Overview of Clinical Trials and Clinical Research

Ann Smith, Clinical & Translational Sciences Institute
Sharon Schooley, Clinical & Translational Sciences Institute
Judy McMillan, Human Resources Protection Program
Topics

• Part 1: Introduction
  - Definitions
  - Overview of Clinical Trial Process
  - Roles and Responsibilities

• Part 2: Clinical Trial Lifecycle
  - Decision to Pursue
  - Study Pre-Award
  - Study Start-up & Management
  - Study Closeout
Part 1: Introduction
Definitions

Clinical Investigation

Clinical Trial

Clinical Research

Research
Clinical Investigation (FDA)

Investigation: Any experiment that involves a test article and one or more human subjects, and that either must meet the requirements for prior submission to the Food and Drug Administration under section 505(i) or 520(g) of the Federal Food, Drug, and Cosmetic Act, or need not meet the requirements for prior submission to the Food and Drug Administration under these sections of the Federal Food, Drug, and Cosmetic Act, but the results of which are intended to be later submitted to, or held for inspection by, the Food and Drug Administration as part of an application for a research or marketing permit. The terms research, clinical research, clinical study, study, and clinical investigation are synonymous for purposes of FDA regulations. [21 CFR 50.3(c), 21 CFR 56.102(c)]
1. Drugs - Clinical investigation means any experiment in which a drug is administered or dispensed to, or used involving, one or more human subjects. For the purposes of this part, an experiment is any use of a drug except for the use of a marketed drug in the course of medical practice. (21 CFR 312.3)

2. Devices - means a clinical investigation or research involving one or more subjects to determine the safety or effectiveness of a device. (21 CFR 812.3)
“Research means a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge. Activities which meet this definition constitute research for purposes of this policy, whether or not they are conducted or supported under a program which is considered research for other purposes. For example, some demonstration and service programs may include research activities.” 45 CFR 46.102(d)
“Human subject means a living individual about whom an investigator (whether professional or student) conducting research obtains:

1) data through intervention or interaction with the individual, or
2) identifiable private information”

45 CFR 46.102(f)

(also known as a study participant)
Clinical Research (NIH)

- **Patient-oriented research:** This type of research involves a particular person or group of people or uses materials from humans. This research can include:
  - Studies of mechanisms of human disease
  - Studies of therapies or interventions for disease
  - *Clinical trials*
  - Studies to develop new technology related to disease

- **Epidemiological and behavioral studies:** These types of studies examine the distribution of disease, the factors that affect health, and how people make health-related decisions.

- **Outcomes and health services research:** These studies seek to identify the most effective and most efficient interventions, treatments, and services.

Studies falling under 45 CFR 46.10 (b) (4) (Exemption 4) are not considered clinical research by this definition.
Research involving the collection or study of existing data, documents, records, pathological specimens or diagnostic specimens, if these sources are publicly available or the information is recorded by the investigator in such a manner that the subjects cannot be identified directly or through identifiers linked to the subjects.
• A research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes.

1See Common Rule definition of research at 45 CFR 46.102(d).

2See Common Rule definition of human subject at 45 CFR 46.102(f).

3The term “prospectively assigned” refers to a pre-defined process (e.g., randomization) specified in an approved protocol that stipulates the assignment of research subjects (individually or in clusters) to one or more arms (e.g., intervention, placebo, or other control) of a clinical trial.

4An intervention is defined as a manipulation of the subject or subject’s environment for the purpose of modifying one or more health-related biomedical or behavioral processes and/or endpoints. Examples include: drugs/small molecules/compounds; biologics; devices; procedures (e.g., surgical techniques); delivery systems (e.g., telemedicine, face-to-face interviews); strategies to change health-related behavior (e.g., diet, cognitive therapy, exercise, development of new habits); treatment strategies; prevention strategies; and, diagnostic strategies.

5Health-related biomedical or behavioral outcome is defined as the pre-specified goal(s) or condition(s) that reflect the effect of one or more interventions on human subjects’ biomedical or behavioral status or quality of life. Examples include: positive or negative changes to physiological or biological parameters (e.g., improvement of lung capacity, gene expression); positive or negative changes to psychological or neurodevelopmental parameters (e.g., mood management intervention for smokers; reading comprehension and/or information retention); positive or negative changes to disease processes; positive or negative changes to health-related behaviors; and, positive or negative changes to quality of life.
Retrospective & Prospective Defined

**PROSPECTIVE** - The study is planned and outcomes are measured after the study starts and as study events occur.
- Surveys
- Clinical trials

**RETROSPECTIVE** - The outcome has already happened prior to the study starting; information is collected about past events.
- Chart reviews
Investigator & Study Coordinator Defined

• **INVESTIGATOR:** An individual who actually conducts the research and has additional responsibilities for the oversight and conduct of human subject research studies.

• **CLINICAL RESEARCH COORDINATOR (CRC):** A specialized research professional working with and under the direction of the clinical principal investigator that supports, facilitates, and coordinates the daily clinical research/trial activities and plays a critical role in the conduct of the study. This includes coordinating people and resources to help ensure a successful outcome. May also be known as a ‘study coordinator’, or a project coordinator or manager.
Study Subject Defined

- **STUDY SUBJECT**: An individual who participates in research studies. May also be referred to as a study participant or study volunteer.
Sponsor & CRO Defined

• **SPONSOR**: An entity that takes responsibility for and initiates a clinical research project or clinical trial protocol. May be an individual or pharmaceutical company, governmental agency, academic institution, private organization, or other organization.

• **CONTRACT RESEARCH ORGANIZATION (CRO)**: A person or an organization (commercial, academic or other) contracted by the Sponsor to perform one or more of a Sponsor's study-related duties and functions.
Monitor Defined

- **MONITOR**: Person employed by the sponsor or CRO who reviews study records to determine that a study is being conducted in accordance with the protocol. A monitor's duties may include, but are not limited to, helping to plan and initiate a study (site initiation visit), and assessing the conduct of studies. Monitors work with the clinical research coordinator to check all data and documentation from the study. Also commonly known as a Clinical Research Associate (CRA).
• **SPONSOR-INITIATED RESEARCH:** An individual or agency initiates and takes responsibility for the research. The sponsor does not actually conduct the investigation (e.g. MSU is paid for providing services, but has no direct input on or influence over the research design or protocol).
INVESTIGATOR-INITIATED RESEARCH: An individual both initiates and conducts an investigation, and assumes all of the sponsor responsibilities defined in the regulations.

- If study is investigator-initiated, the requirements include both those applicable to the investigator and a sponsor.
**PROTOCOL**: The written description of a clinical study. It includes the study's objectives, design, and methods. It may also include relevant scientific background and statistical information.

This could also be referred to as the study design for a clinical research study.

**INVESTIGATOR’S BROCHURE (IB)**: Relevant clinical and non-clinical data compiled on the investigational drug, biologic or device being studied. Typically includes detailed safety information about investigational product.
Case Report Forms Defined

- **CASE REPORT FORMS (CRF):** Forms that are designed to record data on each trial subject during the course of the trial as defined by the protocol. These can be either in paper or electronic (eCRF) format.
Drug & Placebo Defined

- **DRUG** - articles intended for the use in the diagnosis, cure, mitigation, treatment or prevention in man or other animals. Drugs affect the structure or function of the body by chemical action or by being metabolized. Drugs may be ‘approved’ = having received FDA approval, or ‘investigational’= under review of FDA but not yet approve.

- **PLACEBO**: A substance that does not contain active ingredients and is made to be physically indistinguishable (that is, it looks and tastes identical) from the actual drug being studied.
Medical Device Defined

- **MEDICAL DEVICE** - An instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including a component part, or accessory which...

  Is recognized in the official National Formulary, or the United States Pharmacopoeia.

Devices may or may not have chemical structure and can include:

- Bandaids
- Stents
- Health apps under FDA when it becomes a medical device (i.e. App to record pulse, blood pressure, medication use, etc.)
Arm/Multi-Arm Defined

- **ARM**: A group or subgroup of subjects in a clinical trial who receives specific interventions, or no intervention, according to the study protocol. This is decided before the trial begins.

  Multi-Arm studies distinguish between different types of treatment or interventions the group is receiving in a study.
Interventional Groups Defined

- **CONTROL GROUP**: The group that do not receive the experimental article. Usually receive the standard treatment. Use of control groups is common in Phase II and III studies.
  - **Placebo-controlled**: Here the experimental article is tested against an inert substance (e.g., inactive pill) and the subject does not know what s/he is receiving. Usually a between-subjects design; always single-blind, usually double-blind. **NOTE**: It is unethical to use a placebo when an effective treatment is available; exposes subjects to unreasonable risks.

- **EXPERIMENTAL GROUP**: The group that receives the experimental article
SIGNIFICANCE: Subjects are assigned to one of two or more groups (options) by chance; for instance, by the flip of a coin, or by using a computer to select randomly. Ensures that groups are comparable.

OPEN-LABEL: Study is un-blinded; everyone involved knows what article the subject is receiving. Usually, Phase I & IV studies.
• **SINGLE- & DOUBLE-BLINDED (Masked):** In a single-blinded trial, the subjects don't know what they're receiving until the trial is over. In a double-blinded trial, neither the subjects *nor* the researchers know who's receiving what until the trial is over.

• **CROSSOVER:** Midway through the trial, the group receiving the experimental treatment switches to the control treatment or placebo, and vice versa, with neither group knowing which substance is which. Always single-blind, usually double-blind.
Clinical Trial Phases Defined

- **Phase I**: Tests a new biomedical intervention in a small group of people (e.g. 20-80) for the first time to determine efficacy and evaluate safety (e.g., determine a safe dosage range and identify side effects).

- **Phase II**: Study the biomedical or behavioral intervention in a larger group of people (several hundred) to determine efficacy and further evaluate safety.

- **Phase III**: Study to determine efficacy of the biomedical or behavioral intervention in large groups of people (from several hundred to several thousand) by comparing the intervention to other standard or experimental interventions as well as to monitor adverse effects, and to collect information that will allow the interventions to be used safely.

- **Phase IV**: Studies conducted after the intervention has been marketed. These studies are designed to monitor the effectiveness of the approved intervention in the general population and to collect information about any adverse effects associated with widespread use.
A broadly based prospective Phase III clinical investigation (usually involving several hundred or more human subjects) to evaluate an experimental intervention in comparison with a standard or control intervention or to compare two or more existing treatments. The definition includes pharmacologic, non-pharmacologic, and behavioral interventions given for disease prevention, prophylaxis, diagnosis, or therapy. Community trials and other population-based intervention trials also are included.
**Types of Clinical Trials**

**Treatment trials** test new treatments, new combinations of drugs, or new approaches to surgery or radiation therapy.

**Prevention trials** look for better ways to prevent disease in people who have never had the disease or to prevent a disease from returning. These approaches may include medicines, vaccines, vitamins, minerals, or lifestyle changes.

**Diagnostic trials** are conducted to find better tests or procedures for diagnosing a particular disease or condition.

**Screening trials** test the best way to detect certain diseases or health conditions.

**Quality of Life trials** (or Supportive Care trials) explore ways to improve comfort and the quality of life for individuals with a chronic illness.
Examples of Clinical Trial Types

**Treatment trials:**
- Use of new investigational drugs compared to marketed drugs to treat certain conditions such as cancer, seizures, bacterial infections, depression, Parkinson’s disease
- Use of new devices (i.e. stents) to help improve the outcome of cardiac illnesses

**Prevention trials:**
- Use of behavioral interventions such as lifestyle changes and education to prevent pediatric obesity
- Testing of new vaccines to prevent diseases such as the flu, HIV, malaria, etc.

**Diagnostic trials:**
- Compare the performance of MRI vs CT for diagnosis of certain conditions
- Assess if a new test kit works as well as the standard test method in diagnosing an illness

**Screening trials:**
- Use of spirometry in detecting early-stage COPD
- Use of early screening procedures to decrease the risk of dying from prostate, lung, colorectal, ovarian cancers

**Quality of Life trials (or Supportive Care trials)** Explore ways to improve comfort and the quality of life for individuals with a chronic illness.
- Use of acupressure for persistent cancer-related fatigue
- Use of relaxation for women with breast cancer undergoing radiotherapy
Examples- Titles

• A *double-blind, randomized*, study to compare the effectiveness of a new medication for prevention of migraine headache against an approved drug.

• An *open-label* study on the long-term effects of alpha interferon for treatment of Hepatitis C.

• A *single-blind, placebo-controlled* trial of a new cream to treat baldness.

• A *double-blind, randomized, cross-over* study to compare new treatment for depression with standard treatment.
Questions?
Overview of Clinical Trial Process
New Drug Development Timeline

**Phase 1**
- Initial Synthesis
- Range: 1-3 years
  - Avg.: 18 mos.
- Animal testing

**Phase 2**
- Clinical Research and Development
- Range: 2-10 years
  - Avg.: 5 years

**Phase 3**
- Pre-Clinical Testing, Research and Development
- Range: 1-3 years
  - Avg.: 18 mos.

**Long Term**
- Range: 2 mos.
  - 7 years

**Short Term**
- Range: 2 mos.
  - 7 years

**Post-Marketing Surveillance**
- Adverse Event Reporting
- Surveys/Sampling/Testing
- Inspections

**NDA Review**
- NDA Submitted
- NDA Approved
- 30 Day Safety Review
- FDA Time
- Sponsor Time
### Testing in Humans

<table>
<thead>
<tr>
<th>Phase</th>
<th>Number of Patients</th>
<th>Length</th>
<th>Purpose</th>
<th>Percent of Drugs Successfully Tested</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase 1</td>
<td>20–100</td>
<td>Several months</td>
<td>Mainly safety</td>
<td>70 percent</td>
</tr>
<tr>
<td>Phase 2</td>
<td>Up to several hundred</td>
<td>Several months to 2 years</td>
<td>Some short-term safety, but mainly effectiveness</td>
<td>33 percent</td>
</tr>
<tr>
<td>Phase 3</td>
<td>Several hundred to several thousand</td>
<td>1–4 years</td>
<td>Safety, effectiveness, dosage</td>
<td>25–30 percent</td>
</tr>
</tbody>
</table>

For example, of 100 drugs for which investigational new drug applications are submitted to FDA, about 70 percent will successfully complete phase 1 and go on to phase 2; about 33 percent of the original 100 will complete phase 2 and go to phase 3; and 25 to 30 of the original 100 will clear phase 3 (and, on average, about 20 of the original 100 will ultimately be approved for marketing).
Roles and Responsibilities
Roles and Responsibilities

- Investigators
- Sponsor
- Institution
- Subjects
- Federal & State

[Image of a doctor, pills, a state building, and a CT scan]
Federal, State, & Local Requirements

- **Health & Human Services, e.g. 45 CFR 46**
  
  http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm

- **Food & Drug Administration e.g. 21 CFR 50, 56, 312, 812**
  

- **State and Local Laws**
  

- **Institutional Policies and Procedures**
  
  - http://www.hr.msu.edu/documents/facacadhandbooks/facultyhandbook/index.htm
  - http://www.humanresearch.msu.edu/hrpmanual.html

- International rules and regulations apply to studies performed outside of the US
Notice Proposed Rulemaking (NPRM)

- The first revisions to the “Common Rule” since its publication in 1991 were published in the Federal Register on September 8, 2015.

- The link to the NPRM is: www.hhs.gov/ohrp/humansubjects/regulations/nprmhome.html

- Provide responses no later than December 7, 2015.
## Institutional Roles: MSU

<table>
<thead>
<tr>
<th>MSU Office</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Animal Care Program (ULAR) <a href="http://www.animalresearch.msu.edu/index.html">www.animalresearch.msu.edu/index.html</a></td>
<td>Reviews animal use in research, teaching, and testing</td>
</tr>
<tr>
<td>Business Connect (BC) <a href="http://www.businessconnect.msu.edu/">www.businessconnect.msu.edu/</a></td>
<td>Reviews and negotiates industry sponsored contracts</td>
</tr>
<tr>
<td>Clinical and Translational Sciences Institute (CTSI)  <a href="http://www.ctsi.msu.edu/">www.ctsi.msu.edu/</a></td>
<td>Provides resources to facilitate the conduct of translational research within and beyond MSU’s physical barriers</td>
</tr>
<tr>
<td>Clinical Research Billing Compliance (CRBC)  <a href="http://www.ora.msu.edu/crbc-office">www.ora.msu.edu/crbc-office</a></td>
<td>Provide a full range of clinical research billing compliance services</td>
</tr>
<tr>
<td>Conflict of Interest (COI) <a href="http://www.coi.msu.edu/">www.coi.msu.edu/</a></td>
<td>Reviews significant financial interest disclosures</td>
</tr>
<tr>
<td>Contracts and Grants (CGA) <a href="http://www.cga.msu.edu/">www.cga.msu.edu/</a></td>
<td>Performs post award contract and grant management</td>
</tr>
<tr>
<td>Controller’s Office - Accounting <a href="http://www.ctlr.msu.edu/COAccounting/default.asp">www.ctlr.msu.edu/COAccounting/default.asp</a></td>
<td>Oversight of participant stipends</td>
</tr>
<tr>
<td>Environmental Health and Safety (EHS) <a href="http://www.ehs.msu.edu/">www.ehs.msu.edu/</a></td>
<td>Components includes biological safety, radiation safety, chemical hygiene, environmental and occupational health and safety</td>
</tr>
<tr>
<td>Health Team Billing Office <a href="http://www.healthteam.msu.edu/">www.healthteam.msu.edu/</a></td>
<td>Bills services for HT providers and facilities</td>
</tr>
<tr>
<td>Health Team Compliance Office John Hazewinkel (517) 353-5292</td>
<td>Ensure proper billing procedures and HIPAA oversight</td>
</tr>
<tr>
<td>MSU Office</td>
<td>Function</td>
</tr>
<tr>
<td>----------------------------------------------------------------</td>
<td>--------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Human Research Liaison Program</td>
<td>Performs post approval site visits and clinical research compliance</td>
</tr>
<tr>
<td><a href="mailto:HRL@msu.edu">HRL@msu.edu</a></td>
<td></td>
</tr>
<tr>
<td>Human Research Protection Program (HRPP)</td>
<td>Components are the Human Research Liaison Program and the Institutional Review Boards</td>
</tr>
<tr>
<td><a href="http://www.HRPP.msu.edu">www.HRPP.msu.edu</a></td>
<td></td>
</tr>
<tr>
<td>Institutional Review Board (IRB)</td>
<td>Reviews human subject research and clinical investigations</td>
</tr>
<tr>
<td><a href="mailto:irb@msu.edu">irb@msu.edu</a> or <a href="mailto:irbdocs@ora.msu.edu">irbdocs@ora.msu.edu</a></td>
<td></td>
</tr>
<tr>
<td>Internal Audit</td>
<td>Audit research financial records and accounts</td>
</tr>
<tr>
<td><a href="http://www.msu.edu/unit/intaudit">www.msu.edu/unit/intaudit</a></td>
<td></td>
</tr>
<tr>
<td>MSU Technologies (MSUT)</td>
<td>Executes Confidential Disclosure Agreements and Material Transfer Agreements; reviews intellectual property</td>
</tr>
<tr>
<td><a href="http://www.technologies.msu.edu">http://www.technologies.msu.edu</a></td>
<td></td>
</tr>
<tr>
<td>Office of Regulatory Affairs (ORA)</td>
<td>Components are the Animal Care Program, Environmental Health Safety, Human Research Protection Program</td>
</tr>
<tr>
<td><a href="http://www.ora.msu.edu/">www.ora.msu.edu/</a></td>
<td></td>
</tr>
<tr>
<td>Office of Sponsored Projects (OSP)</td>
<td>Manages non-industry sponsored proposals</td>
</tr>
<tr>
<td><a href="mailto:help@osp.msu.edu">help@osp.msu.edu</a></td>
<td></td>
</tr>
<tr>
<td>Pharmacy</td>
<td>May store and dispense investigational products</td>
</tr>
<tr>
<td><a href="http://www.pharmacy.msu.edu">www.pharmacy.msu.edu</a></td>
<td></td>
</tr>
<tr>
<td>Research Offices - College, Department</td>
<td>Oversight and/or approval of research projects</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Sponsor’s Role

• Submission of IND/IDE (if applicable)

• Development of Protocol; Investigator’s Brochure

• Quality Assurance and Control

• Data Safety Monitoring Board (if applicable)

• Hires investigator, by virtue of contract negotiations with investigator’s employer, to conduct the clinical trial

• Adverse event reporting to FDA
Investigator’s Role

• Disclose financial conflicts of interest

• Ensure that adequate resources (facilities and equipment) are available to protect human subjects during the research

• Ensure that individuals conducting the research receive appropriate training prior to contact with research subjects

• Obtain all required approvals prior to starting research

• Maintain adequate and appropriate oversight over the conduct of the research study
Investigator’s Role

- Conduct research in an ethical manner

- Report any activities or circumstances that affect the rights and/or welfare of research subjects.

- Research charges are billed appropriately and research funds allocated properly

- Timely reporting per funding source requirements

- Maintain accurate study documentation and maintain research records for a minimum of three years
Study Coordinator’s Role

• Being the first point of contact for PI and study sponsor

• Regulatory- IRB application submission, renewal and revision submission for protocol amendments

• Recruitment/retention - Involving advertising-marketing, ensuring the subjects remain in the study

• Protocol oversight - making sure PI and subjects follow the protocol and protocol-required visits
Study Coordinator’s Role

• Study subject management - scheduling appointments- not only for study visits but if outside appointments needed for MRI/CTcans/X-Rays etc. Drawing blood for study required labs, taking vital signs, doing ECGs if required.

• Educating the subjects on how to perform some task such as electronic diary, how to take study medication, to call if they are given a new medication by their primary doctor in case it is a prohibited medication

• Reviewing adverse events and reporting if serious
Study Coordinator’s Role

• Data entry in sponsor’s electronic data system

• Meets with sponsor monitors and responds to data correction queries

• Verify completed visits and tasks in support of research administrator financial management of study
Study Subject’s Role

• Making an informed decision to participate in study based on voluntary consent

• Ask Questions

• Follow the Protocol, PI, & coordinator instructions

• Know your rights (e.g. you can withdraw at any time)
Study subject’s Role

• Report any concerns to either the PI or the IRB

• Report any adverse events

• Let other physicians know that they are a subject in a trial if it could potential affect their patient care
CTSI Divisions

• Office of Clinical Research (OCR)
  - Serving as a ‘Researcher Advocate’ for researchers & staff as they navigate the MSU clinical research processes
  - Providing expertise and supportive services to research investigators and staff as needed
    • Project feasibility and cost assessment
    • Budget development and negotiation
    • Financial management education

• Biomedical Research Informatics Core (BRIC)
  - Providing research data management services for clinical research studies
    • Research collaboration
    • Software solutions
    • Data security & storage
    • Data oversight throughout study lifecycle
OCR Service/Support Areas

- Project Feasibility/Needs Assessment
- Study Coordination
- Subject Recruitment & Retention Strategies
- Access to Clinical Research Services Facility
- Biologic Sample Collection & Processing
- Post Award Financial & Invoicing Support
- Research Process Navigation
- Study Logistics & Management Support
- Regulatory Support
CTSI Tools & Resources

- **ResearchMatch** - National Online participant recruitment tool that brings together researchers and people interested in research participation via a secure website.

- **Eagle-i** - National resource discovery platform; search for MSU core laboratory services, reagents, animals, specimens, etc. as well as those available across the country.

- **REDCap** - A secure web application for building and managing online surveys and databases.

- **Translational Research Support Facility (TRSF)** - Clinical research staffing and space service center operation.

- **Great Lakes Research into Practice Network (GRIN)** - A primary care practice-based research network (PBRN). GRIN connects practices with research projects and links practicing clinicians with research investigators.

For more information, please go to [CTSI.msu.edu](https://CTSI.msu.edu)
Questions?
Part 2: Clinical Trial Process Flow
High Level Process Overview

Decision to Pursue
- Confidential Disclosure Agreement
- Protocol Feasibility

Study Closeout

Study Pre-Award
- Parallel Processes
- Budget Preparation
- Clinical Trial Agreements and Negotiation
- Regulatory Reviews

Study Start-Up and Management
- Financial
- Contractual
- Regulatory
What and Who are Involved?

The Process

- Principal Investigators
- Sub-Investigators
- Internal Resources (e.g., Imaging, Pharmacy, Lab)
- External Resources
- Other Compliance staff (IRB, Human Subjects Liaisons)
- Administration (Contracts, Budget & Billing)
- Study Staff (Coordinators, Nurses, Data Managers)
- Compliance staff
Decision to Pursue
- Confidential Disclosure Agreement
- Protocol Feasibility

Study Pre-Award
- Parallel Processes
- Budget Preparation
- Clinical Trial Agreements and Negotiation
- Regulatory Reviews

Study Start-Up and Management
- Financial
- Contractual
- Regulatory

Study Closeout
Confidential Disclosure Agreement (CDA), sometimes referred to as a Non-Disclosure Agreement (NDA) is:

- A legal contract that governs the exchange of proprietary or confidential information.
- Used when there is a need to share proprietary information with an external party for a limited purpose while protecting it from being disclosed to others or the public.
- Also used when there is a need to avoid forfeiture of patent rights due to premature public disclosure.

A CDA creates obligations of confidentiality among the parties and limits the dissemination of confidential information. CDAs define the terms of disclosure between parties by:

- Defining the subject matter and scope of the disclosure
- Limiting the purposes for which the confidential information may be used
- Limiting the timeframe, access, and distribution of confidential information to third parties
Who *Can* Sign a CDA?

- MSU Technologies is the **only MSU group** authorized to sign a CDA
Who **CANNOT** Sign a CDA?

- Principal investigators, coordinators and departmental administrators **CANNOT** sign a CDA

- **Backdoor agreements:**
  - An agreement signed by a PI or other non-authorized individual
  - Puts the individual signing the agreement at personal risk for liability and financial claims
  - May limit the scope of work done as an MSU employee/faculty member
Clinical Research is a BUSINESS and must be run accordingly!
- Involves money, regulation
- Doing it right means more business
- Doing it wrong means out of business
  - Legal, regulatory, financial ramifications
Feasibility Overview
(i.e. Project/Needs Assessment)

A Business best achieves goals by starting with a STRATEGIC PLAN
- Why are you in the business of clinical research?
- What is your market?
- What are your research fixed operating costs, and how will you fund them through clinical research?
- How will you attract and retain high-quality staff?
Feasibility Overview (i.e. Project/Needs Assessment)

- Know your subject base and have recruitment plans
  - Payment is generally based on completed subject visits
- Be aware of project logistics and your available resources
  - Labor needs (study coordination, financial management, PI)
  - Space, equipment, service needs
- Be aware of financial obligations of the study
  - Labor costs
  - Equipment or test costs, other fees
  - Subcontracts
- Use of business tools
  - Operational Budgets
  - Project Budget Templates
  - Break-Even Analysis
  - Clinical Research Management Systems
Feasibility Overview
(i.e. Project/Needs Assessment)

- Is the research important to the Department/College?
- Beware of over-enthusiastic PIs
High Level Process Overview

Decision to Pursue
- Confidential Disclosure Agreement
- Protocol Feasibility

Study Closeout

Study Pre-Award
- Parallel Processes
- Budget Preparation
- Clinical Trial Agreements and Negotiation
- Regulatory Reviews

Study Start-Up and Management
- Financial
- Contractual
- Regulatory
Simultaneous Institutional Evaluation (Pre-Award)

Department / College Approvals

- Budget Review
- Contract Review by Appropriate Office
- Submit IRB Application
- Additional Required Reviews?

Obtain All Needed Institutional Reviews &/or Approvals, CGA Account Setup, & Notify All Parties
Pre-Award: Parallel Processes

- Multiple processes occur in parallel
  - Medicare Coverage Analysis (CRBC)
  - Clinical Trial Agreement review (OSP, BC)
  - Institutional Review Board review (IRB, SIRB, CRIRB)
  - Any other regulatory / compliance reviews as required

- MSU offices work together
Budget Preparation Overview

• Analyze the protocol and study documents to determine the required study services and tasks
  - Consider all anticipated costs associated with a study
  - Determine preliminary break-even analysis (# of subjects needed to cover projected study costs)

• Create overall study budget
  - Upfront/start up costs (labor, fees)
  - Per-subject costs (labor and expenses)
  - Variable costs (items invoiced when they occur)
  - Produce study billing grid (routine vs. research)

• Start early to prevent delays
Budget Negotiation Overview

• Why negotiate budget and payment terms?
  - Initial sponsor budget often does not cover internal study budget expenses
    • Sponsors culture is profit-oriented, offering the lowest budget possible
  - MSU as a non-profit cannot subsidize for-profit entities because it jeopardizes our tax status
  - Need to ensure:
    • Projected internal costs are covered
    • Payment terms are favorable to ensure a timely cash flow

• Do not just accept what the sponsor offers without knowing your internal costs!
Clinical Trial/Research Agreement Overview

- Clinical Trial Agreements (CTAs):
  - Define the rights and obligations of each party
  - Document the remedies available to each party
  - Protect interests
    - University
    - Principal investigator and project staff
    - Research subjects
    - Sponsor
  - States payment amount and terms for work done on project
- Similar agreements are used for clinical research
Critical Clause Types

- Subject Injury
- Indemnification
- Confidentiality
- Ownership of Records
- Intellectual Property Rights
- Publication Rights
Who Currently Negotiates What?

- Clinical Trial & Clinical Research Agreements
  - Office of Sponsored Programs (Federal & all other non-profit agency Sponsored)
  - MSU Business CONNECT (Industrial Sponsored)

- Study Budgets and Payment Terms
  - Office of Regulatory Affairs (CRBC)
  - CTSI
  - Principal investigator or study coordinator
  - Sometimes department staff
Who Develops the Budget?

- Departments/Colleges
  - Research administrators, PIs

- Support Offices
  - CTSI - can assist with cost discovery, budget development, connection to external services and collaborators.
  - CRBC - offers optional budget development services. Studies with potential billable events require Medicare Coverage Analysis.
Who *Can* Sign a CTA?

- Signature authority delegated from the Board of Trustees of MSU to:
  - Vice President for Finance and Operations
  - Directors of the Office of Sponsored Programs and Contract & Grant Administration
  - Assistant Directors of the Office of Sponsored Programs and Contract & Grant Administration
  - Managers of both the Office of Sponsored Programs and Contract and Grant Administration
  - Business CONNECT
Who **CANNOT** Sign a CTA?

- Principal investigators, coordinators and departmental administrators, etc.

- **Backdoor agreements**
  - MSU faculty, staff are employees of MSU
  - Cannot individually represent the university in legal matters

More information on this topic is currently available at the OSP home site at http://www.cga.msu.edu/Default.aspx
Master Agreements

- An agreement between MSU and a sponsor that governs all clinical trials/research supported by the company
  - Minimizes negotiations
  - Accelerates contract approvals
  - Allows for individual study budget negotiation as addendums or attachments
  - Enables rapid study initiation

Examples include Bayer, Biogen, Neogen, Novo Nordisk, Amgen, Novartis
Regulatory Review Overview

- Determine what reviews are needed
  - MSU IRB, other IRBs
  - Biosafety
  - Animal care
  - Radiation safety
  - Stem cell
  - *COI
    *There are new COI requirements
  - Export controls

- Determine if additional training is needed (e.g. biosafety)

- Contact Regulatory Affairs if questions
Common Process Delays

- Many factors can delay project execution
  - Departmental delays
    - Submission not in parallel
    - Communication delays
  - Contract negotiations
    - Intellectual property rights, indemnification, subject injury, confidentiality, ownership of records, publication rights
  - Budget negotiations
    - Cost coverage, payment terms
  - IRB approval
    - Consent form subject injury language, costs to subjects
  - Conflict of interest review and approval
    - Transmittal and IRB application sections
When Can Research Begin?

• Only After . . .
  ✓ Contract is fully executed
  ✓ If applicable, a Subcontract is fully executed (i.e. with Sparrow Health System)
  ✓ All Regulatory reviews are completed
Questions?
High Level Process Overview

Decision to Pursue
- Confidential Disclosure Agreement
- Protocol Feasibility

Study Start-Up and Management
- Financial
- Contractual
- Regulatory

Study Pre-Award
- Parallel Processes
- Budget Preparation
- Clinical Trial Agreements and Negotiation
- Regulatory Reviews

Study Closeout
Study Start-Up and Management

• Study start-up and management encompasses many areas of a clinical trial
• This section is intended to highlight several of the areas
  - Financial management
  - Fulfilling contract terms, managing changes
  - Regulatory management
    • IRB
    • ICH/GCP
    • Data Security
    • Record Retention
Financial Management

• Pre-Award
  - Budget development & internal costing
    • Subcontract budget development if needed
  - Billing grid generation for proper billing (3rd party for routine billing vs study funds for research-related charges)

• Post-Award
  - Track sponsor payments; review for accuracy
  - Invoice sponsor for line items, tracking of receivables
  - Payables to service providers per billing grid
  - Labor distributions & effort reporting
  - Study subject stipends and 1099
  - Study closeout of finances
The study contract or the CTA is a contract and MSU is bound to the terms in the executed agreement.

Fulfilling the contract terms of the CTA is an essential component of study management.

Contract terms may be modified through appropriate procedures as the study progresses.
Who Is Responsible for Fulfilling CTA Obligations?

- Principal Investigator
- Project staff
- Office of Sponsored Programs
- Contract & Grant Administration
- MSU Business CONNECT
- IRB
- Health Team Billing & Compliance
- Sponsor
What Kinds of CTA Obligations?

• Adhere to protocol
• Comply with all applicable rules, regulations, laws and statutes
• Maintain confidentiality of sponsor information
• Perform study in accordance with professional standards
• Report information and maintain communications with the sponsor
When Are CTA Obligations Fulfilled?

- **During the study**
  - Enrollment goals met
  - Reporting completed

- **After study completion**
  - Close-out visits from CRO or Sponsor’s monitor
  - Drug/device accountability

- **After the contract has ended or terminated**
  - Storage of research records, documentation
  - Intellectual property, publication
Impact of Contract Changes

• May necessitate
  - Protocol modification(s)
  - Budget and/or payment schedule Revisions

• Analyze the impact
  - To budget/financials
  - To study subjects
  - To MSU
Examples of Contract Modifications

• Significant modifications to the protocol
  - Changing, adding or increasing/decreasing the frequency of procedures, visits, etc.
  - Extending the period of the trial
  - Increasing or decreasing number of subjects

• Adding or eliminating CRO involvement
• Adding or eliminating third-party laboratories
• Adding or eliminating research sites
• Change in PI
Who Should Be Informed About Contract Changes?

• Principal Investigator
• Department Administration
• Institutional Review Board
• Business CONNECT
• Office of Sponsored Programs
• Contract and Grant Administration
• Office of Regulatory Affairs
• Clinical Research Billing Compliance
Communication is Key

Protocol-Related Correspondence:
• The University relies on Investigators to keep the IRB informed on matters such as proposed modifications to existing protocols, adverse event reports, and notices of imminent quality control reviews and audits
• All protocol-related correspondence sent to Investigators by Sponsors should be forwarded to the IRB for review

Contract-Related Correspondence:
• The University relies on Investigators to involve Contracts Officers in all aspects of research contract negotiation
• All contract-related correspondence sent to Investigators by Sponsors should be forwarded to Business CONNECT, Office of Sponsored Programs and/or CGA.
Regulatory Management

- Revisions: obtain approval for changes before implementing them

- Renewals: obtain renewal for your study before approval expires

- Unanticipated Problems: report unanticipated problems that may involve risks to subjects or others immediately to the IRB

- Closures: communicate the completion of your study to the IRB
Data Security

- Investigators are required to describe data security measures when preparing the IRB application
  - Describe what is feasible and appropriate
  - This includes both paper and electronic documents
- Be familiar with what was described in the IRB application and assure that practice matches the description
- When the HRLs conduct a site visit, they will look at data security
The FDA has several requirements related to record retention:

- **21 CFR 11:** What standards need to be met to consider electronic document equivalent to paper / electronic signature equivalent to paper
- **21 CFR 312, 812:** How long records must be retained
  - Investigator responsibilities:
    - Disposition drug / device
    - Case histories
    - 2 years following date marketing application is approved for the drug for the indication for which it is being investigated OR if no application is to be filed or if application not approved for the indication, until 2 years after the investigation is discontinued and the FDA notified

- IRB specific requirements require records to be maintained for a minimum of three years after completion of the research

- Research Data Management Guidance - Training
  - [http://www.lib.msu.edu/rdmg/training/](http://www.lib.msu.edu/rdmg/training/)
High Level Process Overview

Decision to Pursue
- Confidential Disclosure Agreement
- Protocol Feasibility

Study Pre-Award
- Parallel Processes
- Budget Preparation
- Clinical Trial Agreements and Negotiation
- Regulatory Reviews

Study Closeout

Study Start-Up and Management
- Financial
- Contractual
- Regulatory
What Obligations Survive Research & Trial Closeout?

- **Sponsor**
  - Subject injury
  - Indemnification
  - Insurance

- **MSU Technologies**
  - Inventions and patents
  - Use/protection of confidential information
  - Publication

- **MSU Archives**
  - Records retention and access

- **Institutional Review Board (HHS, FDA)**
  - Record retention
What Happens When Obligations Are Not Fulfilled?

• Breach of contract
  - Time-limited period to cure the breach
  - Non-breaching party pursues remedies

• Obligations commonly not fulfilled
  - Timely submission of case report forms (study data)
  - Payment by sponsor
Study Close-Out Overview

- Submit any reports and other deliverables
- Manage fixed Price contract balances
- Submit closure application to the MSU IRB
- Maintain required records
Questions?
Thanks for attending!