Clinical & Translational Research, “What is it and Why Should I Care?”

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What is Clinical Research?

- Clinical Research
- Clinical Trials
- FDA Clinical Investigations
- Industry Initiated
- Investigator Initiated
- Human Research
- Research
Let me ask you a personal question:

How many of you know someone who has cancer or had cancer?

Does anyone know what role MSU has played in helping people with cancer?
In 1978, Barnett Rosenberg and coworkers at Michigan State University discovered that certain platinum-containing compounds inhibited cell division and cured solid tumors resulting from cancer.

This discovery led to “cisplatin” a chemotherapy drug, approved by the FDA in 1978. Cisplatin was the first platinum-compound chemotherapy developed.

1989, MSU developed a second chemotherapy cancer drug, Carboplatin.

Carboplatin vastly reduced side-effects compared to its parent compound cisplatin.
Many people’s lives have been saved as a result of these drugs being developed by MSU.

Michigan State has collected over $160 million in royalties from cisplatin and carboplatin.

These royalties have been used to support other research grants through the MSU Foundation.
Why is it important to understand what clinical research is?

Important to understand from the financial standpoint, as clinical research studies and trials are different from a typical grant in that in many of these studies payment is tied to the participants, if you don’t recruit you don’t get paid.

Important to understand the difference between Sponsor-initiated vs Investigator-initiated, as this impacts the F&A rate and the regulatory rules and the amount of effort needed to conduct these studies.

Completion of the MSU transmittal requires being able to identify what the project nature is. We find that departments are typically not currently completing this information correctly.

This is important as the data from the transmittal are used to identify clinical research is currently taking place on campus. This data is used for a variety of external reporting and not having correct data means MSU is underreporting clinical research and this can impact our rankings against peer institutions.
A clinical study involves research using human volunteers (also called participants) that is intended to add to medical knowledge. There are two main types of clinical studies: clinical trials (also called interventional studies) and observational studies. ClinicalTrials.gov includes both interventional and observational studies.
“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)
What is Clinical Research (NIH)?

- **Patient-oriented research:** Involves a particular person or group of people or uses materials from humans. Examples of types for cancer:
  - Studies of mechanisms of human disease (how cancer causes illness, what causes cancer)
  - Studies of therapies or interventions for disease (cancer disease or cancer symptom treatments)
  - *Clinical trials* (cancer drugs)
  - Studies to develop new technology related to disease (cancer diagnosis techniques)

- **Epidemiological and behavioral studies:** Examine the distribution of disease, the factors that affect health, and how people make health-related decisions. *(Social, environmental, health decision trends and cancer development)*

- **Outcomes & health services research:** These studies seek to identify the most effective and most efficient interventions, treatments, and services. *(analysis of health policies, and cancer prevention and support programs)*
What is a 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.
Investigation: Any experiment that involves a test article and one or more human subjects, and meets certain requirements of the FDA regarding submission.\(^1\)

Test Article: Any drug (including a biological product for human use), medical device for human use, human food additive, color additive, electronic product, or any other article subject to regulation\(^2\) subject to specific regulations. Includes drugs (including botanicals, biologicals, and gene therapy, and genetically derived products that meet the definition of a “drug”), and medical devices for human use.

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)]
For clinical investigations or research involving devices, the definition of “subject” includes the use of specimens, even if the specimen is unidentified. While such research is not considered “human subjects” under the DHHS regulations, such research would be considered “subjects” under the FDA regulation for certain types of research.
**Types of Clinical Trials**

Treatment trials test new treatments, new combinations of drugs, or new approaches to surgery or radiation therapy. *(Cisplatin, carboplatin, radiation treatments for cancer)*

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. *(Lifestyle and dietary changes to prevent cancer; flu vaccines to prevent the flu)*

Diagnostic trials are conducted to find better tests or procedures for diagnosing a particular disease or condition. *(Cancer early diagnosis methods so early treatment can be most effective)*

Screening trials test the best way to detect certain diseases or health conditions. *(Identifying those at risk prior to development of cancer; genetic testing for cancer genes)*

Quality of Life trials (or Supportive Care trials) explore ways to improve comfort and the quality of life for individuals with a chronic illness. *(Treatment and management of pain resulting from cancer)*
Sponsor-Initiated vs. Investigator-Initiated

- **Sponsor-initiated**: is defined as an individual or agency who 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). *(Pharmaceutical company asks MSU physician to enroll subjects in the company’s cancer clinical trial)*

- **Investigator-initiated**: is an individual who both initiates and conducts an investigation, and assumes all of the sponsor responsibilities defined in the regulations. *(MSU investigator has cancer study idea, asks for funding in support of this research)*

  - If study is investigator-initiated, the requirements include both those applicable to the investigator and a sponsor.
Overview of Clinical Trial Process
New Drug Development Timeline

Pre-Clinical Testing, Research and Development
- Initial Synthesis
- Animal testing
  - Range: 1-3 years
    Avg.: 18 mos.

Clinical Research and Development
- Phase 1
  - Range: 2-10 years
    Avg.: 5 years
- Phase 2
- Phase 3
  - Range: 2 mos.–7 years
    Avg.: 24 mos.

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

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

Short Term
- 30 Day Safety Review

Long Term
- FDA Time
- Sponsor Time
What is Translational Research?

Discovery Phase

Development Phase

Delivery Phase

Outcomes Phase

What and Who are Involved?

The Process

- **Principal Investigators**
- **Sub-Investigators**
- **Internal * External Resources (ie. Imaging, Pharmacy, Lab)**
- **Study Staff (Coordinators, Nurses, Data Managers)**
- **Administration (Contracts, Budget & Billing)**
- **Other Compliance staff (IRB, Human Subjects Liaisons)**
High Level Process Overview of Clinical Research

Decision to Pursue
- Confidential Disclosure Agreement (CDA)
- 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
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
• 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?
  - 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
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
Who Processes Agreements at MSU

- All **Industrial Sponsored** Clinical Trials & Research Agreements are handled by MSU Business Connect, Randy Sheets

- All **Federally Sponsored or Non-Profits** Clinical Trials & Research Agreements are handled by the Office of Sponsored Programs

- Appropriate application of the clinical trial F&A cost rate
  - 26% of direct costs for Industrial Sponsored clinical research
  - 53.5% for federally sponsored investigator-initiated research
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, pharmacy, imaging, labs, regulatory prep and amendment fees, Safety report review fees, supplies, record archiving)
  - Variable costs (items invoiced when they occur)
  - Ongoing Administrative costs
  - Produce study billing grid (routine vs. research)

- Start early to prevent delays
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.
• 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 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
Financial Management

• Post-Award
  - Track sponsor payments; review for accuracy
  - Invoicing sponsor for line items
  - Payables to service providers per billing compliance plan
  - Labor distributions & effort reporting
  - Study subject stipends and 1099
  - Subrecipient Monitoring

• Close Out
  - Study closeout of finances
Where to go for Assistance
Vice President for Research & Graduate Studies

Clinical & Translational Sciences Institute (CTSI)

Biomedical Research Informatics Core (BRIC)
- Research Collaboration
- Data Mgt. & Informatics, Access to Software Tools
- Data Security & Data Storage
- Data oversight throughout study lifecycle

Develop New Opportunities With Research Partners
- Biologic Sample Collection & Processing
- Subject Recruitment & Retention Strategies
- Pre & Post Award Financial Training & Support
- Research Process Navigation Project Feasibility / Needs Assessment

Office of Clinical Research (OCR)
- Access to Clinical Research Personnel & Facilities
- Training & Support
- Biologic Sample Collection & Processing
- Subject Recruitment & Retention Strategies
- Pre & Post Award Financial Training & Support
- Research Process Navigation Project Feasibility / Needs Assessment
Clinical and Translational Sciences Institute

visit us at ctsi.msu.edu
Office of Clinical Research (OCR):

Assists research investigators with the development, implementation, management, and completion of clinical research conducted at MSU and through its community partner network

Project feasibility
- Research subject availability
- Resource needs assessment

Study logistics & management support
- Research process navigation
- Connection to internal & external resources
- Subject remuneration processes

Recruitment & retention
- Recruitment & retention strategies
- ResearchMatch & other social networking resources
Office of Clinical Research (OCR): continued

Pre-award consultation
- Project feasibility and cost assessment
- Budget development and negotiation
- Financial management education

Post award management consultation
- Payment receipt & tracking assistance for per-patient & milestone payments
- Processes for paying external entities
- Internal payment allocation per initial cost projections

Translational research space & personnel
- Study coordination
- Research exam rooms, laboratory equipment
- Biological sample collection, processing, shipping
Biomedical Research Informatics Core (BRIC):

Provides research data management services to clinical research studies.

Research collaboration
- Data collection consultation
- Utilize best practice guidelines for defining variables
- Address evolving technical requirements
- Help investigators comply with CFR 21 Part 11

Data oversight throughout study lifecycle
- Database Creation
- Testing electronic versions of your study instruments
- Ongoing surveillance of data quality & reporting
- Prepare data for analysis
Software solutions
• Web-based Data collection software (REDCap, OpenClinica)
• Mobile & offline options
• Tailor existing software to streamline study workflow
• Create novel software

Data Security & Storage
• Live data stored on encrypted redundant backup drives
• Redundant power sources to protect against power service interruptions
• Servers housed in HIPPA - Class security facility
Clinical and Translational Research (internal funding)
CTS1 Pilot Project/Seed Grant Program - Funding is Available for pilot clinical and translational projects. Applications accepted at anytime.

MSU/Sparrow Center for Innovation and Research
Spring 2015 Letter of Intent Announcement for Center for Innovation and Research – Research Support and Translation Support. Call due date: January 14, 2015 by 5:00 p.m.

SciVal Funding
SciVal® Funding is a subscription service provided to the MSU research community to help faculty identify funding opportunities based on specific terms and criteria. Faculty profiles in the MSU Scholars database can be linked to the SciVal Funding tool to allow faculty to set up automatic alerts of funding opportunities that match their expertise.

MSU Office of the Vice President for Research and Graduate Studies (VPRGS)
The office facilitates and expands scholarship, research and economic development by providing leadership, resources, coordination, oversight and innovation. View their Funding Opportunities Database.

NIH Funding
View the Weekly Issue of the NIH Guide for Grants and Contracts. The NIH Guide for Grants and Contracts is the official publication of the NIH.
Tools available for Researchers

MSU Scholars
Use the MSU Scholars site to search for expertise, identify research opportunities, and facilitate collaborations. read more...

Search for MSU Core facilities and services via eagle-i
Eagle-i allows MSU researchers to discover needed core laboratory services, reagents, animals, specimens, etc. that are available on campus and nationally. Secondly, it allows us to expose our own resources to external researchers who need them. read more...

ResearchMatch
ResearchMatch is a national recruitment registry that brings together researchers and people who are interested to learn more about research studies via a secure website. Researchers at Michigan State University and its affiliates can use this tool for feasibility assessment and recruiting. read more...

REDCap
REDCap is a secure web application for building and managing online surveys and databases. BRIC adds additional custom functionality through REDCap’s plugin system; for example, expanding the output of available real-time reports, and automating email activity reminders. read more...

Great Lakes Research into Practice Network (GRIN)
CTSI Tools & Resources

- **ResearchMatch**: National Online participant 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 and study data.

- **Translational Research Services Facility (TRSF)** includes access to space and equipment for conducting studies, study coordinators and phlebotomy staffing for hire, recruitment assistance.

For more information, please go to [CTSI.msu.edu](http://CTSI.msu.edu)
What is ResearchMatch?

- A way for volunteers and researchers to get connected
- A free and secure disease-neutral database developed by major academic research institutions across the country with the mission of helping today’s research studies make a difference for everyone’s health
- A complementary recruitment tool to help address the problem of research studies ending too soon because of a lack of volunteers
- A way for volunteers of any age, race, ethnicity, or health status to indicate their interest in participating in research
- A way to search for studies for specific medical conditions and find clinical trials
- Sponsored by the NIH National Center for Advancing Translational Sciences (NCATS)
What is ResearchMatch?

- 118 participating institutions
- 44 partnering organizations
- Over 91,142 volunteers
- 1312 in Michigan

Questions?