Overview of Clinical Trials and Clinical Research

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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
Research Categories

Clinical Investigation

Clinical Trial

Clinical Research

Research
“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 subject, study participant, or study volunteer)
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.*
Clinical investigation means 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), 507(d), or 520(g) of the act, or need not meet the requirements for prior submission to the Food and Drug Administration under these sections of the 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 term does not include experiments that must meet the provisions of part 58, regarding nonclinical laboratory studies. The terms research, clinical research, clinical study, study, and clinical investigation are deemed to be synonymous for purposes of this part. 21 CFR 56.102(c)

Human subject means an individual who is or becomes a participant in research, either as a recipient of the test article or as a control. A subject may be either a healthy human or a patient. 21 CFR 50.3(g)
Drug?

• Articles (other than food) 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*.
  
  - **Note regarding biologics**
    
    • Sub-set of drug
    
    • Defined as a “virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or analogous product, ... applicable to the prevention, treatment, or cure of a disease or condition of human beings.” Section 351 of the Public Health Service (PHS) Act
    
    • Include blood-derived products, vaccines, in vivo diagnostic allergenic products, immunoglobulin products, products containing cells or microorganisms, and most protein products
Clinical Investigation?

• "Clinical investigation" means any experiment in which a drug is administered or dispensed to, or used involving, one or more human subjects.

• 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(b))

• “Off Label Use” or “Unlabeled Indication”
  - 21 CFR 312 does not apply to use in practice of medicine for an unlabeled indication of a new drug product approved or of a licensed biological product
Device?

- Instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part, or accessory, which is—
  - (1) recognized in the official National Formulary, or the United States Pharmacopeia, or any supplement to them,
  - (2) intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or
  - (3) intended to affect the structure or any function of the body of man or other animals, and

AND

- Which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of its primary intended purposes.
• "Investigation" means a clinical investigation or research involving one or more subjects to determine the safety or effectiveness of a device. (21 CFR 812.3(h))

• This definition is different than that for a drug
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.
Clinical Trial (NIH) revised 10/24/14

- A research study\(^1\) in which one or more human subjects\(^2\) are prospectively assigned\(^3\) to one or more interventions\(^4\) (which may include placebo or other control) to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes.\(^5\)

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

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

\(^3\)The 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.

\(^4\)An *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.

\(^5\)*Health-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
NIH Clinical Trials Decision Tree

NIH Definition of Clinical Trial Decision Tree

Does the study involve one or more human subjects?
- Yes
  - Does the study involve the use of one or more interventions?
    - Yes
      - Does the study prospectively assign human subject(s) to an intervention(s)?
        - Yes
          - Does the study have a health-related biomedical or behavioral outcome(s)
            - Yes
              - The study is a clinical trial.
            - No
        - No
    - No
  - No
- No

The study is not a clinical trial.
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
• **AGENCY-INITIATED RESEARCH**: A non-MSU individual or agency/sponsor initiates and takes responsibility for the research. MSU provides services/data, but has no direct input on or influence over the research design or protocol.

- Another institution/researcher, who asks MSU to participate in the their investigator-initiated research project, is considered an ‘agency’.
MSU INVESTIGATOR-INITIATED RESEARCH: An MSU 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.
Additional Helpful Definitions
Case Studies
Project Natures

Current Applicable Project Nature Choices:

- Research - Clinical Trial with Human Subjects - Agency Initiated
- Research - Clinical Trial with Human Subjects - MSU Investigator Initiated
- Research - Clinical with Human Subjects - Agency Initiated
- Research - Clinical with Human Subjects - MSU Investigator Initiated
- Research - Non-Clinical with Human Subjects
- Research - Without Human Subjects
Case Study #1

Case #1: A study will test de-identified, archived, human blood samples for which the researchers will not have access to identifying information. The study will evaluate the levels of cardiac troponin in patients undergoing cancer treatment with doxorubicin compared to cancer patients undergoing chemotherapy with agents other than doxorubicin.

- Is this study a clinical trial?

- What project nature should be indicated on the transmittal?

All case studies adapted from the NIH Case Study Examples, http://auth.osp.od.nih.gov/sites/default/files/Case%20Studies%20-%202016%20UPDATED.pdf
Case #2: A study is designed by an MSU researcher to randomly assign individuals to either an experimental intervention to promote weight loss, or to a control intervention. After a year, participants’ behaviors will be assessed to measure their adherence to exercise regimens.

- Is this study a clinical trial?

- What project nature should be indicated on the transmittal?
Case Study #3

Case #3: Selected as a study site by an industry sponsor, an investigator plans to administer a new experimental product to patients suffering from advanced stage Wilms tumors (rare and malignant kidney tumors). Due to the rarity of the disease, only five patients will be enrolled in the study. All patients will receive the new experimental product. Tumor size and the incidence of metastatic disease will be evaluated.

- Is this study a clinical trial?

- What project nature should be indicated on the transmittal?
Case #4: A study is designed by a U of M investigator to evaluate the efficacy of an in-vitro diagnostic device to detect circulating antibodies. MSU has subcontracted to collect banked blood samples from identifiable, patients diagnosed with lupus and from patients who do not have lupus; these samples will be used to evaluate the device’s ability at MSU to detect circulating antibodies.

- Is this study a clinical trial?

- What project nature should be indicated on the transmittal?
Case Study #5

Case #5: An industry sponsor has contracted with an MSU investigator to collect data from patients already using the sponsor’s blood coagulation product as standard of care. Participating in the study will not dictate the course of therapy, other than to be eligible for the study the patient has to already be using the sponsor’s product. The purpose of this observational study registry is to get information on routine clinical care for patients with the blood clotting disorder.

• Is this study a clinical trial?

• What project nature should be indicated on the transmittal?
Case Study #6

Case #6: MSU Investigators are designing a study to evaluate the effects of providing cash incentives for STD testing on the rate of agreement for counseling and treatment (if needed). Cash is provided to visitors if they agree to be tested, after which they will be offered free counseling and/or treatment. The rate of visitors undergoing counseling and/or treatment after providing cash incentives will be compared to the rate observed in the two years prior to the study.

- Is this study a clinical trial?

- What project nature should be indicated on the transmittal?
Questions?
Overview of Clinical Research/Trial Process
Translational Research Process

Discovery Phase

Development Phase

Delivery Phase

Outcomes Phase


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.
New Drug Development Timeline

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

Phase 2
- Pre-Clinical Testing, Research and Development
- Range: 2-10 years
- Avg.: 5 years

Phase 3
- Clinical Research and Development
- Range: 2 mos.
- Avg.: 24 mos.

NDA Review
- NDA Submitted
- NDA Approved
- Range: 2 mos.
- Avg.: 24 mos.
- Range: 7 years

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

Sponsor Time

FDA Time

30 Day Safety Review
# FDA Clinical Trial Phases

## Testing in Humans

<table>
<thead>
<tr>
<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>
</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>
</tr>
<tr>
<td>Phase 3</td>
<td>Several hundred to several thousand</td>
<td>1–4 years</td>
<td>Safety, effectiveness, dosage</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

Subjects

Federal & State

Institution
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
  • http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cf/cfr/CFRSearch.cfm?CFRPart=50&showFR=1
  • http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cf/cfr/CFRSearch.cfm?CFRPart=56&showFR=1
  • http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cf/cfr/CFRSearch.cfm?CFRPart=312

- State and Local Laws

- Institutional Policies and Procedures
  • http://www.hr.msu.edu/documents/faccadhandbooks/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.

- Responses were due December 7, 2015.

- Implementation date?
<table>
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<tr>
<th>MSU Office</th>
<th>Function</th>
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</thead>
<tbody>
<tr>
<td>Animal Care Program (ULAR) animalcare.msu.edu</td>
<td>Reviews animal use in research, teaching, and testing</td>
</tr>
<tr>
<td>Business Connect (BC) businessconnect.msu.edu</td>
<td>Reviews and negotiates industry sponsored contracts</td>
</tr>
<tr>
<td>Clinical and Translational Sciences Institute (CTSI) ctsi.msu.edu/</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) hrpp.msu.edu/crbc-office-0</td>
<td>Provides clinical research billing compliance services</td>
</tr>
<tr>
<td>Conflict of Interest (COI) coi.msu.edu/</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">www.ctlr.msu.edu/COAccounting</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>
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</table>
# Institutional Roles: MSU

<table>
<thead>
<tr>
<th>MSU Office</th>
<th>Function</th>
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| Human Research Liaison Program  
HRL@msu.edu                                                                                 | Performs post approval site visits and clinical research compliance                                                                      |
| Human Research Protection Program (HRPP)  
www.HRPP.msu.edu                                                               | Components are the Institutional Review Boards and the Compliance Offices                                                                |
| Institutional Review Board (IRB)  
irb@msu.edu or irbdocs@ora.msu.edu                                              | Reviews human subject research and clinical investigations                                                                               |
| Internal Audit  
msu.edu/unit/intaudit/                                                     | Audit research financial records and accounts                                                                                           |
| MSU Technologies (MSUT)  
http://www.technologies.msu.edu                                               | Executes Confidential Disclosure Agreements and Material Transfer Agreements; reviews intellectual property                                   |
| Office of Regulatory Affairs (ORA)  
www.ora.msu.edu/                                                               | Components are the Animal Care Program, Environmental Health Safety, Human Research Protection Program                                     |
| Office of Sponsored Projects (OSP)  
help@osp.msu.edu                                                              | Manages non-industry sponsored proposals                                                                                                |
| Pharmacy  
www.pharmacy.msu.edu                                                         | May store and dispense investigational products                                                                                         |
| Research Offices - College, Department                                         | Oversight and/or approval of research projects                                                                                          |
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
• 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 regulatory and contractual 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
- Data entry in sponsor’s electronic data system
- Meets with sponsor monitors and responds to data correction queries
Study Coordinator’s Role (cont’d)

- 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

- 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 their rights (e.g. they can withdraw from the study at any time)

• 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
Questions?
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
- Access to Clinical Research Services Facility
- Study Coordination, Regulatory Support
- Research Process Navigation
- Budget & Payment Term Negotiation
- Biologic Sample Collection & Processing
- Subject Recruitment & Retention Strategies
- Internal Cost Discovery, Budget Development
- Post Award Financial & Invoicing 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](http://CTSI.msu.edu)
Part 2: Clinical Trial/Research Process Flow
What and Who are Involved?

The Process

Principal Investigators

Sub-Investigators

Internal & External Resources (i.e. Imaging, Pharmacy, Lab)

Study Staff (Coordinators, Nurses, Data Managers)

Administration (Contracts, Budget & Billing)

Other Compliance staff (IRB, Human Subjects Liaisons, CRBC)
High Level Process Overview

Decision to Pursue
- Confidential Disclosure Agreement
- Protocol Feasibility

Study Closeout

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

Study Start-Up and Management
- Financial
- Contractual
- Regulatory
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
Feasibility Overview (i.e. Project/Needs Assessment)

• 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

• A Business best achieves goals by starting with a STRATEGIC PLAN
  - Why are you in the ‘business’ of clinical research?
  - Is the research important to the college/department?
  - 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 (CRMS)

- Be aware 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/Research Agreements and Negotiation
- Regulatory Reviews

Study Start-Up and Management
- Financial
- Contractual
- Regulatory
Pre-Award: Parallel Processes

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

• Departments/Colleges/MSU offices work together
Simultaneous Institutional Evaluation (Pre-Award)

Department / College Work-Up, Submission:

Coverage Analysis (if required) → Contract Review by Appropriate Office → Submit IRB Application → Additional Required Reviews?

Obtain All Needed Institutional Reviews &/or Approvals, CGA Account Setup, & Notify All Parties
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)
  - Obtain Coverage Analysis (CRBC) to determine costs that require sponsor coverage vs insurance billable

- 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!
Who Develops/Negotiates the Budget?

- Departments/Colleges
  - Research administrators, PIs, study coordinators

- Support Offices
  - CTSI (OCR)- can assist with cost discovery, budget development, budget and payment term negotiation, and connection to external services and collaborators
A prospective coverage analysis (CA) is required for all new studies that generate a billable event. If the project is determined not to meet the criteria as a Medicare Qualifying Clinical Trial, the Principal Investigator will be notified. For qualifying clinical trials, the HRPP Compliance office will create a Billing Grid for Coverage Analysis (BGCA) and the research team will use the BGCA to complete the Billing Compliance Plan (BCP).
Why do a Coverage Analysis?

• If insurance is proposed to be billed, there are rules on what can be billed to a subject’s insurance.

• Determinations need to be made on who pays for what. Who is covering the cost . . . sponsor, department, subject, insurance, etc.?

• The function of clinical research billing compliance is to help ensure proper billing of health care services and items according to federal, state, and local regulations.
Coverage Analysis Process

1. HRPP Compliance office will conduct a prospective coverage analysis.
   - Determine if the study meets the Medicare National Coverage Decision (NCD) 310.1 criteria for a qualifying clinical trial
   - Understand what items and services may be billed to the patient/insurance
   - Understand which items and services are non-billable

2. Billing Grid for Coverage Analysis is returned with the coverage analysis determinations completed.

3. The PI or designee can move forward with sponsor negotiations for industry sponsored or finalize the study budget for federally funded.
4. Compliance Office will work closely with the department and HealthTeam to ensure the patient is registered as a subject. Part of a TEACH visit.

5. Compliance Office will review the BG-CA to run audit reports and to review billing claims prior to the subject or their insurance being billed.

6. On site post approval monitoring visits will also include a review of billing compliance.
**Regulatory Review Overview**

- **Determine what reviews are needed**
  - MSU IRB, other IRBs
  - Compliance Office (e.g. Billable events, FDA regulated, ICH-GCP, HIPAA, ClinicalTrials.gov)
  - Biosafety
  - Animal care
  - Radiation safety
  - Stem Cell Committee
  - Conflict of Interest (COI)
  - Export controls

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

- **Contact Regulatory Affairs if questions**
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
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

MSU examples include Biogen, Novo Nordisk, Amgen, Novartis, Children’s Hospital of Philadelphia (CHOP), Big Ten Cancer Research Consortium (BTCRC)
Critical Clause Areas

• 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
  - CTSI (OCR)
  - Principal investigator or study coordinator
  - Sometimes department staff
Who **Can** Sign a CTA/Research Agreement?

Signature authority delegated from the Board of Trustees of MSU to:

- Assistant Vice President of Research and Graduate Studies
- 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/Research Agreement?

- Principal investigators, coordinators and departmental administrators, etc.

See www.OSP.msu.edu, search ‘signature authority’ for more information
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 Closeout

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

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

• Study start-up and management encompasses many areas of a clinical trial/clinical research project
• 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
  - Coordination with billing offices (CRBC Billing Compliance Plan indicating 3rd party billing for routine care charges vs use of 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, subcontract
  - Labor distributions & effort reporting
  - Study subject stipends and 1099
  - Study closeout of finances
The study agreement is a ‘contract’ and MSU is bound to the terms in the executed agreement:
- Fulfilling the contract terms of the agreement is an essential component of study management
- Contract terms may be modified through appropriate procedures as the study progresses

Obligations include:
- Adherence to protocol
- Compliance with all applicable rules, regulations, laws and statutes
  - Proper billing of study procedures
- Maintaining confidentiality of sponsor information
- Performing study in accordance with professional standards
- Report information and maintain communications with the sponsor
Contract Responsibilities

For Fulfilling Obligations:

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

To Be Informed on 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
Contract Changes- Impact

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

Examples: Changing the study visit schedule, study procedures; extending the period of the study; changing the # of study subjects; changing CROs/Sponsors; changing the PI

• Analyze the impact
  - To budget/financials
  - To study subjects
  - To MSU
When Are Contract/CTA Obligations Fulfilled?

• During the study
  - Enrollment goals met
  - Reporting completed
  - Proper billing per the Billing Compliance Plan

• 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
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
• **HRPP Manual, Section 6-6, Privacy, Confidentiality, and Anonymity**
  
  (7) When appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.” 45 CFR 46.111, 21 CFR 56.111

- In order to approve research, IRB will determine that, when appropriate, research protocol or plan contains adequate provisions to maintain confidentiality of identifiable data. The IRB should consider:
  
  - Number of individuals with access to data
  - Location of data storage
  - Use of identifiers and storage with data
  - Who has access to subject identifiers
  - Length of data storage and what will be done with the data at conclusion of research
  - Security of data (e.g. locked filing cabinet, password protected computer, etc.)
  - Sensitivity of data
  - Risk to subjects based on breach of confidentiality and whether safeguards are adequate
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 HRPP Compliance conducts a site visit, data security will be examined
• Research Data: Management, Control and Access
  -Best practices

• MSU Institutional Data Policy
• Investigational Drugs
  - An investigator shall administer drug only to subjects under investigator's personal supervision or under supervision of a sub investigator responsible to investigator.
  - Investigator shall not supply investigational drug to any person not authorized under this part to receive it. 21 CFR 312.61

• Investigational Devices
  - An investigator shall permit an investigational device to be used only with subjects under the investigator's supervision.” 21 CFR 812.110(c).
HRPP Manual Section 7-1, Research Involving Investigational Drugs and Devices

- Investigator must describe plan for storage, handling, and control of test article.

- If clinical investigation is being conducted at a clinical facility, facility’s procedures for control of pharmaceuticals, medical devices, and controlled substances should be followed.

- IRB members will evaluate investigator’s plan, including assessment of:
  - Storage and security of test article
  - Administration by appropriate individuals
  - Plans for documentation and maintenance of records

- Proper handling and storage may also be assessed during site visits by the human research liaisons.
HRPP Manual Section 12-2, Storage and Handling of Investigational Drugs and Devices

- Accountability plan elements:
  - Maintenance of records of test article delivery to institution
    - Records with dates, quantities delivered, serial/batch numbers, expiration dates.
    - Retention of shipping inventory/packing slips in records.
  
  - Maintenance of inventory of test article at study site
    - Inventory records updated and signed.
  
  - Documentation of use of test article by each subject
    - Identify test device, date subject received test device, quantity/dosage dispensed, and signature of dispenser on accountability logs.
HRPP Manual Section 12-2, Storage and Handling of Investigational Drugs and Devices

- Secure storage of test article
  - Store test articles separately from standard clinical inventory
  - Lock/secure storage area. Limit access to study staff.
  - Store non-dispensed test articles separately from returned dispensed test articles
  - Provide environmental controls (ambient / controlled room temperature, refrigeration, freezer) appropriate for storage of test article.
  - Controlled substances must be stored in a locked location with storage and usage in compliance with federal and state regulations. For requirements on controlled substances, see MSU Environmental Health and Safety web site.
Record Retention

- 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.

- The contract may specify an addition period of required retention

- Research Data Management Guidance - Training
  - http://www.lib.msu.edu/rdmg/training/
FDA Requirement: Investigational New Drugs

Investigational Drugs

- Investigator shall retain records required to be maintained for a period of:
  - 2 years following date marketing application is approved for drug for indication for which it is being investigated; or,
  - if no application is to be filed or if application is not approved for such indication, until 2 years after investigation is discontinued and FDA is notified. 21 CFR 312.62(c)

Investigational Devices

- Investigator or sponsor shall maintain records required during investigation and for period of 2 years after latter of following two dates:
  - Date on which investigation is terminated or completed, or
  - Date that records are no longer required for purposes of supporting a premarket approval application or a notice of completion of a product development protocol. 21 CFR 812.140

- Investigator or sponsor may withdraw from responsibility to maintain records and transfer custody of records to any other person who will accept responsibility for them, including requirements of 812.145. Notice of transfer shall be given to FDA not later than 10 working days after transfer occurs. 21 CFR 812.140
IRB Requirement

- Records required shall be retained for at least 3 years, and records relating to research which is conducted shall be retained for at least 3 years after completion of research. All records shall be accessible for inspection and copying by authorized representatives of department or agency at reasonable times and in a reasonable manner. 45 CFR 46.115 (b)

- Records required by FDA shall be retained for at least 3 years after completion of research, and records shall be accessible for inspection and copying by authorized representatives of the FDA at reasonable times and in a reasonable manner. 21 CFR 56.115 (b)

- Longer record retention periods may be required by the study agreement
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What Obligations Survive Research & Trial Closeout?

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

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

- **MSU Archives**
  - Record 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 as required by regulations and the research agreement
Thanks for attending!