ISAC Book

ISAC Team

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Contents

Chapter 1

Human Subject Protection and Research Regulation

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1.1 Introduction

1.1.1 Module Goal

The goal for this module is to introduce the essential elements of human subjects' protections and regulatory requirements pertinent to the conduct of clinical trials. Essential aspects of human subjects' protections and regulatory requirements provided in this module include:

- Institutional Review Boards
- Federal Wide Assurances (no longer full section. Keep here or delete?)
- Health Insurance Portability and Accountability Act (HIPAA)
- Data Use Agreements
- ClinicalTrials Registration
- Data Safety Monitoring
- Informed Consent
- Adverse event monitoring and reporting

Note: This module does not address regulatory issues pertaining to animal research.

1.1.2 General Considerations about federal regulations

The regulation of clinical trials can be complex. What may be seen by investigators as trivial regulations or minor misdemeanors can have serious consequences for the individual investigator, their institutions, and trial subjects. Therefore, it is wise to be over-cautious and anticipate problems before they arise. As regulatory issues can play a critical role in your trial design, it is strongly advised to consider these issue from the very start of project planning (e.g. grant preparation) by consulting with your institutional review board (IRB), and making sure you understand existing regulations and institutional policies (see Resources).

The current system of protection for human research subjects carried out or supported by most US federal agencies is based primarily on the Code of Federal Regulations Title 45: Public Welfare, part 46 (45 CFR 46).

Federal agencies including the U.S. Food and Drug Administration (FDA) and the National Institutes of Health (NIH), make and enforce regulations to ensure the safety of participants in clinical trials, and retain

final authority for determining whether an institution has been compliant. Investigators should review the specific regulations of the funding or over-seeing agency and confer with the IRB to determine whether additional regulations or policies apply.

FDA Regulated Trials A key initial step is to determine whether or not your trial falls under the regulatory jurisdiction of the FDA which generally oversees drug and device trials. While complete discussion of FDA regulations is beyond the scope of this module, several useful links are provided (see Resources).

Office of Human Research Protections (OHRP): The OHRP is the federal body responsible for compliance monitoring. Under Title IV of the Public Health Service Act (42 USC 281 et seq.), OHRP has the authority to investigate complaints about human subject protections in HHS-funded research, or other research covered by the institution's Assurance of Compliance. (See link in resources below)

1.1.3 Resources

For general regulatory issues, particularly for federally funded trials, the OHRP website provides extensive resources at http://www.hhs.gov/ohrp/. At Hebrew Senior Life, institutional IRB policies and procedures are available at: http://www.instituteforagingresearch.org/resources/research-administration/institutional-review-board and its internal HSL "HUB" at http://thehslhub/Departments/Roslindale/HSL-IFAR/Institutional-Review-Board.

The Belmont Report – ethical principles and guidelines for research involving human subjects: http://www.hhs.gov/ohrp/regulations-and-policy/belmont-report/.

International Conference on Harmonization (ICH) guidelines for Clinical Good Practice (GCP) http://www.ich.org/products/guidelines/efficacy/article/efficacy-guidelines.html (Not referenced. Should it still be included as resource?)

US Food and Drug Administration – the FDA has multiple sets of regulations governing the use of drugs, biologics, and devices with human subjects. The FDA has their own set of human subject regulations and regulations governing IRB activities. All of these regulations can be found here: http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/ucm155713.htm

World Health Organization, (http://www.who.int/about/en/) (Not referenced. Should it still be included as resource?)

1.2 Institutional Review Board

1.2.1 What

An institutional review board (IRB) is an appropriately constituted group formally designated to review, approve and monitor research involving human subjects to ensure it is conducted in accordance with applicable federal regulations, institutional policies, and ethical guidelines.

This module provides general information about IRB's. While IRBs all adhere to the same regulations, (see http://www.hhs.gov/ohrp/regulations-and-policy.) each IRB is required to have its own institutional policies, and therefore each IRB operates differently. It is important to understand the requirements of the IRB overseeing your project. Specific information relevant to HSL IRB can be found at: http://www.instituteforagingresearch.org/resources/research-administration/institutional-review-board and its internal HSL "HUB" at http://thehslhub/Departments/Roslindale/HSL-IFAR/Institutional-Review-Board).

1.2.1.1 Categories of IRB oversight

Depending on the study design and degree to which human subjects are involved, the IRB will review the research and will make a determination on the appropriate review level. The basic levels of review include:

Exempt (determination by IRB Chair or her designee) Expedited (review/approval by IRB Chair or her designee) Full Board (review/approval by the convened IRB) Most clinical trials will require full IRB review.

1.2.1.2 IRB Applications and Reviews

IRB applications include:

- Initial application
- Annual/continuing review
- Amendments/modifications to the protocol or study materials
- Incident Reports for:
  - Unanticipated problems
  - Non-Compliance

1.2.1.3 Initial Review of Research Application

All human subjects' research must be reviewed and approved by an IRB before human subjects activities can begin. This includes recruitment efforts, and receiving or collecting data. Per Federal and Institutional policy, no funds for research involving human subjects activities will be released until the appropriate IRB approval has been secured.

1.2.1.4 Annual/Continuing Review

Investigators must receive continuing approval of their research at least annually. On some occasions, more frequent review may be required by the IRB. Continuing approval is required until all activities with human subjects are complete (this includes access to data with participant identifiers or with codes that can be linked back to research participants).

1.2.1.5 Amendment Submissions

Investigators must submit all changes to the research or research materials and receive IRB approval for those changes prior to implementation (except when necessary to eliminate apparent immediate hazards to research participants).

1.2.2 Why

The IRB assures that a clinical trial is in compliance with federal and state regulations, institutional policies, and accepted ethical guidelines, to protect the rights and welfare of research subjects.

1.2.3 How

1.2.3.1 IRB Review for Single Site Trials

The procedures for IRB review differ by institution but have common main elements. It is wise before you embark on your IRB application to consult with the IRB office to review the general study design and anticipate key review considerations.

The HSL IFAR IRB uses an electronic submissions system (Cayuse). Forms are templated and will guide you through the required elements. Application submissions must meet deadlines stipulated in the HSL IFAR IRB Standard Operating Procedures as found on the HSL IFAR IRB website.[Create link?].

1.2.3.2 IRB Review for Multi-Site Trials

Many clinical trials involve multiple sites and/or investigators from multiple institutions. Many clinical trials involve multiple sites that are clearly engaged in human subjects' research (i.e., site personnel are recruiting subjects, implementing an intervention, or collecting data). Regulatory oversight of these trials can be done either by:

Single IRB review (one IRB reviews the research, and the other IRBs rely on the reviewing IRB) Multiple IRB reviews (e.g. each institution conducts its own IRB review/approval) In June 2016, the NIH established a policy effective May 25, 2017, requiring a single IRB for all NIH-funded multisite studies, with only rare exceptions.

http://grants.nih.gov/grants/guide/notice-files/NOT-OD-16-094.html

1.2.3.3 Relying on an External IRB ('ceded review')

IRBs of engaged sites and investigators may cede oversight responsibility to the IRB reviewing the research (also referred to as the IRB of record). Relying on an external IRB, or ceded review, is documented with a formal agreement between the reviewing and relying site IRBs and must be signed by an Institutional Official. Note: If you are conducting research with Harvard affiliates, you may rely on the Harvard Catalyst Reliance Agreement, rather than an IRB Authorization Agreement. See the HSL IRB office for more information.

1.2.3.4 Oversight for Institutions without an IRB

Some study sites engaging in human subjects' research (e.g., community nursing homes) may not be associated with an IRB. In this case the reviewing IRB may agree to provide IRB oversight for the external site through a formalized agreement (Individual Investigator Agreement) between the two parties. Alternatively, a commercial IRB may be engaged in a contract to provide oversight for that external site. Sites that receive direct federal awards for research purposes may also need a FederalWide Assurances. These determinations will be made by the prime IRB responsible for the trial.

1.2.4 Special considerations for older subjects

There are two special considerations for special protections governing research with elderly subjects: cognitive impairment and institutionalization. Under those conditions, the following must be taken into consideration (see also Informed Consent Section related to the decision making capacity XXXX): (http://www.hhs.gov/ohrp/archive/irb/irb_chapter6.htm). HSL IRB's Standard Operating Procedures (SOPs) [ADD link].

1.2.5 Common Pitfalls

Not seeking IRB guidance in the process of trial design and well in advance of your planned start date. Underestimating the time it takes to get IRB approval. Underestimating regulatory requirements. Failure to meet requirements could lead to serious consequences for yourself and your institution. Be overly cautious and always report anything of potential concern to your IRB. Flippant or casual comments about human subjects' or regulatory issues about your trial via emails or text. If a problem occurs, all related communication may be become eventually become relevant.

1.2.6 Resources

HHS, Office for Human Research Protections, Regulations and Policy, http://www.hhs.gov/ohrp/regulations-and-policy/guidance/index.html
http://grants.nih.gov/grants/guide/notice-files/NOT-OD-16-094.html

S. Food and Drug Administration, http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/
HSL IRB: http://www.instituteforagingresearch.org/resources/research-administration/institutional-review-board and its internal HSL "HUB" at http://thehslhub/Departments/Roslindale/HSL-IFAR/Institutional-Review-Board