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

Basics for EPA Project Officers and Grants Specialists

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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)
- 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

Some General Characteristics of Public Health Practice Activities

- Designed to provide a specific health benefit to a defined group
- Conducted by an entity with appropriate legal basis for engaging in public health practice
- Uses accepted practice interventions

Distinguishing Public Health Practice from HSR

- Public health practice and HSR projects exist along a continuum without a clear, sharp border
- Deciding whether or not a particular project is HSR is not always easy or straightforward and requires careful application of the regulatory definitions
- Some of the features of HSR are routinely encountered in public health practice activities, even when the activity is not HSR and is not subject to the HSR regulations

Distinguishing Public Health Practice from HSR

- Public health practice and HSR may coexist in the same project
- Public health practice activities that start out as non-HSR may become HSR during execution
- Data derived from public health practice may later be used for HSR

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

Engagement in HSR

- *Engagement* refers to particular activities carried out by an institution during the course of non-exempt HSR conducted or supported by any Common Rule agency
- Not all activities associated with a research project constitute engagement
- Institutions whose employees or agents interact or intervene with subjects for research purposes are always considered to be engaged
- Direct awardees – *even when all HSR activities are subcontracted to another institution* – are also engaged, except in *very rare* circumstances

Engagement in HSR

- If an institution is engaged in non-exempt HSR, it must have an assurance of compliance on file with the Common Rule agency conducting or supporting the research, and the research must be approved by an IRB listed on that assurance

- An *assurance* is a document certifying that the institution will comply with the requirements of the Common Rule

- A Federalwide Assurance (FWA) filed with the HHS Office for Human Research Protections is accepted by EPA and most Common Rule agencies for this purpose

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 pre-award submissions that propose work in which data may be obtained from or about humans during the period of support
- HSRRO approval of the funding award *prior to making the award* for those pre-award proposals in which HSR may be involved during the period of support
- Post-award approval of any HSR developed under the award by the IRB of record with certification to EPA
- Final approval (or determination of exemption from the HSR regulations) by the EPA HSRRO before any human subject is involved in the research

Grant & Contract Specialist Responsibilities

- Ensure that a documented HSR/non-HSR determination has been made by the HSR Officer in the Program or Regional Office making the award (or by the Agency HSRRO) prior to finalizing an award for any work that may involve obtaining data from or about humans during the period of support.

- If the award is for work that may involve HSR:
  - Ensure that a funding award approval memo has been obtained from the Agency HSRRO prior to making the award.
  - Include in the award document a clause requiring compliance with EPA Regulation 40 CFR 26.

Project Officer Responsibilities

- Include a documented HSR/non-HSR determination from the HSR Officer in your Program or Regional Office (or from the Agency HSRRO) in the funding package for any work that may involve obtaining data from or about humans during the period of support.

- If the award is for work that may involve HSR, include the funding award approval memo from the Agency HSRRO in the funding package.

Project Officer Responsibilities

- After the funding award has been made, ensure that written approval (or determination of exemption from the HSR regulations) has been obtained from both the IRB of record *and* the EPA HSRRO for any HSR protocol developed under the award
- Also ensure that the PI is aware that *both* approvals are required before subject recruitment can begin.
- Monitor the project during its execution to assure ongoing compliance with regulations governing HSR

Information and Documents Required for HSRRO Review

- For funding award approvals:
  - Copy of the application, work plan, or other pre-award document
  - The primary awardee's FWA Number
- For study approvals and exemption determinations:
  - Copy of the study protocol(s) as actually submitted to the IRB(s) (the pre-award document is not sufficient)
  - Copy of the IRB approval or exemption letter(s)
  - Copy of the IRB-approved consent forms, patient recruitment materials, etc., if applicable
  - Copy of all supplementary IRB correspondence

HQ HSR Resource Persons

- OA:
  - OPEI: Chris Dockins
- OPPTS:
  - OPP: John Carley and Kelly Sherman
- ORD:
  - NHEERL and NERL: Robert Truckner
  - NRMRL (Cincinnati): Subhas Sikdar
  - RTP Campus: Robert Truckner

Regional HSR Resource Persons

- R1: Rick Sugatt
- R2: Roland Hemmet
- R3: Ronald Landy
- R4: Thomas Baugh
- R5: Vacant
- R6: Jeffrey Riley
- R7: Brenda Groskinsky
- R8: Patti Tyler
- R9: Winona Victery
- R10: Jean Zodrow
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