECTS OF BIOMEDICAL AND BEHAVIORAL RESEARCH

ESTABLISHMENT OF COMMISSION

42 USC 289*l*-1 note.

SEC. 201. (a) There is established a Commission to be known as the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (hereinafter in this title referred to as the "Commission").

Membership.

(b)(1) The Commission shall be composed of eleven members appointed by the Secretary of Health, Education, and Welfare (hereinafter in this title referred to as the "Secretary"). The Secretary shall select members of the Commission from individuals distinguished in the fields of medicine, law, ethics, theology, the biological, physical, behavioral and social sciences, philosophy, humanities, health administration, government, and public affairs; but five (and not more than five) of the members of the Commission shall be individuals who are or who have been engaged in biomedical or behavioral research involving human subjects. In appointing members of the Commission, the Secretary shall give consideration to recommendations from the National Academy of Sciences and other appropriate entities. Members of the Commission shall be appointed for the life of the Commission. The Secretary shall appoint the members of the Commission within sixty days of the date of the enactment of this Act.

Term.

Compensation.

(2)(A) Except as provided in subparagraph (B), members of the Commission shall each be entitled to receive the daily equivalent of the annual rate of the basic pay in effect for grade GS–18 of the General Schedule for each day (including traveltime) during which they are engaged in the actual performance of the duties of the Commission.

5 USC 5332 note.

(B) Members of the Commission who are full-time officers or employees of the United States shall receive no additional pay on account of their service on the Commission.

Travel expenses.

(C) While away from their homes or regular places of business in the performance of duties of the Commission, members of the Commission shall be allowed travel expenses, including per diem in lieu of

STATUTE-88-Pg342.pdf (govinfo.gov)

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Requirements for IRB Review

Section 474:

*The Secretary shall by regulation require that each entity that applies for a grant or contract under this Act for any project or program which involves the conduct of biomedical or behavioral research including human subjects submit in or with its application for such grant or contract assurances satisfactory to the Secretary that it has established (**in accordance with regulations which the secretary shall prescribe**) a board (to be known as an Institutional Review Board) to review biomedical and behavioral research involving human subjects conducted at or sponsored by such entity in order to protect the rights of the human subjects of such research.*

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Charge of the National Commission

- Identify the basic ethical principles which should underlie the conduct of biomedical and behavioral research involving human subjects
- Develop guidelines which should be followed in such research to assure it is conducted in alignment with such principles

Charge of the National Commission (continued)

- The commission was specifically charged with considering:
  - The boundaries between biomedical or behavioral research involving human subjects and the accepted and routine practice of medicine
  - The role of risk-benefit criteria in the determination of the appropriateness of research involving human subjects
  - Appropriate guidelines for selection of human subjects for participation in biomedical and behavioral research
  - The nature and definition of informed consent in various research settings
  - Mechanisms for evaluating & monitoring the performance of IRBs

Why Ethics?

- Must be able to distinguish subjects as people
- People cannot be used as a means to accomplish a scientific end

- "Codes consist of rules, some general, others specific, that guide the investigators or the reviewers of research in their work. Such rules often are inadequate to cover complex situations; at times they come into conflict, and they are frequently difficult to interpret or apply. Broader ethical principles will provide a basis on which specific rules may be formulated, criticized and interpreted."

The Belmont Report - Three Ethical Principles

- Respect for Persons
  - Recognize & Respect Individual Autonomy
  - Protect those with diminished Autonomy

    [Informed Consent Process, Special Protections for Vulnerable Populations]
- Beneficence
  - Do No Harm
  - Maximize potential Benefits/Minimize Potential Harms

    [Study design, Risk/Benefit Ratio]
- Justice
  - Fairness in selection of subjects
  - Be sure access to research is not denied from certain subjects
  - Be sure research burden is not imposed on certain populations

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What is an IRB?

Institutional Review Board
Under FDA regulations, an IRB is an appropriately constituted group that has been formally designated to review and monitor biomedical research involving human subjects. In accordance with FDA regulations, an IRB has the authority to approve, require modifications in (to secure approval), or disapprove research. Institutional Review Boards (IRBs) and Protection of Human Subjects in Clinical Trials | FDA

An **IRB** is a committee that performs ethical review of proposed research. https://www.hhs.gov/ohrp/irbs-and-assurances.html

- Must include sufficient expertise to review the research
- Must include at least 5 members
- Membership must be diverse with regard to race, gender and cultural backgrounds
- **Must be sensitive to community concerns**
- Types of Members
  - Scientist
  - Non-scientist
  - Member unaffiliated with the organization

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Approval Criteria

- **Risks are minimized**
- **Risks are reasonable in relationship to the potential benefits**
- **Subject selection is equitable**
- **Informed Consent is obtained and documented**
- **Plans for monitoring are appropriate to ensure safety**
- **Protections for privacy & confidentiality are adequate**
- **Additional Protections are in place for vulnerable participants**

Informed Consent

- Ensures that participants have adequate information to make a decision about study participation, including:
  - Information about the research procedure
  - Purpose of the research
  - Must describe procedures for protecting subject confidentiality
  - Explanation of anticipated risks/benefits
  - Must identify research participation as voluntary
  - Must provide person to contact for questions about the research
  - Must provide key information first
- Information must be provided at an 8th grade reading level in the primary language spoken by the participant
- Information must be free of coercive elements or undue influence

Are IRBs Enough?

"I remember hearing many observers predict back in the mid-1970s that IRBs, after widely adopted and well developed, would solve many, if not most of the ethical and "public perception" problems in research. Would it be that easy"…

Joan Rachlin
Former Executive Director
Public Responsibility in Medicine and Research (PRIM&R)

What is a Human Research Protections Program (HRPP)?

"AAHRPP accreditation standards are divided into three domains: **Organization, IRB or EC, and Researcher and Research Staff**. These domains represent the three primary spheres of responsibility within a HRPP."

Reference: Summers, E.I., Feige, M. (2018). Chapter 5, Accreditation of Human Research Protection Programs, p. 66.

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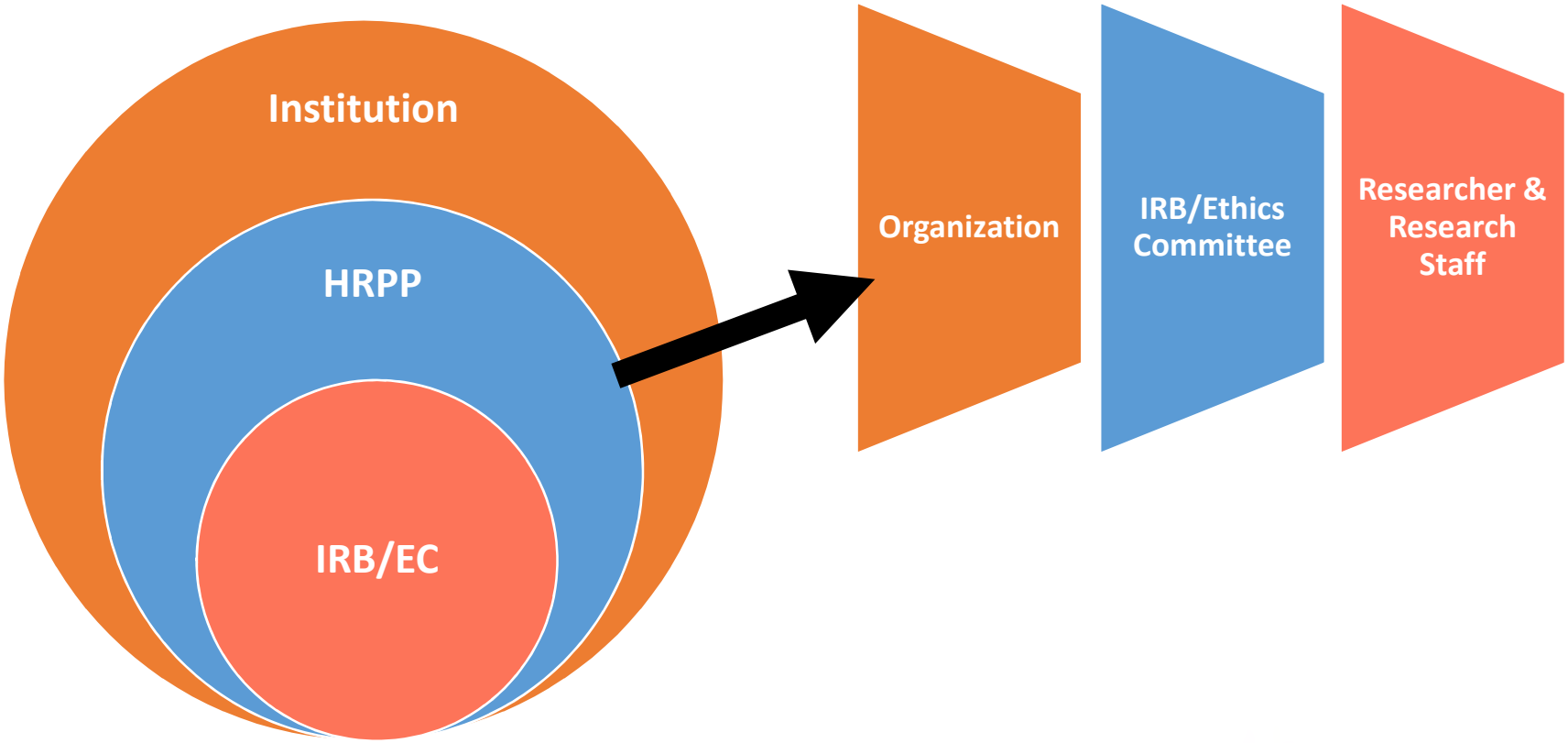
Human Research Protections Programs (HRPPs)



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Current Challenges

Movement away from Local IRB oversight

Increasing emphasis on research conducted in the absence of consent (e.g. AI, Research with biospecimens)

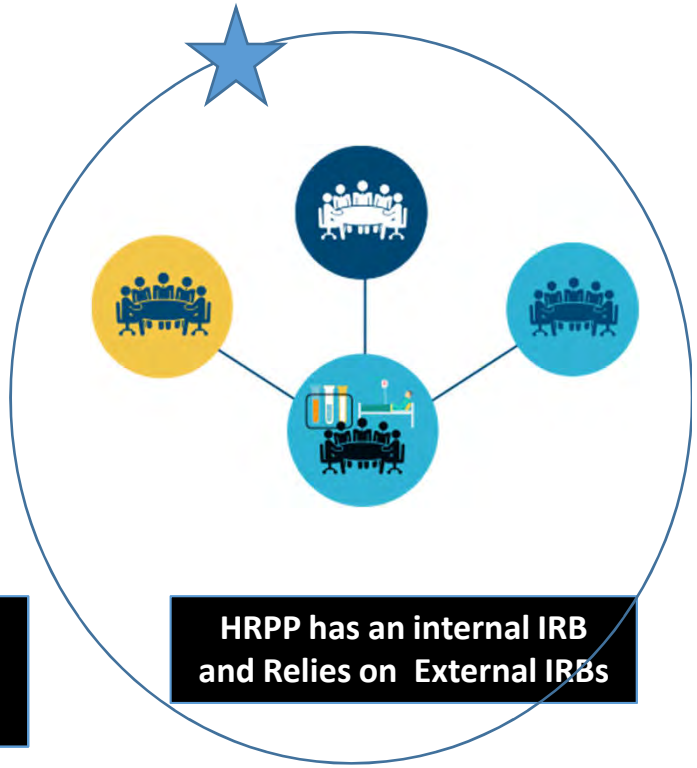
Added complexity to the Investigator/Participant relationship – Decentralized Trials

Increased Complexity of the Regulatory Environment

HRPP/IRB Models

HRPP has no internal IRB
Relies on External IRBs

HRPP has an internal IRB
Does not Rely on External IRBs



HRPP has an internal IRB
and Relies on External IRBs

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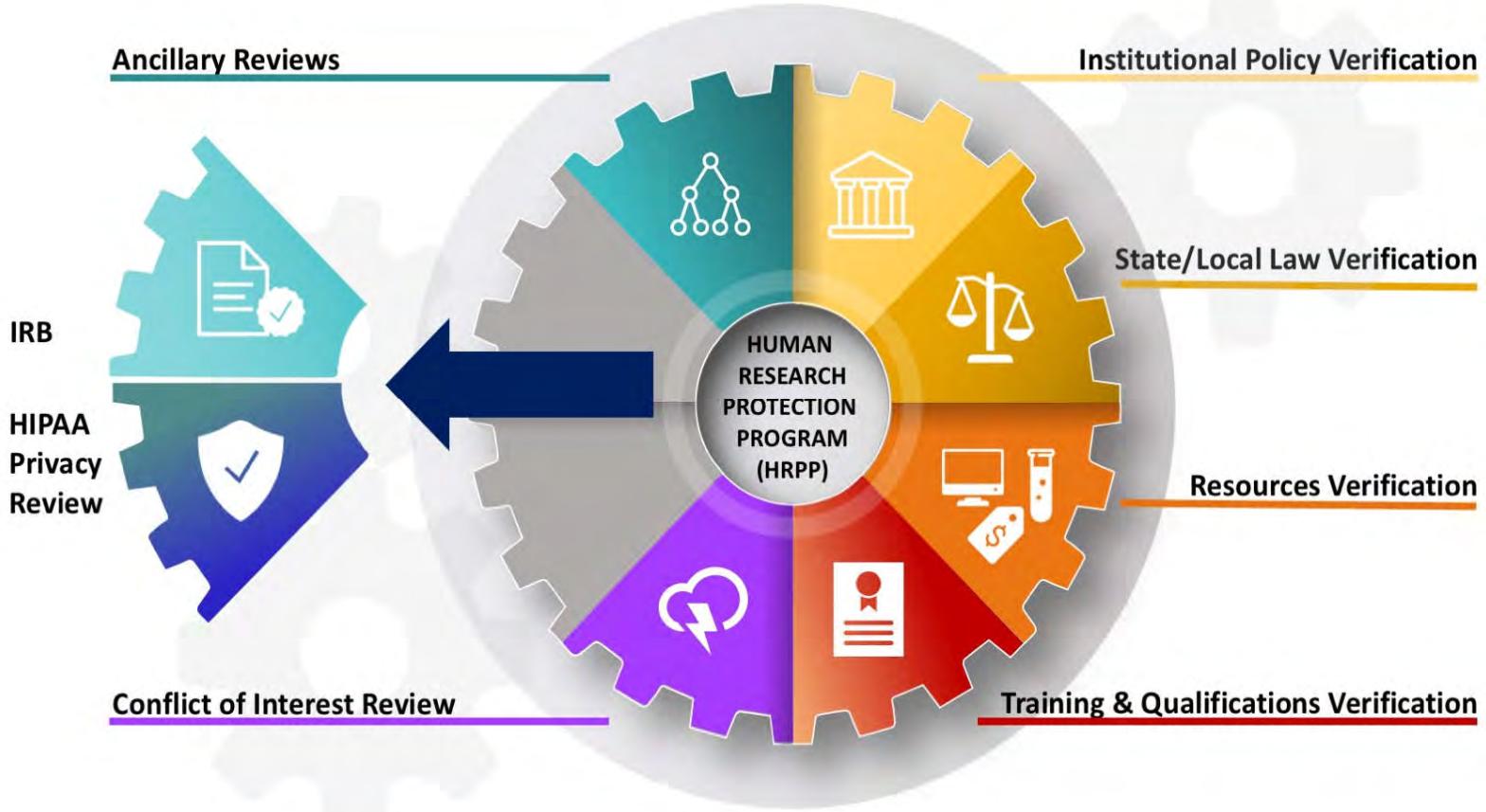
The Impact of sIRB Review



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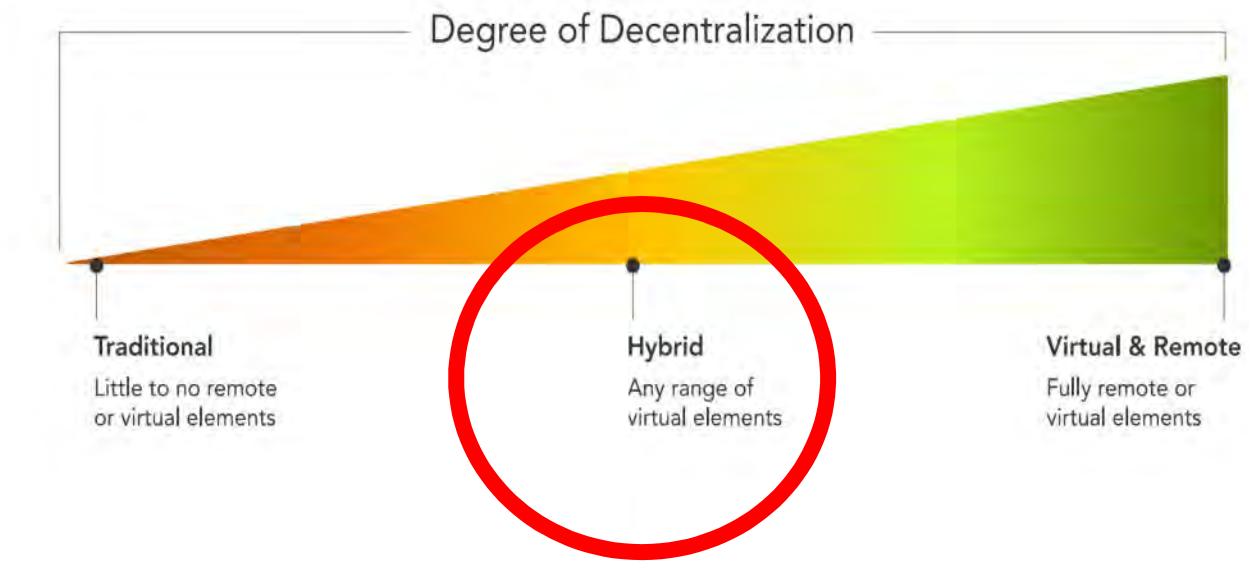
The Shift to Decentralized Trials



Challenges in DCTs:

- Communication
- Connections with Research Participants
- Compliance
- Oversight of 3rd party entities

Reference: Decentralized Clinical Trials
https://www.advarra.com/solutions-for/clinical-technology-by-need/decentralized-clinical-trials/

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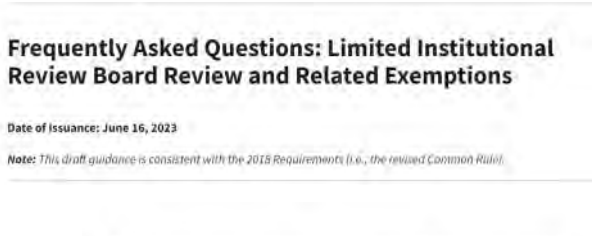
Change is Continual



Frequently Asked Questions: Limited Institutional Review Board Review and Related Exemptions

Date of Issuance: June 16, 2023

Note: This draft guidance is consistent with the 2018 Requirements (i.e., the revised Common Rule).

GUIDANCE DOCUMENT

Informed Consent

Guidance for IRBs, Clinical Investigators, and Sponsors

AUGUST 2023

Download the Final Guidance Document | Read the Federal Register Notice

Final

GUIDANCE DOCUMENT

Decentralized Clinical Trials for Drugs, Biological Products, and Devices

MAY 2023

Download the Draft Guidance Document | Read the Federal Register Notice

Draft | Level 1 Guidance

Not for implementation. Contains non-binding recommendations

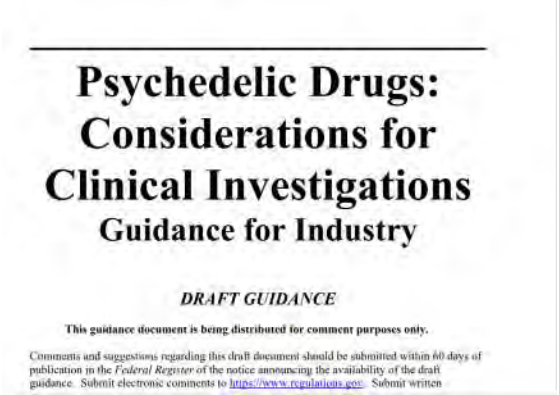
FEDERAL REGISTER

The Daily Journal of the United States Government

Proposed Rule

Institutional Review Boards; Cooperative Research

A Proposed Rule by the Food and Drug Administration on 09/28/2022



Psychedelic Drugs: Considerations for Clinical Investigations

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written

GUIDANCE DOCUMENT

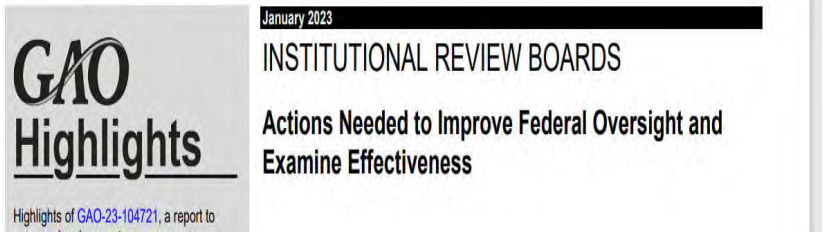
Institutional Review Board (IRB) Review of Individual Patient Expanded Access Submissions for Investigational Drugs and Biological Products

Guidance for IRBs and Clinical Investigators

SEPTEMBER 2023

Download the Final Guidance Document | Read the Federal Register Notice

Final | Level 1 Guidance



GAO Highlights

Highlights of GAO-23-104721, a report to

January 2023

INSTITUTIONAL REVIEW BOARDS

Actions Needed to Improve Federal Oversight and Examine Effectiveness

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Case Discussion: Case # 1

A trial tests a new investigational medication for asthma in children delivered via an investigational nebulizer. The trial will also evaluate the ability of caregivers to successfully use the new device. Parents and children are introduced to the trial at clinical sites and then if enrolled, are connected with a sponsor-contracted third party research agency who will send sponsor-trained professionals to homes to train parents on use of the device, monitor delivery of the investigational medication, collect samples for analysis and record outcomes while on site.

1. What does the study team need to think about to prepare for this trial?
2. Are there any potential human research protections concerns?

Case Discussion: Case # 2

Case 2:
A study is evaluating the use of a new AI tool to better detect potential lesions of concern in follow-up CT scans of the lung for individuals being monitored for potential metastases after treatment for a primary breast cancer. As the algorithm is still being developed, the study proposes to route CT scans for their standard clinical read and simultaneously for a read by the AI tool. The AI read will not be shared with patients or clinicians, even if different than the clinical read as it is not yet known whether the AI tool is effective at reading the scans. The research team plans to compare the AI output to the clinical read to assess the tool's effectiveness. The comparison data will be recorded and the reads from the AI tool will be destroyed. The study team requests a waiver of consent as it would not be practicable to consent all participants who are having scans.

1. Are there any potential human research protections concerns?

Case Discussion- Case 3

Dr. Smith is an investigator at Hospital A, a participating site in an NIH-funded multi-site study of an investigational medication to control blood sugar levels in Type 1 diabetics. The IRB of record (single IRB) for this multi-center study is IRB C. One participant enrolled in the study at Hospital A was administered an incorrect dose of study medication and was hospitalized for adverse effects experienced related to the dosing error. Dr. Smith reports the dosing error to IRB C per their reporting requirements. IRB C finds the error to constitute serious noncompliance and reports the determination to OHRP and the FDA.

The HRPP at Hospital A receives a copy of the reporting letter per the reliance agreement. Upon receipt, the HRPP Director at Hospital A reaches out to the local investigator and asks about the root cause of the error. Upon closer look at the study files, the investigator identifies that there was an error in the medication order set. The review also uncovers the fact that 5 other participants enrolled in the trial at Hospital A have experienced similar dosing errors.

- **What human research protections issues are raised with this case?**

JHM IRB Request a Consult

Need help navigating the IRB review process?
Use the QR code or visit the IRB website: https://www.hopkinsmedicine.org/institutional-review-board/about/contact to request a consult and be matched with IRB staff who will address your needs.

Sample topics we can help with:

- Protocol planning
- Determining IRB review type & forms
- IRB regulations and policies
- Recruitment & consent
- Responding to IRB review

Consult requests will receive a response within 24 hours – please reach out!

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Questions/Discussion

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