ClinicalTrials.gov: Oversight and Compliance at a Diverse Academic Research Center

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Outline

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- Structural challenges of a university with a diverse research portfolio and large cancer research center

- Oversight processes, compliance tracking mechanisms, and reporting tools

- Best practices & tips to pro-actively manage ClinicalTrials.gov records

- Growing influence of ClinicalTrials.gov

- Adapting to ongoing regulatory and policy change

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Poll

How many of our audience members come from:

- a large university (more than 3 schools or colleges)?
- a cancer center?
- the federal government?

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University of Michigan

- # 1 U.S. public university in research and development expenditures[1]: $1.55 billion[2]
- 63,177 Students Enrolled[3]
- 19 Schools & Colleges
- 170 departments & divisions
- 6 research institutes
- 3 Hospitals & <125 Health Clinics / Centers
- 2.4 million patient visits in 2018[4]

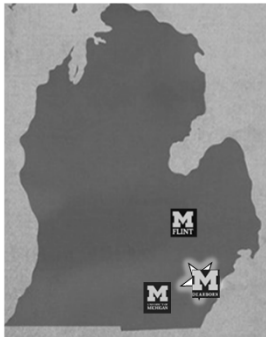1. https://ncsesdata.nsf.gov/herd/2017/html/herd2017_dst_36.html
2. https://www.research.umich.edu/research-u-m/office-research
3. https://2018.annualreport.umich.edu/
4. https://umich.edu/facts-figures/

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Research Diversity at University of Michigan

- 3 campuses
- University and Academic Medical Center
- Medical, Science, Social Research
- Some faculty have joint appointments with VA
- Rogel Cancer Center & Oncology Clinical Trial Support Unit
- Clinical Trial Support Office & Clinical Trial Support Units & new Clinical Research Management Team
- Michigan Institute for Clinical & Health Research (MICHR)

ClinicalTrials.gov Implication: *diverse research input into a very structured system*

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ClinicalTrials.gov at Michigan

- 2 organizational ClinicalTrials.gov accounts:
  - Rogel Cancer Center
    - Cancer Trials
  - University of Michigan group structure
    - 14 out of 19 Schools
    - Dearborn & Flint Campuses
    - UM Transportation Research Institute
- <1,160 user accounts
- 50 administrators
- <1,200 Records
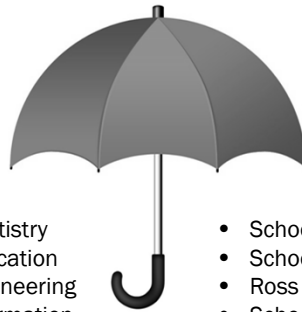
University of Michigan's ClinicalTrials.gov Records

[CATEGORY NAME] [VALUE]

Rogel [CATEGORY NAME] [VALUE]

[CATEGORY NAME] [VALUE]
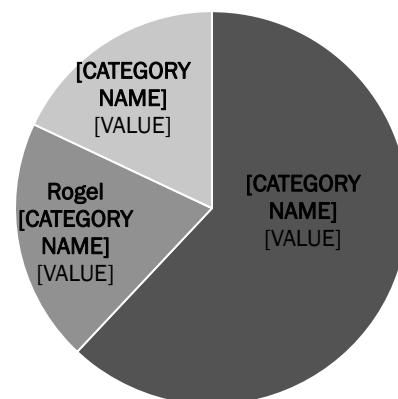
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Regulatory Oversight for Human Subjects Research

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University of Michigan Office of Research (UMOR)
Office of Research Compliance Review (ORCR)

- School of Dentistry
- School of Education
- School of Engineering
- School of Information
- Institute for Social Research (ISR)
- School of Kinesiology
- College of Literature, Science, and the Arts
- School of Medicine
- School of Nursing

- School of Pharmacy
- School of Public Health
- Ross Business School
- School for Environment and Sustainability (SEAS)
- School of Social Work
- Dearborn
- Flint
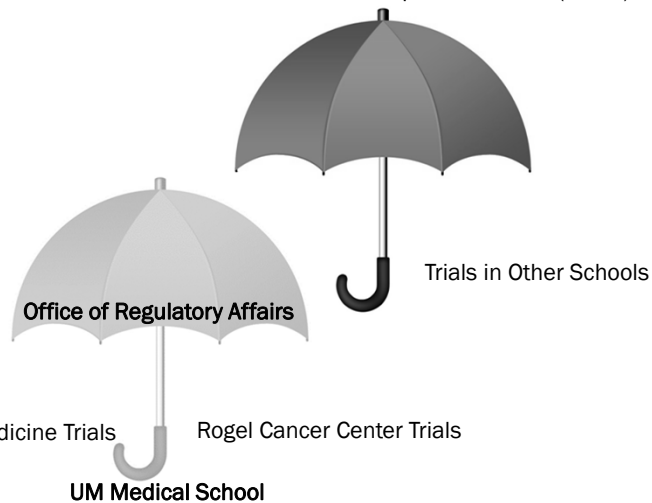- University of Michigan Transportation Research Institute (UMTRI)

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Regulatory Oversight for ClinicalTrials.gov

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University of Michigan Office of Research (UMOR)
Office of Research Compliance Review (ORCR)

Trials in Other Schools

Office of Regulatory Affairs

School of Medicine Trials   Rogel Cancer Center Trials

UM Medical School

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University of Michigan Rogel Cancer Center

- Rogel Cancer Center is a National Cancer Institute (NCI)-designated comprehensive cancer center

- Awarded the NCI P30 Cancer Center Support Grant (CCSG) since 1988

- The Support Grant funds cancer research infrastructure and enhances the center's ability to fund numerous research projects
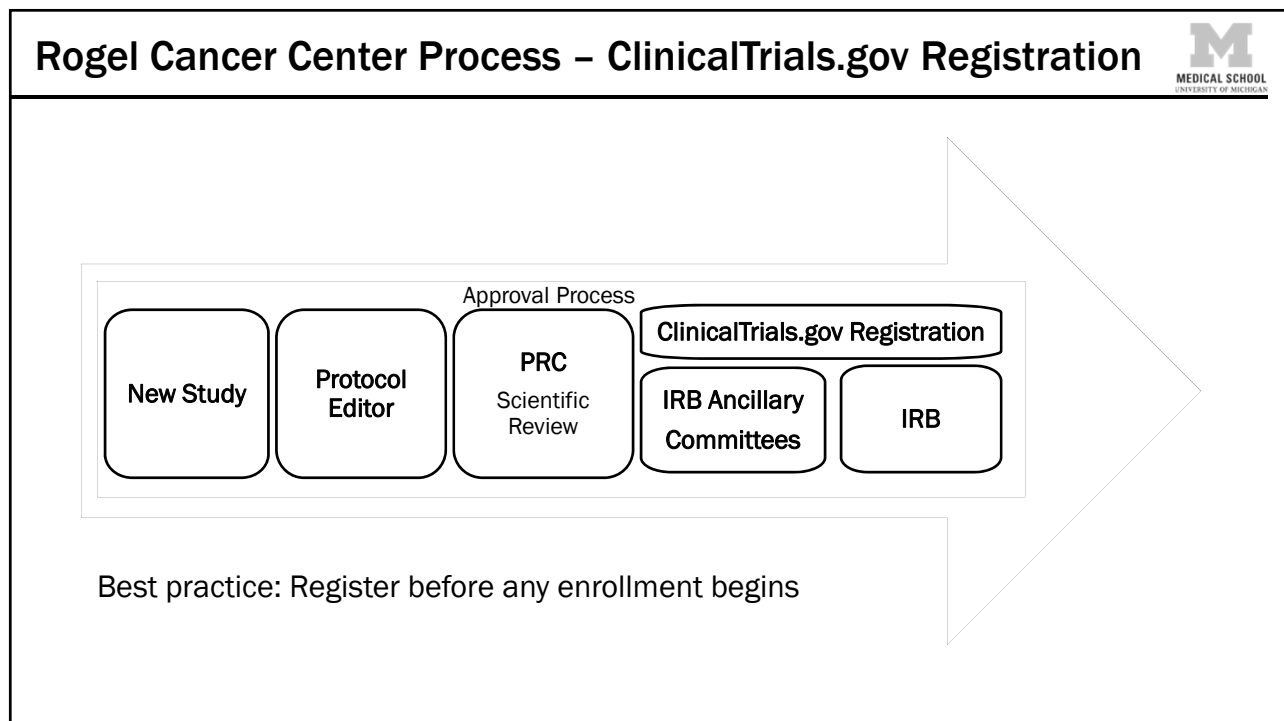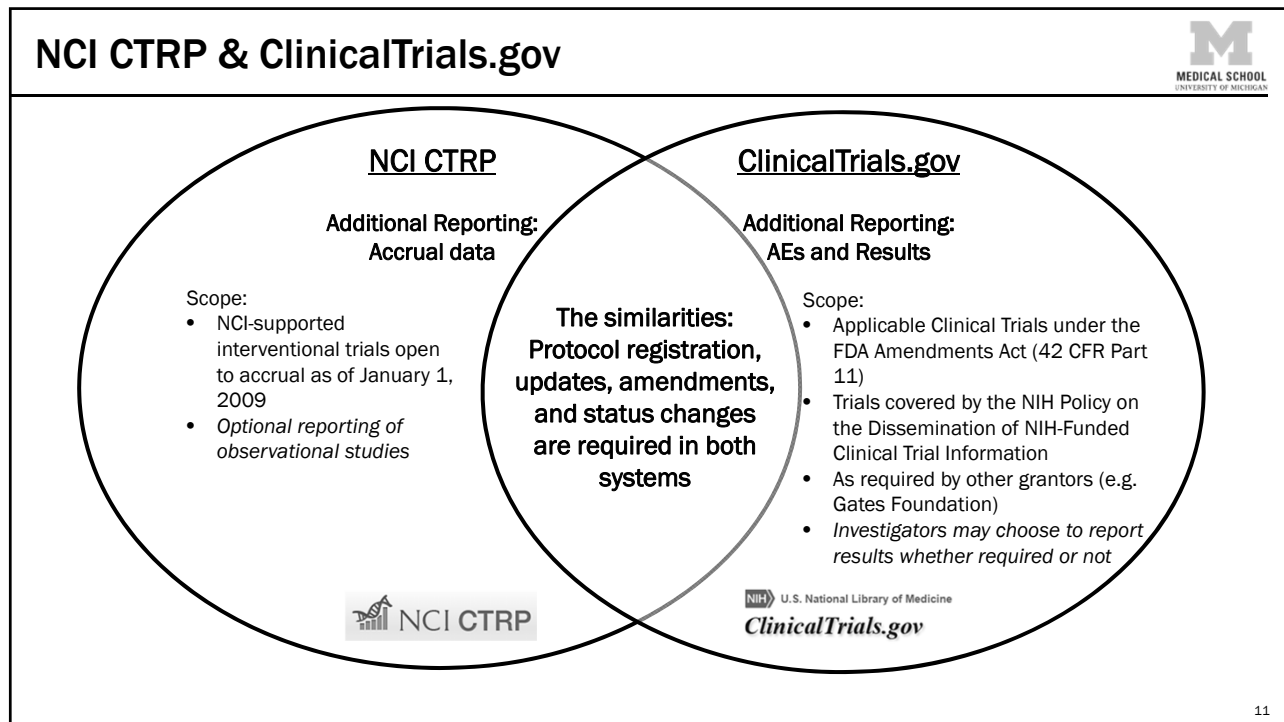

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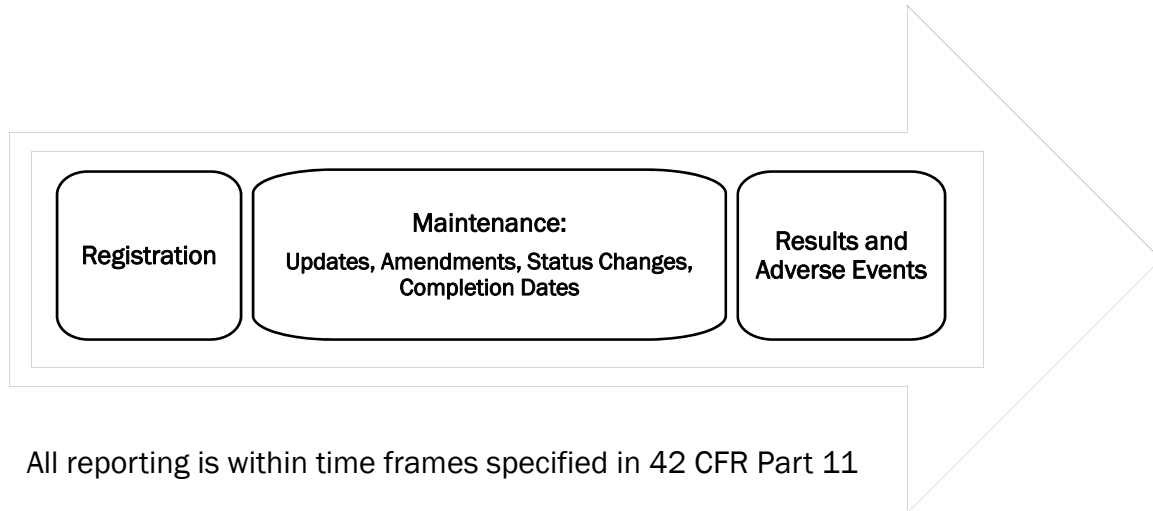## Oncology Clinical Trial Support Unit (O-CTSU)

The O-CTSU serves as the centralized administrative core for clinical research conducted by investigators at the Rogel Cancer Center

- Through the O-CTSU, the Rogel Cancer Center provides services to support U-M's NCI oversight and reporting obligations

- O-CTSU facilitates data reporting required by NCI's Cancer Center Support Grant (CCSG) and Clinical Trials Reporting Program (CTRP)

- O-CTSU is also responsible for ClinicalTrials.gov oversight and reporting for investigator-initiated trials that are sponsored by UM
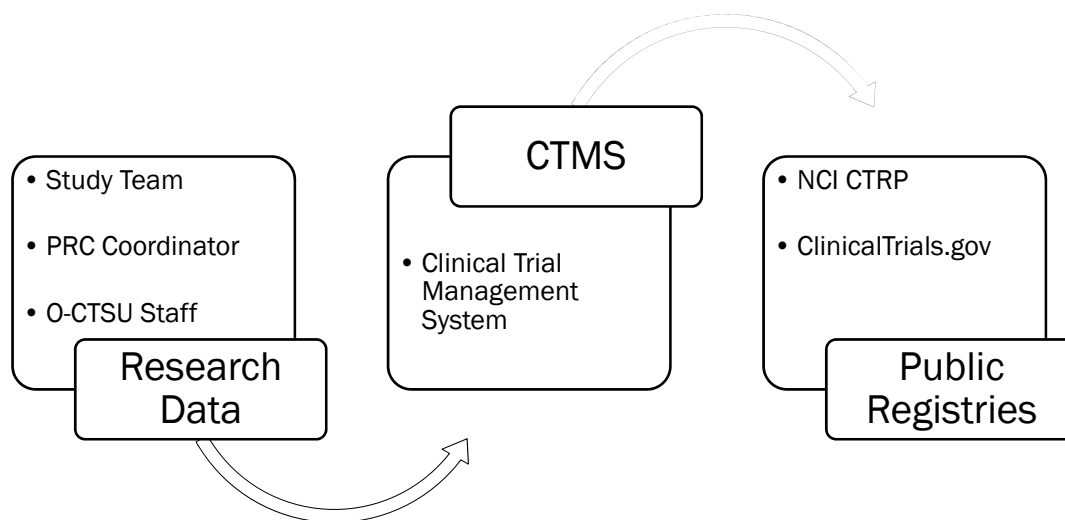
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NCI CTRP & ClinicalTrials.gov

NCI CTRP

Additional Reporting:
Accrual data

Scope:
- NCI-supported interventional trials open to accrual as of January 1, 2009
- *Optional reporting of observational studies*

ClinicalTrials.gov

Additional Reporting:
AEs and Results

Scope:
- Applicable Clinical Trials under the FDA Amendments Act (42 CFR Part 11)
- Trials covered by the NIH Policy on the Dissemination of NIH-Funded Clinical Trial Information
- As required by other grantors (e.g. Gates Foundation)
- *Investigators may choose to report results whether required or not*

The similarities: Protocol registration, updates, amendments, and status changes are required in both systems

NCI CTRP

NIH U.S. National Library of Medicine
ClinicalTrials.gov

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Rogel Cancer Center Process – ClinicalTrials.gov Registration

Approval Process

New Study | Protocol Editor | PRC Scientific Review | ClinicalTrials.gov Registration / IRB Ancillary Committees | IRB

Best practice: Register before any enrollment begins

Rogel Cancer Center Process – ClinicalTrials.gov Reporting

Registration

Maintenance:
Updates, Amendments, Status Changes, Completion Dates

Results and Adverse Events

All reporting is within time frames specified in 42 CFR Part 11

Rogel Cancer Center Process – Data Reporting

- Study Team
- PRC Coordinator
- O-CTSU Staff

Research Data

CTMS

- Clinical Trial Management System

- NCI CTRP
- ClinicalTrials.gov

Public Registries

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Clinical Trials Support Units (CTSU)

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New Centralized ClinicalTrials.gov Registration Service

- CTSU refers new Medical School Investigator-Initiated Clinical Trials to MICHR Clinical Research Management Team (CRM Team)

- Includes:
  - Protocol review
  - Evaluation of primary and secondary outcome measures
  - Registration on ClinicalTrials.gov
  - General guidance and notifications to help manage ongoing obligations (i.e. annual updates)
  - Consultations with the Office of Regulatory Affairs for interpretation of federal regulations and policies

*MICHR CRM Team now registers about **2/3** of all new Med School clinical trials and expected to continue to increase*

Interventional and Observational Studies by School

Types of Interventional Trial by School*

* Active Records
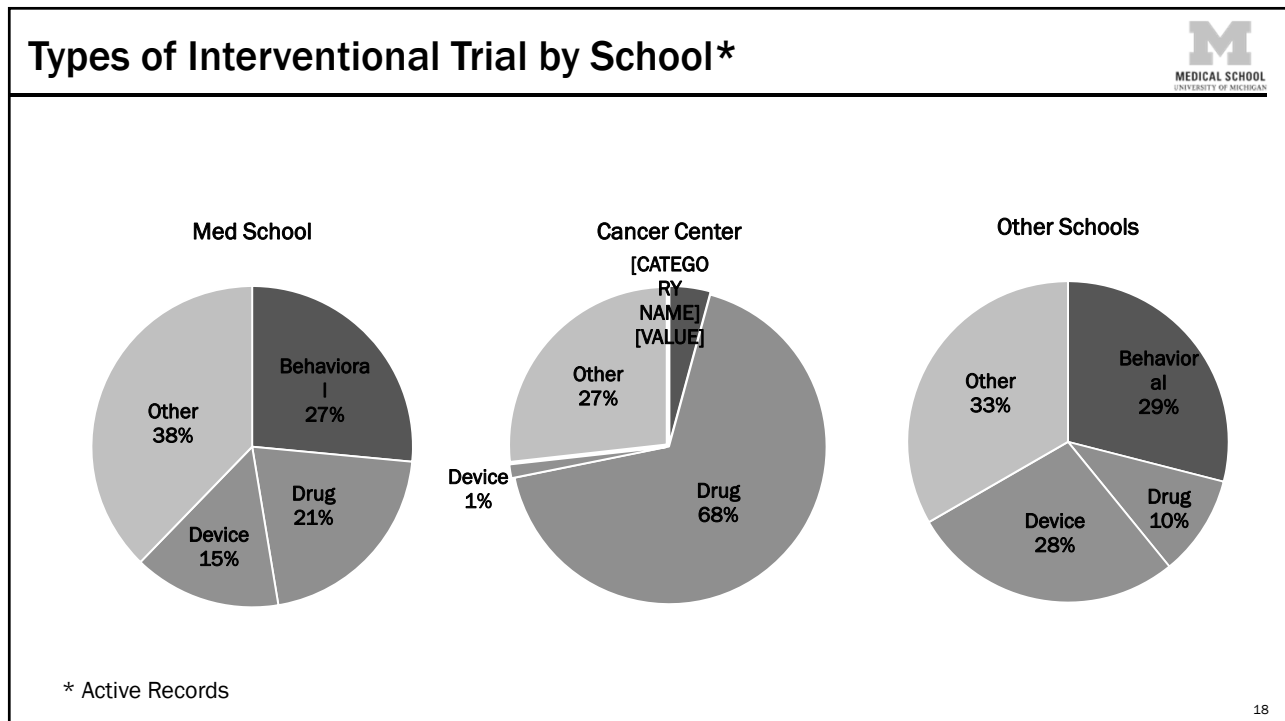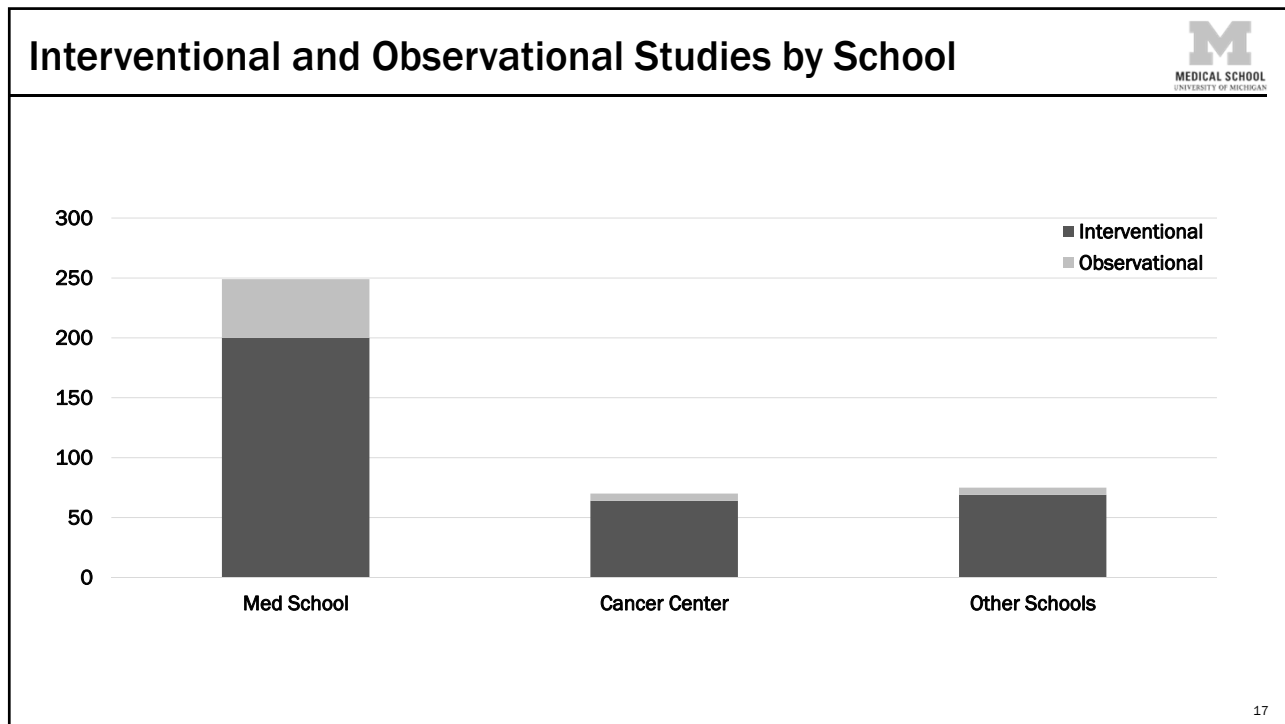
Organizational Structure & Impact on ClinicalTrials.gov Oversight

Will record management be centralized or decentralized?

	Rogel Cancer Center (O-CTSU)	Other Schools	Med School Studies	Med School CRM Trials
Model	Centralized	Decentralized, with centralized support	Decentralized, with centralized support	Centralized registration
Reason	Overlaps with some of the NCI CCSG reporting responsibilities	PI autonomy & accountability	PI autonomy & accountability	Improve quality and efficiency
Responsible Party	Institution / Sponsor	PI	PI	PI
Registration	Completed by Oncology Clinical Trial Support Unit (O-CTSU) w/content approved by PI	Completed by Study Team with assistance available from ORCR	Completed by Study Team with assistance available from Regulatory Affairs	Completed by MICHR CRM with input from Study Team
Maintenance	O-CTSU with input from Study Team or PI	Completed by Study Team with reminder from ORCR	Completed by Study Team with reminder from Regulatory Affairs	Completed by Study Team
Results Reporting	O-CTSU with input and approval from PI and statistician	Completed by Study Team with assistance from ORCR	Completed by Study Team with assistance from Regulatory Affairs	Completed by Study Team with Assistance from Regulatory Affairs
Escalation for ClinicalTrials.gov Non-Compliance	O-CTSU & Regulatory Affairs	ORCR	Regulatory Affairs	Regulatory Affairs

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Best Practices & Tips to Pro-actively Manage ClinicalTrials.gov Records

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Problems Prevention Using the Planning Report

Many errors are preventable

- Use the Planning Report to identify records that:
    - will be due to report results
    - require an annual update
    - are anticipated to start in the near future
    - are anticipated to finish in the near future
    - are funded by NIH

- Identify records that require outreach

- Conduct outreach with PI and study team

Challenge:

The system is only as good as the data entered. What other systems could we use as a cross-reference?

PRS Archive

Historical view shows when any record was updated and how it was changed

- Edits or deletions will be displayed in red
- Additions will be displayed in green
- Hover over the "Recruitment Status" to see how the study's recruitment status changed

Use Quality Assurance processes to submit accurate, understandable content

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Methods

- Training & education
- PRS Test
- ClinicalTrials.gov as a resource
- Outreach
  - Consultation & assistance
  - User instructions
  - Email templates
  - Reputation as helper
  - Customized approach
- Compliance
  - Tracking
  - Communication between administrators

The Growing Influence of ClinicalTrials.gov

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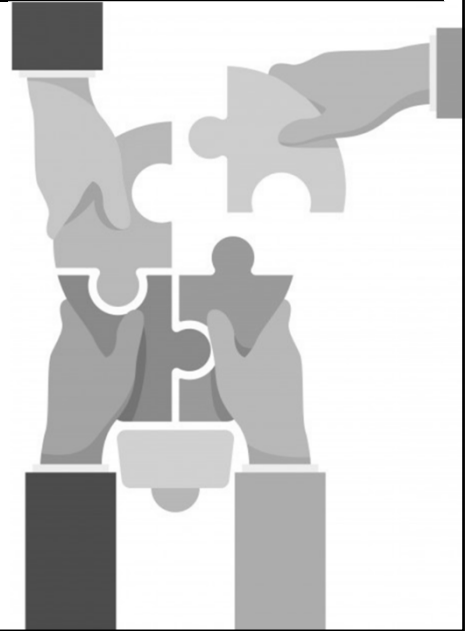
Changes Impacting ClinicalTrials.gov

- The Common Rule
- Data Sharing

  - ICMJE INTERNATIONAL COMMITTEE of MEDICAL JOURNAL EDITORS

  - pcori PATIENT-CENTERED OUTCOME RESEARCH INSTITUTE

  - NIH National Institutes of Health
    Turning Discovery Into Health

  - Implications for Informed Consent Documents
- NIH Policy
- Protocol Upload

Common Rule Informed Consent Requirement (46.116)

- Implementation date: January 21, 2019
- Applies **only to federally-conducted or supported clinical trials**
- Upload informed consents to either:
  - ClinicalTrials.gov or
  - regulations.gov Docket folder: HHS-OPHS-2018-0021
- Upload one IRB-approved version of informed consent document that has been used to enroll participants
- **After** the clinical trial is closed to recruitment
- Post consents **no later than 60 days** after the last study visit by any subject

The Michigan Way:

Upload informed consent document after study is closed to enrollment

Use a version that coheres with the final protocol

Challenge:

How can ClinicalTrials.gov help us to monitor for compliance?

Data Sharing

- Sharing data may be required to comply with federal funding or journal publisher guidelines

- Federal government expects results to be publically available

- Increase research impact and benefit the greater research community

Data Sharing – ICMJE

- Ethical obligation to share data
- Expect sharing de-identified individual-patient data (IPD)
- ICMJE now requires data sharing statement with manuscript
- Trials enrolling their first participants beginning in 2019 must disclose plan in ClinicalTrials.gov
  - Will IPD be available?
  - What data will be shared?
  - What documents will be available? (protocol, SAP, analytic code)
  - When will data be made available?
  - With whom?
  - For what types of analyses?
  - By what mechanism? (link or email)

http://www.icmje.org/news-and-editorials/data_sharing_june_2017.pdf
http://www.icmje.org/recommendations/browse/publishing-and-editorial-issues/clinical-trial-registration.html#two

Data Sharing Statement Examples

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	Example 1	Example 2	Example 3	Example 4	Example 5
Will individual participant data be available (including data dictionaries)?	Yes	Yes	Yes	No	Undecided
What data in particular will be shared?	All of the individual participant data collected during the trial, after deidentification.	Individual participant data that underlie the results reported in this article, after deidentification (text, tables, figures, and appendices).	Individual participant data that underlie the results reported in this article, after deidentification (text, tables, figures, and appendices).	Not available	**Warning: Undecided does <u>not</u> meet ICMJE policy**
What other documents will be available?	Study Protocol, Statistical Analysis Plan, Informed Consent Form, Clinical Study Report, Analytic Code	Study Protocol, Statistical Analysis Plan, Analytic Code	Study Protocol	Not available	
When will data be available (start and end dates)?	Immediately following publication. No end date.	Beginning 3 months and ending 5 years following article publication.	Beginning 9 months and ending 36 months following article publication.	Not applicable	
With whom?	Anyone who wishes to access the data	Researchers who provide a methodologically sound proposal.	Investigators whose proposed use of the data has been approved by an independent review committee ("learned intermediary") identified for this purpose.	Not applicable	Not available
For what types of analyses?	Any purp...	To achieve aims in the approved proposal.	For individual participant data meta-analysis.	Not applicable	Not available
By what mechanism will data be made available?		Proposals should be directed to xxx@yyy. To ...estors will need to sign a data access agreement. Data are available for 5 years through a third party	Proposals may be submitted up to 36 mo... publication. Inform...tion regarding accessing dat... may be found at (Link to b... provided).	...t available	

All data will be shared ←——————→ **No data will be shared**

The Michigan Way: Data Sharing

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- ClinicalTrials.gov Administrators:
  - Work with investigators to register trial
  - Refer to specialized library team for data sharing questions
- Taubman Health Sciences Library Staff:
  - Consult with investigators on new ICMJE requirement
  - Help investigators identify funder-specific guidance/sharing requirements (if any)
  - Provide language for data sharing plan if requested and appropriate
  - Refer investigators to Data Office for Clinical & Translational Research if appropriate
  - Refer investigators to Inter-university Consortium for Political and Social Research or other repositories, if appropriate

https://guides.lib.umich.edu/c.php?g=682739&p=6631773
https://www.icpsr.umich.edu/icpsrweb/content/datamanagement/dmp/framework.html

PCORI Policy

- Data management and data sharing plan must be submitted as part of the protocol
- Requires data sharing among PCORI-funded researchers
- Differing specific requirements depending on the type of study

IRB-approved informed consent form must document:

- all collected data will be de-identified
- de-identified data will be used for secondary research purposes
- de-identified data will be shared with other researchers

https://www.pcori.org/about-us/governance/policy-data-management-and-data-sharing

NIH Proposed Plan – Data Sharing

NIH sought public input to inform the development of a draft NIH policy:

- definition of scientific data
- requirements for data management and sharing plans
- optimal timing of implementation and how potential phasing could impact improvements in data infrastructure, resources, and standards

https://grants.nih.gov/grants/guide/notice-files/NOT-OD-19-014.html
https://www.nlm.nih.gov/NIHbmic/nih_data_sharing_policies.html

Informed Consent Language & Data Sharing Expectations

- Patient-Centered Outcomes Research Institute (PCORI), NIH, and some journals will require de-identified data
- Are we required to disclose to participants the plan to share de-identified IPD?
- If we're sharing IPD, we have an ethical obligation to disclose
- We want consent for everything we're doing
- Recommended best practice: disclose in the informed consent

At present, we're using a consistent baseline across the institution

NIH & ClinicalTrials.gov

- All NIH-funded clinical trials that applied for funding and began after January 18, 2017 (regardless of study phase or type of intervention) must register and report results in ClinicalTrials.gov
- It is important to identify NIH funded studies because this impacts the PI's registration and reporting obligations
- Same requirements & timelines for NIH funded studies as ACTs
- NIH protocol templates for interventional and behavioral trials

Challenge:

How to trace indirectly funded trials?

https://e-protocol.od.nih.gov/#/home
https://nexus.od.nih.gov/all/2019/04/01/the-protocol-template-for-behavioral-and-social-sciences-research-involving-humans-is-here/

Protocol Upload

- Required for *any study that reports results*

- Upload at time of results submission

- Applies to Protocol and Statistical Analysis Plans

- Cover page
  - Official title
  - NCT
  - Version date

- Upload in PDF Archive (PDF A) format

> **The Michigan Way:**
> *Do not upload protocol prior to results reporting*

Implications of Protocol Upload

- Protocols **must** be suitable to share with the public

- FDA, grantors, and ICMJE may check for coherence

- Outcome measures in protocol and ClinicalTrials.gov must align

- Outcome measures must be clearly delineated in the protocol as either primary, secondary, or exploratory

- Outcome measures not identified as exploratory or other will be considered secondary and be required to report results (42 CFR 11.48(a)(5))

- Protocols and Informed Consent documents should cohere (applicable to federally funded trials)

How We Adapt to Change

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Keeping Up With Change

Compliance means understanding what laws & policies apply to you, and following them

Challenges:

Evolving laws, policy, technology, standards, scope, equate to a moving target!

Different parts of the organization respond differently and at different paces

What Works for Us

- Monitor government websites (Federal Register, FDA, NIH)

- Subscribe to federal newsletters, news sources, and free webinars

- Meet regularly with counterparts to coordinate initiatives

- Develop relationship with other teams to develop organizational capacity as regulatory & policy changes arise

- Regulatory journals

- ClinicalTrials.gov articles and website

- Communicate regularly with external network

Challenges:

Reaching all PIs and study coordinators about changes that affect them

Finding the time to do it all!

ClinicalTrials.gov Taskforce

Summary

- For our large, diverse institution, one size does **not** fit all
- Change is constant

Internal	External
• Systems • Processes • Experience • Strategies	• Expectations (e.g. transparency) • Regulations • Policies • Systems

- What's enhanced our success:
  - Best use of available resources
  - Coordination and planning
  - Communication
  - Relationships

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Questions?