Registration and Results Reporting on ClinicalTrials.gov

Kim Mitchell
Director, Protocol Services Section
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Agenda

- Background
- Requirement to Register a Protocol
- Updating Protocol Information
- Results Reporting
- Compliance

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Background

- Food and Drug Administration Modernization Act (FDAMA) mandates registry 1997
  - Investigational IND trials for serious and life-threatening diseases or conditions
  - Register before participant enrolled
- ClinicalTrials.gov launched February 2000
- International Classification of Medical Journal Editors (ICMJE) required registration of trials 2005
  - Prospective registration required to be considered to publication
  - All interventional trials
- Food and Drug Administration Amendments Act (FDAAA) Section 801 - 2007
  - Expands registration requirements and adds results
  - Requires registration less than or equal to 21 days of enrollment of first participant
- Final Rule/NIH Policy on Dissemination of NIH-Funded Clinical Trial Information 2017

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Requirement to Register a Protocol

- Food and Drug Administration Amendments Act (FDAAA)
  - Final Rule took effect in January of 2017
  - Expanded the collection of information and required results reporting for applicable clinical trials (ACT)
  - ACT defined as:
    - Primary completion date on or after December 2007,
    - Interventional Study,
    - Other than Phase I trial of a drug/biologic, or device feasibility study
    - Studies a US FDA Regulated Drug/Device/Biologic, AND
    - Is under an IND/IDE or has one location in the US, or manufactured in the US and exported to another country

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Requirement to Register

- NIH Policy on the Dissemination of NIH-Funded Clinical Trial Information
  - Implemented Concurrently in January of 2017
  - Promote broad and responsible dissemination of NIH-federally funded research
  - Requires registration and results reporting of clinical trials regardless of study phase, type of intervention, or whether it meets the definition of an ACT under the Final Rule.
  - Defined as:
    - Primary Completion Date on or after January 18, 2017
    - Meets the NIH Definition of a clinical trial
      - Does the study involve human participants?
      - Participants prospectively assigned to an intervention?
      - Study defined to evaluate the effect of the intervention on the participants?
      - Is the effect being evaluating a health-related biomedical or behavioral outcome?
    - Includes Basic Experimental Studies with Humans (BESH)
      - Must meet both the NIH definition of clinical trial and basic research
      - "…a BESH…has the purpose of understanding a phenomenon without any sort of specific application towards a process or product…the interventions are often experimental manipulations [used] to understand a basic phenomenon… And the intervention, or the experimental manipulation, isn't intended to change the health status of the participant in any way." – Pam Kearney

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Who is Responsible for Registering

- Responsible Party responsible for registration and results reporting
- Responsible Party is the sponsor of the trial
- Sponsor defined as:
  - Under an IND/IDE, the IND/IDE holder is the sponsor
  - Trials not conducted under an IND/IDE, the sponsor is considered to be the party funding the trial.

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What Protocols are Registered

- Protocols:
  - Under the Final Rule or NIH Policy AND
  - when the Responsible party is the IRP
- Observational Protocols when the Responsible Party is the IRP
- Repository/Secondary Research Protocols are **not** registered, as well as Screening protocols

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How are Protocols Registered

- Protocol Services Section registers protocols for the IRP on behalf of RP
- Upon receipt of the Initial Protocol from the IRBO **AND** receipt of the PQS Protocol Information Action
- Protrak Query System (PQS) is the source to collect protocol information required and displayed on CTG and IRP websites
  - PQS Protocol Information Action completed and submitted to PSS
  - Includes identification of the Responsible Party
- Once registered, the PI/PC receives notification via email, with link to protocol
- Posted within 1-3 days

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Updating Protocol Information on CTG

- CTG requires review at least yearly for accuracy
- Review of information on PQS should be conducted at least yearly
  - Goal – track submission of PQS Protocol Information from PQS
  - Protocols with an accrual status of "Completed Study; data analysis ongoing" do not require yearly review after reporting the status to PSS
    - Do need to report when protocol closed
  - Modifications approved by IRB are updated by PSS
    - Email sent to PI/PC/SC when modification impacts data and PQS submission needed.
- Protocol data sent nightly to CTG to update

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Time-Frames to Report Changes

- Accrual Status – 30 calendar days after a change
  - Overall accrual status and individual enrollment sites
- First participant enrolled – 30 calendar days after the first subject is enrolled
- Primary Completion Date – 30 calendar days after the trial reaches its primary completion date
- Study Completion Date – 30 calendar days after the trial reaches its study completion date
- Responsible Party – 30 days after a change in name/contact information
- Intervention Name(s) – 30 calendar days after a nonproprietary name is established
- IRB Board Status – 30 calendar days after a change in status
- Record Verification Date – review of protocol information for accuracy not less than every 12 months

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Results Reporting

- Required when:
  - Applicable Clinical Trials under the Final Rule
    - PCD met on or after December 2007
  - Protocols meeting the NIH Definition of Clinical Research per NIH Policy
    - PCD met on or after January 18, 2017
  - Protocols with a status of "Withdrawn" are not required to report results
- Results Submitted no later than one-year from the Primary Completion Date
  - Considered met when, "The date that the final participant was examined or received an intervention for the purpose of final collection of data for the primary outcome, whether the clinical study concluded according to the pre-specified protocol or was terminated. In the case of clinical studies with more than one primary outcome measure with different completion dates, this term refers to the date on which data collection is completed for all the primary outcomes."

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Results Reporting

- One-year starts from:
  - Primary Outcomes Met
    - Report as "Actual" with the "Primary Completion Date" in PQS
  - Accrual Status changed to "Completed Study/data analysis" defaults the PCD as met
    - Prompts an email to study team by PSS to verify PCD
- Guidance to consider:
  - When did the last patient/interaction occurred
  - If approaching 10 months and not sure if new participants will enroll, consider requesting extension. If new participant are enrolled, one-year clock resets.
  - If accruing new patients/new funding falls through for any reason, and last patient/interaction occurred over 12 months – protocol is out of compliance.

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Results Reporting

- Notifications Sent:
  - 1st notification when PCD is reported as met/accrual status changes to "Completed Study"
    - Time-frame is dependent of when PCD is reported as met
    - Opportunity to confirm PCD date and submission deadline
    - Sent to PI/IC Contact
    - Ownership transferred to Responsible Party
  - 9-month Notification (PI/IC Contact)
  - 6-month Notification (PI/IC Contact)
  - 3-month Notification (PI/IC Contact)
  - 30 days prior to deadline (PI/IC Contact, SD, CD)
  - Day after Submission Deadline
    - NIHCC Chief Scientific Officer sends notification to PI, IC Contact, SD, CD, Branch Chief
    - Given 30-days to comply
    - Scientific Approval withheld for new protocols while out of compliance

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Results Reporting

- NLM Quality Review Process
  - Focus on validity, meaningful entries, logic and internal consistency, and formatting
  - May take up to 30 days
  - Comments identified should be addressed within 45 days
  - Major comments will delay results being posted to the public
  - Minor comments allow results to be posted to the public with comment(s)
- NLM – How to Submit Results
  - https://clinicaltrials.gov/ct2/manage-recs/how-report
- NIH IRP Sourcebook
  - IC Contact List
  - BTRIS Contact

https://oir.nih.gov/sourcebook/intramural-program-oversight/intramural-data-sharing/guide-fdaaa-reporting-research-results/assistance-available-help-results-reporting

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Results Reporting

- Certification for Delayed Submission/Good Cause Extension
  - Must be submitted before the results submission deadline
  - Submitted via CTG Protocol Registration and Results System (PRS)
    - MC 3007 requires approval of CD and NIHCC CSO prior to submitting in RS
  - Extension Request Must Include:
    - Description of the reason why results cannot be provided by the deadline/justification
    - Anticipated date results information will be submitted
  - NLM has 30-days to evaluate and make a final decision
    - If request is not granted, study is out of compliance as of the original due date
    - Appeal process exists
  - Submission requirements for each are on found under the FAQs "Results Information and Submission Deadlines" https://www.clinicaltrials.gov/policy/faq#fr_43

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Compliance

- MC 3007 Clinical Trial Registration and Results Information Reporting (January 2022)
  - Requirements for registration and results reporting
  - Roles and responsibilities
  - Consequences for Non-Compliance
    - Notification to IC Leadership
    - Notification to the NIH Director
    - Immediate withholding approval of PI new clinical protocol scientific review
    - Documentation by a supervisor in annual PMAP of failure to comply timely
    - Disciplinary action ranging from Letters of Reprimand

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Compliance

- IG Audit (December 2020)
  - Protocols required to submit results in calendar year 2019 and 2020
  - Focus on intramural and extramural
  - Recommendations:
    - Improve compliance procedures
    - Take enforcement actions when results submitted are late or not submitted
    - Work to understand challenges related to CTG and implement procedures

https://oig.hhs.gov/oas/reports/region6/62107000.asp

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Compliance

- IC Report

Protocol Number	Accrual Inst	PI	Responsible Party	Accrual Status	Primary Completion Date	Reporting Results Require	Date Results Need To Be Entered	Date Results First Submitted to CT.gov for QA	Date Results Last Sent/Updat	Results Reported In Time	Results Published on CT.GC
04-CC-0178	CC	Richard Chang, M.D.	Richard Chang, M.D.	Study Closed - Terminate	3/31/2010	Yes	3/31/2011	2/8/2011	10/31/2014	Yes	Yes
05-CC-0082	CC	Scott R. Penzak, Pharm.D.	Scott R. Penzak, Pharm.D.	Study Closed - Terminate	1/1/2011	Yes	1/1/2012	12/12/2011	3/13/2012	Yes	Yes
11-CC-0082	CC	Bradford Wood, M.D.	Nadine Abi-Jaoudeh, M.D.	Terminated	8/5/2015	Yes	8/5/2016	8/4/2016	12/4/2017	Yes	Yes
14-CC-0065	CC	Henry Masur, M.D.	Henry Masur, M.D.	Study Closed - Terminate	3/1/2016	Yes	3/1/2017	3/1/2017	4/13/2017	Yes	Yes
15-CC-0137	CC	Elliot B. Levy, M.D.	Elliot B. Levy, M.D.	Terminated	3/7/2018	Yes	3/7/2019	2/26/2019	3/29/2019	Yes	Yes
15-CC-N064	CC	Henry Masur, M.D.	Henry Masur, M.D.	Study Closed - Terminate	6/15/2016	Yes	6/15/2017	6/15/2017	7/16/2018	Yes	Yes
17-CC-0111	CC	Leighton Chan, M.D.	Leighton Chan, M.D.	Completed Study; data analyses ongoing	2/25/2021	Yes	2/25/2022	2/1/2022	4/14/2022	Yes	Yes
19-CC-0052	CC	Henry Masur, M.D.	Henry Masur, M.D.	Study Closed - Terminate	8/9/2019	Yes	8/9/2020	6/29/2020	7/23/2020	Yes	Yes
19-AT-0089	NCCIH	Alexander T. Chesler, Ph.D.	Alexander T. Chesler, Ph.D.	Completed Study; data analyses ongoing	11/17/2020	Yes	11/17/2021	9/9/2021	9/9/2021	Yes	Yes

- IRP Report

	Protocols Registered[1]	Number of Protocols Requiring Results[2]	Primary Completion Date Met (<=06/26/2024)	Within the one-year reporting time-frame	Overdue for results reporting	Submitted Results Records (undergoing Quality Review by NLM)	Results Posted	# of Protocols with Results Submitted In-Time
NIH Intramural	1143	1092	741	20	2	22	697	381
			68%	2%	1%	3%	94%	51%
Compared To April 10, 2024	1137	1087	729	26	0	20	683	367
			67%	3%	0%	3%	94%	50%

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Compliance Informed Consent Document

- Post copy of consent document to ClinicalTrials.gov
  - Posted after recruitment closes and no later than 60 days after last study visit
  - Purpose: to be more transparent about the consent forms used and overtime, improve the quality of consent forms
  - Requirement:
    - One consent form that was used to enroll subjects
    - Must be in English
    - Completed Cover Sheet attached
- Protocol Services Section can assist by emailing central mailbox

  CC_Protocol_Services@cc.nih.gov

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Compliance Informed Consent Document

- Include statement in consent document relating to posting of clinical trial information at ClinicalTrials.gov
  - FDA Guidance on Informed Consent Elements, 21 CFR 50.25(c)

"A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information thata can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time."

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References/Resources

- MC 3007 Clinical Trial Registration and Results Information Reporting https://policymanual.nih.gov/3007
- NIH Policy on the Dissemination of NIH-Funded Clinical Trial Information https://grants.nih.gov/policy/clinical-trials/reporting/understanding/nih-policy.htm
- ClinicalTrials.gov Results Definitions https://clinicaltrials.gov/policy/results-definitions
- Final Rule https://clinicaltrials.gov/policy/fdaaa-801-final-rule
- ClinicalTrials.gov Results Data Element Definitions for Interventional & Observational Studies https://clinicaltrials.gov/policy/protocol-definitions
- Frequently Asked Questions https://www.clinicaltrials.gov/policy/faq

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References/Resources

- PRS User's Guide: https://clinicaltrials.gov/submit-studies/prs-help/user-guide
- NIH Sourcebook: https://oir.nih.gov/sourcebook/intramural-program-oversight/intramural-data-sharing/guide-fdaaa-reporting-research-results/assistance-available-help-results-reporting
- Human Subjects & Clinical Trial Decision Tool: https://grants.nih.gov/policy/clinical-trials/training-resources.htm
- BESH: https://grants.nih.gov/policy/clinical-trials/besh.htm#answering
- Posting of Informed consent document: https://www.hhs.gov/ohrp/regulations-and-policy/informed-consent-posting/informed-consent-posting-guidance/index.html
- ClinicalTrials.gov Results Definitions: https://clinicaltrials.gov/policy/results-definitions

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Thank You!

Questions?

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