Ethics and Regulations Governing Human Subjects Research (HSR) at EPA

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Introductory Background

- The regulations governing HSR are based on fundamentally ethical considerations and have been carefully developed to help assure its ethical conduct.
- Data derived from HSR are essential to the Agency's risk assessments and to the setting of environmental standards, so EPA is involved in HSR at multiple levels.
- EPA's public health practice activities are also governed by ethics, and when they systematically obtain data from or about humans, they have the potential to cross the border into research and become subject to the HSR regulations as well.

A Short History of Human Subjects Research

- The Nazi experiments and the Nuremburg Code.
- The Declaration of Helsinki (1964).
- Beecher HK. Ethics and clinical research. *N Engl J Med* 1966.
- The Tuskegee Syphilis Study (1932-1971).
- 45 CFR 46 (1974), the National Commission (1974) and the Belmont Report (1979).
- The Common Rule (1991).

The Ethical Principles of the Belmont Report

- *Respect for Persons* – respect autonomous agents and protect persons with diminished autonomy.
- *Beneficence* – maximize benefits, minimize harms, and do not harm intentionally.
- *Justice* – distribute the benefits and burdens of research fairly.

Regulatory Application of the Belmont Principles

- *Respect for Persons*
  - Informed consent and assent requirements.
  - Special protections for vulnerable groups.
  - Protection of privacy and confidentiality.
- *Beneficence*
  - Minimize risk to subjects.
  - Conduct analysis to determine reasonable risk/benefit ratio.
  - Monitor research to ensure subject safety.
- *Justice*
  - Equitable selection of subjects.

The Common Rule

- A regulatory document adopted by multiple Federal Agencies in 1991, including EPA, for which the Belmont principles provide the core ethical justification.
- Defines the conditions under which HSR conducted, supported, or regulated by the Federal Government may be undertaken.
- Establishes the Institutional Review Board (IRB) and the informed consent process as the pillars of human research subject protection.
- Can be found at Subpart A of the current EPA HSR Rule (EPA Regulation 40 CFR 26).

The EPA HSR Rule (40 CFR 26)

- Applies the provisions of the Common Rule to all HSR conducted, supported, or regulated by EPA.
- Adds 3 Subparts beyond the Common Rule for HSR conducted or supported by EPA in which:
  - *Intentional exposure* research is distinguished from *observational* research.
  - Intentional exposure research is categorically banned in children and pregnant or nursing women.
  - Special additional protections are applied to observational research involving children and pregnant or nursing women.
- Adds additional Subparts that specifically address third-party HSR for pesticides subject to regulation by EPA under the pesticide laws.

Regulatory Definition of *Research*

- A systematic investigation.
- Designed to develop or contribute to generalizable knowledge.
- Includes research development, testing and evaluation.
- May be conducted under a program which is not considered research for other purposes (e.g., a service or demonstration program or a public health practice activity).

Regulatory Definition of *Human Subject*

- Living individual about whom an investigator obtains:
  - Data through intervention or interaction with the individual, or
  - Identifiable private information.

- Intervention includes:
  - Physical procedures by which data are gathered (e.g., venipuncture).
  - Manipulations of the subject or the subject's environment for research purposes.

- Interaction includes:
  - Communication between investigator and subject.
  - Interpersonal contact between investigator and subject.

Regulatory Definition of *Human Subject*

- Private information includes:
  - Information about behavior that occurs in a context where an individual can reasonably expect that no observation or recording is taking place.
  - Information which has been provided for specific purposes and which the individual can reasonably expect will not be made public (e.g., a medical record).
- Individually identifiable means:
  - The identity of the subject is or may readily be ascertained by the investigator, or
  - The identity of the subject is or may readily be associated with the information.

Exempt HSR

- Certain categories of human research are exempt from the requirements of the Common Rule.
- These categories are defined by the Common Rule itself—in EPA's version they are found at 40 CFR 26.101(b).
- They encompass domains of research in which the risks are such that the protections of the Common Rule are not deemed necessary.

Exemption Category (4)

- Research, involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens, if these sources are publicly available or if the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects.

EPA Regulations and Policies Governing HSR

- EPA Regulation 40 CFR 26 *(Protection of Human Subjects)*
- EPA Order 1000.17 Change A1 *(Policy and Procedures on Protection of Human Subjects in EPA Conducted or Supported Research)*

What EPA's HSR Policies Require

- An HSR/non-HSR determination by the Program or Regional Office for all proposed projects in which data may be obtained from or about humans.
- Approval (or determination of exemption from the HSR regulations) by the EPA HSRRO for any project determined to be HSR.
- Approval of any non-exempt HSR by the IRB of record.

Secondary Use of Existing Data

- Secondary data use may or may not be HSR.
- The EPA HSRRO is available for consultation with any Program or Regional Office on any HSR/non-HSR determination.
- If the secondary data use is HSR, it may or may not be exempt HSR under exemption category (4).
- EPA policy requires that the exemption determination in all cases be made by the Agency HSRRO.

Secondary Use of Existing Data

- If the secondary data use is non-exempt HSR, it must be reviewed and approved by both the IRB of record and the EPA HSRRO.

- EPA has a standing contract for IRB services with the University of North Carolina in Chapel Hill (UNC) which can be used by any EPA investigator in any Agency component, including NCEA.

- The ORD Human Research Protocol Office, directed by Robert Truckner, is the Agency's interface with the UNC IRB, if needed, and works closely with the Office of the HSRRO.

Secondary Non-HSR (or Exempt HSR) Use of Data Derived from HSR

- Ethical Considerations:
  - Is the secondary use consistent with the consent provided by the subjects in the HSR that produced the data?
  - Was the HSR itself ethical at the time it was conducted?

- Regulatory and Policy Considerations:
  - The regulatory status of inconsistency with an original consent is not clearly established.
  - 40 CFR 26 Subpart Q establishes ethical standards for HSR from which data may be used by EPA in actions taken under FIFRA and FFDCA.
  - There are no current EPA policies or regulations governing other secondary HSR data use if that use is not itself HSR.
  - The standards in Subpart Q are reasonable and can be helpful in ethical decision-making about other secondary HSR data use.

The Subpart Q Standards

- Prohibition on use of data from HSR involving intentional exposure of pregnant women, nursing women, or children.
  - A useful guideline if the exposure is to a pesticide or other toxic substance.
  - Not a useful guideline if the exposure is to certain other substances, such as a nutritional substance or a therapeutic substance.

The Subpart Q Standards

- Prohibition on the use of data from HSR initiated before April 7, 2006 (the effective date of the rule) if there is clear and convincing evidence that the conduct of the research was fundamentally unethical (*e.g.*, the research was intended to seriously harm participants or failed to obtain informed consent), or was significantly deficient relative to the ethical standards prevailing at the time the research was conducted.
  - A generally useful guideline for any secondary HSR data use.

The Subpart Q Standards

- Prohibition on the use of data from HSR initiated after April 7, 2006 (the effective date of the rule) unless EPA has adequate information to determine that the research was done in substantial compliance with 40 CFR 26 Subparts A through L, or if conducted in a foreign country, under procedures at least as protective as those in 40 CFR 26 Subparts A through L.
  - A useful guideline except for ethically desirable research currently prohibited by an unintended effect of Subpart B.

The Subpart Q Standards

- Procedures for otherwise unacceptable use of HSR data in order to protect the public health:
  - The views of the EPA Human Studies Review Board are obtained concerning the proposal to use the data.
  - EPA has provided an opportunity for public comment on the proposal to use the data.
  - EPA has determined that using the data is crucial to a decision that would impose a more stringent regulatory decision that would improve protection of public health.
  - EPA publishes a full explanation of its decision to use the data, including a thorough discussion of the ethical deficiencies of the underlying HSR and the full rationale for finding that the cruciality standard was met.

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