Fundamentals of Research

Health Care Compliance Association’s Research Compliance Conference
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Today’s Presenters

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Session Agenda

- Human Subject Protection
- The Business of Clinical Research
- Other Fundamental Issues
- Questions & Answers
Law and Regulations Governing Clinical Research

Federal Agencies within the Department of Health and Human Services:
- Food and Drug Administration (FDA)
- Office of Human Research Protection (OHRP)
- Office of Research Integrity (ORI)
- Office of Inspector General (OIG)
HUMAN SUBJECT PROTECTION

- The Belmont Report
- Federal Laws and Regulations on the Protection of Human Subjects
  - Informed Consent
  - Institutional Review Boards (IRBs)
  - Basic HHS policy (“Common Rule”)
The Belmont Report
Basics of the Belmont Report

- National Commission for the Protection of Human Subjects of Biomedical & Behavioral Research
- Based on the Commission’s report, HHS revised and expanded regulations for protection of human subjects (45 CFR part 46)
- Milestone in Federal responsibility, leadership and commitment
Fundamental Ethical Principles for all Human Subject Research

1. Respect for persons
2. Beneficence
3. Justice
Informed Consent
Scope: Protection of human subjects in clinical investigations regulated by the FDA or used to support research applications or marketing permits for FDA-regulated products

General rule: Investigator may only involve a human being as a research subject if a legally effective informed consent is obtained.
21 C.F.R. §50.20
General requirements for informed consent:

- Must be obtained in advance and not through coercion or undue influence.
- Research subject must understand the terms of the consent.
- May not serve as a waiver of subject’s legal rights or a release from liability for negligence.
21 C.F.R. §50.25
Basic elements of informed consent:

- Notice that study involves research, the research’s purpose, and expected duration of subject’s participation.
- Description of reasonably foreseeable risks or discomforts.
- Expected research benefits.
- Disclosure of alternative procedures or courses of treatment.
Basic elements of informed consent (cont.)

- Describes scope of record confidentiality.
- Contact person for questions regarding study.
- Statement that participation is voluntary and participants are not otherwise disadvantaged.
- When there is potential for more than minimal risk, notice regarding available compensation and/or medical treatments should injury occur.
- Additional elements to address unique situations.
21 C.F.R. §50.27
Documentation of informed consent

- A comprehensive consent form signed by research subject; or
- A short form for consent, which accompanies an oral presentation with a witness present.
- Subject must sign short form and written summary.
- IRB must approve written summary of oral presentation that is made to subjects.
21 C.F.R. §§50.23, 50.24

Exceptions from informed consent requirements:

- Human subject confronts a life-threatening situation necessitating use of test article.
- Informed consent cannot be obtained due to subject’s inability to communicate or lack of legal capacity.
- Insufficient time to obtain consent from subject’s legal representative.
Exceptions to informed consent (cont.)

- No alternative treatment with equal or greater chance of life-saving potential is available.
- IRB approves investigation without requiring patient consent.
- Presidential waiver to use investigational new drug for armed forces.
Institutional Review Boards (IRB)
Scope: General requirements and standards for Institutional Review Boards (IRBs) that oversee clinical investigations regulated by the FDA.

General rule: IRBs must satisfy regulations related to composition, operation, and responsibilities for IRBs to be recognized by the FDA.
21 C.F.R. §56.103
Circumstances in which IRB review is required

- IRBs are required to approve and monitor clinical investigations subject to FDA jurisdiction.
- FDA may ignore clinical evidence derived from a clinical investigation that was not approved by an IRB.
There are several exemptions from the IRB requirements, including:

- Old, ongoing investigations (circa 1981);
- Emergency use of a test article;
- Qualifying taste and food quality evaluations; and
- FDA waiver in response to a sponsor petition.
IRB membership:

- At least five members;
- Varying professional backgrounds to reflect clinical and community perspectives;
- Encourage members of both genders to participate;
- One member with no affiliation to institution; and
- Protect against conflicts of interest in IRB review process.
IRB functions and operations require written procedures:

- For conducting initial and ongoing reviews of clinical investigations and other functions;
- For reporting adverse outcomes or non-compliance to IRB, institution, or FDA

Majority of IRB members must be present for votes, and protocol approvals required a majority vote of attending members
IRB’s scope of review:

- Authority to approve, require modifications in, or disapprove all FDA-regulated research activities.
- Require documentation of informed consent.
- Ongoing reviews conducted at appropriate intervals based on degree of risk, but not less than once a year.
- Apply regulatory criteria for approval.
The Common Rule
Scope: Basic HHS policy, known as the Common Rule, for protection of human research subjects applicable to any federal department or agency that adopts it.

Responsible agency: Office of Human Research Protection

General rule: These regulations govern IRB proceedings and patient subject notice requirements that apply to HHS-related clinical research that is not FDA-related.
A model code for all federal agencies.

Similar in structure to FDA’s more comprehensive rules.

- Addresses informed consent in the context of Public Health Service funded research.
- Contains rules regarding composition of IRBs and their functions and powers.
Special rules that provide additional protection for clinical research involving:
- Pregnant women;
- Human fetuses;
- Neonates;
- Prisoners; and
- Children
THE BUSINESS OF CLINICAL RESEARCH

- Financial disclosures
- Investigational new drugs (INDs)
- Investigational medical devices
- Clinical trials in Europe
Financial Disclosures
**Scope**: Financial disclosures required by applicants of FDA-regulated studies or products.

**General rule**: FDA requires disclosure of certain financial relationships related to research which it will use when considering the reliability of study data.
Requirements apply to any applicant who submits a marketing application for a new drug, device, or biologic.

Applicant must submit a list of all clinical investigators to be used in a study.

Applicant is responsible for making certifications or disclosure statements for its investigators.

- Applicant is required to collect data from investigators.
- FDA form 3453 to certify no financial relationship.
- FDA form 3455 to report certain financial relationships.
21 C.F.R. §54.5
Agency evaluation of financial interests

- FDA will evaluate disclosure statement and steps taken to limit bias.
- FDA will consider study design and purpose in assessing potential bias.
- FDA may take “any action it deems necessary” to ensure reliability of data.
Applicants are required to keep information on certain financial arrangements:

- Financial arrangements and/or payments between sponsors and clinical investigators; and
- Financial interests held by clinical investigators in the outcome of the research.

Record retention period is for two years after the date of FDA approval for the test article.
Investigational New Drugs (INDs)
Scope: Procedures and requirements governing investigational new drugs (INDs), including the IND application process for federal approval.

General rule: Use of a new drug subject to FDA approval must comply with these procedures and requirements until the IND application is approved.
21 C.F.R. Part 312

- Procedures and requirements governing use of investigational new drugs (INDs).
- Drugs under IND applications are exempt from FDA pre-market approval and can be lawfully shipped for clinical trial purposes.
- IND rules are extensive.
21 C.F.R. Part 312 (cont.)

- Addresses:
  - Labeling;
  - Promotion and charges for new drugs;
  - FDA waivers;
  - Phases of a new drug investigation;
  - Scope and content of required FDA reports;
  - Emergency use of new drugs;
  - Responsibilities of sponsors and investigators; and
  - Special rules for drugs for life-threatening and severely debilitating illnesses.
Investigational Medical Devices
 Scope: Procedures and requirements governing investigational medical devices, including the process for seeking an investigation device exemption (IDE) and ultimate FDA approval.

 General rule: Use of an investigational device subject to FDA approval must comply with the IDE procedures and requirements until FDA approves the device for marketing.
21 C.F.R. Part 812

- Medical devices under an IDE are exempt from FDA pre-market approval and can be lawfully shipped for investigatory purposes.

- Part 812 addresses:
  - Labeling;
  - Promotion and charges for investigational devices;
  - FDA waivers;
  - Prohibition of promotion and other practices;
  - Investigational plan;
  - Scope and content of required FDA reports; and
  - Responsibilities of sponsors and investigators.
Impact on Medicare Coverage

- FDA will categorize the device as either:
- FDA’s categorization affects Medicare coverage
- Medicare permits coverage of Category B devices
- 42 C.F.R. Part 405, Subpart B – Medical Services Coverage Decisions that Relate to Health Care Technology
Impact on Medicare Coverage (cont.)

- Local Medicare contractors make decisions regarding coverage of Category B devices.
- Coverage of medical devices affects coverage of related services.
- All other Medicare coverage rules, national and local, apply.
Impact on Medicare Coverage (cont.)

- Since September 2000, Medicare coverage for “routine costs” related to qualifying clinical trials and services necessary to address any complications.
  - Coverage Manual §30.1

- MMA requires coverage expansion of IDE related services to Category A devices effective January 1, 2005.
  - MMA §731(b) added 42 U.S.C. §1395y(m)
Clinical Trials in Eastern Europe
Legal Regimes in Eastern Europe

- Part of EU Clinical Trials Directive
  Regime: Bulgaria, Czech Republic, Estonia, Hungary, Latvia, Lithuania, Poland, Romania, Slovak Republic, Slovenia
Legal Regimes in Eastern Europe

- Independent legal regimes: Albania, Bielo-Russia, Bosnia-Herzegovina, Croatia, Georgia, Macedonia, Moldavia, Montenegro, Serbia, Russia, Ukraine
Directive 2001/20/EC

- Background and scope
- Significant innovations
- Achievements and limitations
Background of the Directive

- Framework required to protect clinical trials subjects
- Absence of harmonization among Member States
- Lack of legal text on the application of GCP and GMP
- Unification of information and pharmacovigilance
Scope of the Directive

- All European Union (EU) Member States are involved in the EU Directive
- All trials except for non-interventional trials
- Broader definition of clinical trials
  - Refers to trials in “human subjects” which includes healthy volunteers
  - Does not differentiate between commercial and non-commercial trials
Significant Innovations of the Directive

- **Database on clinical trials (EudraCT)**
  - Regulatory overview of clinical trials
  - Exchange of information

- **Protection of clinical trial subjects**
  - Benefit from the trial
  - Informed consent
  - Specific rules concerning minors and incapacitated adults
  - Data protection measures
  - Insurance
Significant Innovations (cont.)

- **Harmonization of the authorization procedure**
  - Application review within 60 days
  - Parallel submissions to Ethics Committee (EC) and Competent Authority (CA)
  - “Single opinion” rule for multi-center trials

- **Increased responsibilities of the sponsor**
  - Quality insurance and quality control
  - Notification/submission to regulatory authorities
  - IMP/GMP compliance
  - Ongoing safety evaluation and adverse event reporting
  - Sponsor may delegate aspects of clinical trials (e.g. to CRO) whilst retaining overall responsibility
Major Achievements and Limitations

- **Achievements**
  - Free movement of Investigational Medicinal Products (IMPs)
  - Timeline can be monitored
  - Standardization of the documentation
  - Generation of a competitive market for clinical trials in Europe

- **Limitations**
  - Strengthening the protection of clinical trials subjects
  - IMPs only manufactured at licensed manufacturing sites
  - Inspections to assess compliance with GMP and GCP
  - Establishment of a legal representative for non EU sponsor
  - Lack of centralization (in particular with Ethics Committees)
  - Incomplete harmonization
  - Challenges in implementation process and through diverging interpretations of local authorities
Comparison of Clinical Trials in the EU and the US

- Regulatory documents submissions
- Protection of clinical trial subjects
- Investigational medical product (IMP) issues
Regulatory Document Submission

**EU**
- Application Submission
  - One CA submission per Member State (MS)
  - 25 countries / 25 authorizations
- Protocol
  - Stand alone submission to CA for each protocol
  - 60 day review timeframe
  - MS can impose shorter timeframe per national law

**US**
- Application Submission
  - One regulatory authority at the federal level – the FDA
  - Single submissions
    - Single authorizations
- Protocol
  - New protocol submitted as amendment to IND of the investigational product
  - 30 day FDA review timeframe
  - No official review timeframe for amendments to the IND
## Protection of Clinical Trial Subjects

<table>
<thead>
<tr>
<th>EU</th>
<th>US</th>
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<tbody>
<tr>
<td>Minimal detail on ICD</td>
<td>Detailed list of ICD requirements</td>
</tr>
<tr>
<td>Minors &amp; incapacitated adults</td>
<td>All subjects</td>
</tr>
<tr>
<td>- No incentives or financial inducements allowed</td>
<td>- Disclosure of anticipated prorated payment, if any, to the subject for participation</td>
</tr>
<tr>
<td>Some countries require insurance info to be put into ICD</td>
<td>No requirement for insurance info on ICD</td>
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<tr>
<td>No provisions outlined for emergency consent</td>
<td>Provisions for emergency consent</td>
</tr>
<tr>
<td>European Commission Directive 95/46</td>
<td>Local sites required to incorporate HIPAA regulations into consent process</td>
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Investigational Medicinal Products

Issues

**EU**

- Manufacturing and Import
  - Must be manufactured to a standard “at least equivalent” to EU GMP
  - Import authorization required via application to a CA
  - Once within EU, shipment between MS does not require any further import authorization

**US**

- Manufacturing and Import
  - Must satisfy US GMP
  - Import of investigational product provided to a consignee as defined in the IND
  - Unrestricted shipment between US states
Investigational Medicinal Products Issues (cont.)

<table>
<thead>
<tr>
<th>EU</th>
<th>Labeling</th>
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<tr>
<td>□  Label samples may be required by ECs</td>
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<tr>
<td>□  Must be in the official language(s) of the MS on the outer package, or where not outer package, on the immediate packaging</td>
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<tr>
<td>□  Labels require expiration date</td>
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<table>
<thead>
<tr>
<th>US</th>
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<tbody>
<tr>
<td>□  Label samples not required by IRBs</td>
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<tr>
<td>□  Label must bear specific language (“Caution: new drug limited by…”)</td>
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<tr>
<td>□  Labels do not require expiration dates</td>
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Eastern Europe Beyond the EU

Upsides

- Large population (Russia and Ukraine alone 200 million inhabitants)
- Centralised health care systems
- Large, highly specialized hospitals with important roles in oncology, cardiology, rheumatology
Eastern Europe Beyond the EU

Upsides

- Partly highly qualified investigators
- Faster recruitment process
- Treatment naive populations
- Good clinical data
- Low cost per implemented case
Eastern Europe Beyond the EU

Downsides

- No harmonized procedures
- No free movement of IMP between countries
- Less developed legal and court system result in less legal security
- Partly high level of corruption
- Strong local presence and expertise required
OTHER FUNDAMENTAL ISSUES

- Privacy and research
- Scientific misconduct
- Good clinical practices (GCP)
- Good manufacturing practices (CMP)
Privacy and Research
Privacy and Research

- Health Insurance Portability and Accountability Act of 1996 (HIPAA)
- Protected health information (PHI)
  - Created or received by a health care provider, health plan, or health care clearinghouse.
  - Either identifies or could be used to identify an individual.
  - Relates to a physical or mental health condition, the related patient care, and payment.
  - Transmitted or maintained in an electronic format or media.
Privacy and Research (cont.)

- **Notice of Privacy Practices**
  - Informs patients regarding use and disclosure of PHI.
  - Patients sign an acknowledgement and consent for the use of disclosure of PHI for treatment, payment, or health care operations.
  - Usually included in patient consent forms for clinical research projects.
Privacy and Research (cont.)

- Potential uses for study data present privacy compliance challenge.

- Uses and disclosures:
  - Patient consent in privacy acknowledgement;
  - Other disclosures not requiring patient consent;
  - “De-identified” data (subject and objective);
  - Limited data sets; and
  - FDA-related activities.
Scientific Misconduct
Research misconduct means:
- Fabrication
- Falsification
- Plagiarism

Does not include honest error or differences of opinion
Significant departure from accepted practices of the relevant research community; and

Misconduct must be committed *intentionally, knowingly, or recklessly*; and

Allegation must be proven by a preponderance of the evidence
Scope:
- Rules that govern federal grantee’s response to, and reporting of, scientific misconduct
- Regulations impose responsibility to promote objectiveness in research.

Responsible agency: Office of Research Integrity (ORI), Office of Public Health Service and Science

General rule: Instances of potential scientific misconduct must be reviewed, investigated, and, as appropriate, reported to ORI.
| Regulations promote objectivity in research and govern institutions that apply for PHS grants or cooperative agreements. |
| Establish standards to ensure that the design, conduct and reporting on federally funded or directed research will not be biased by conflicting financial interests of an investigator. |
42 C.F.R. §50.604
Institutional responsibility regarding conflicting interests of investigators

- Policies and procedures maintained and communicated to investigators.
- Maintain records of all financial disclosures and conflict of interest remedial actions for three years after last report is filed.
Designated official must review all conflicts of interests and work to manage, reduce, or eliminate such conflict.

Conflicts may be managed by:
- Public disclosure of conflict;
- Monitoring research by independent reviewers;
- Modified research plan;
- Disqualification of investigator;
- Divestiture of financial interest; or
- Severance of relationships that create the conflict(s).
If a conflict of interest violation has biased the design, conduct, or report of a study, then the institution must notify federal government.

- Government may inquire regarding these issues at any time and may suspend grant funding, if appropriate, due to a violation.
Good Clinical Practices (GCP)
Good Clinical Practices

- Generally accepted, international best practices for conducting clinical trials and device studies.
  - International ethical and scientific standard for designing, conducting, recording, and reporting trials that involve human subjects.
  - Not statutes or regulations.
  - Compliance provides assurance that the rights and safety of the participants are protected and that the data arising from the study is credible.
Thirteen Principles of GCP Guidance

1. Clinical trials should be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with GCP and the applicable regulatory requirements.

2. Before a trial is initiated, foreseeable risks and inconveniences should be weighed against the anticipated benefit for the individual trial subject and society. A trial should be initiated and continued only if the anticipated benefits justify the risk.
3. The rights, safety, and well-being of the trial subjects are the most important considerations and should prevail over interests of science and society.

4. The available non clinical and clinical information on an investigational product should be adequate to support the proposed clinical trial.

5. Clinical trials should be scientifically sound, and described in a clear, detailed protocol.

6. A trial should be conducted in compliance with the protocol that has received prior institutional review board/independent ethics committee approval/favorable opinion.
7. The medical care given to, and medical decisions made on behalf of, subjects should always be the responsibility of a qualified physician or, when appropriate, of a qualified dentist.

8. Each individual involved in conducting a trial should be qualified by education, training, and experience to perform his or her respective tasks.

9. Freely given informed consent should be obtained from every subject prior to clinical trial participation.

10. All clinical trial information should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation, and verification.
11. The confidentiality of records that could identify subjects should be protected, respecting privacy and confidentiality rules in accordance with the applicable regulatory requirements.

12. Investigational products should be manufactured, handled, and stored in accordance with applicable good manufacturing practice (GMP). They should be used in accordance with the approved protocol.

13. Systems with procedures that assure the quality of every aspect of the trial should be implemented.
GCP Risk Areas

- Investigators
  - Protocol deviations
  - Misuse of products
  - Lack of communication on safety issues
- Scientific misconduct
- Human subject protection and IRBs
- Off-label use of Humanitarian Device Exemptions (HDE) devices
- HIPAA
Good Manufacturing Practices (GMP)
Good Manufacturing Practices

- Regulations that:
  - Describe the methods, facilities and controls required for producing drugs, devices, foods, and biologicals.
  - Promulgated and enforced by the FDA.

- Current Good Manufacturing Practices (cGMP)s
  - Based on industry best practices that continually evolve as science, technology, and manufacturing techniques change
  - 21 C.F.R. Parts 210 and 211
Questions?