UNC THE NORTH CAROLINA TRANSLATIONAL & CLINICAL SCIENCES INSTITUTE

THE UNIVERSITY of NORTH CAROLINA at CHAPEL HILL NRP Network for Research Professionals

UNC OFFICE OF CLINICAL TRIALS

ORIENTATION FOR NEW CLINICAL RESEARCH PERSONNEL

MODULE 6

Presented by

NC TraCS Institute

UNC Office of Clinical Trials

UNC Network for Research Professionals

Online Logistics

- I will be monitoring the chat window for questions and will ask those questions to the presenter at the end of each talk, or during breaks in the conversation when the presenter invites questions.

- Slides will be emailed to everyone after the presentation, along with the evaluation link and any announcements.

- If you would like a certificate for ACRP/SOCRA credit, please complete the evaluation at the end of the presentation and send me an email – marie_rape@med.unc.edu

- Feel free to reach out to me either in the chat window or by email, I'm happy to help with anything you need.

Overall Agenda for Orientation

- **Module 1:** Introduction, NRP/ Education, and Office of Clinical Trials
- **Module 2:** IRB Processes, Conflict of Interest
- **Module 3:** GCP, Documentation, Informed Consent, Research Monitor Access
- **Module 4:** Contracts, Clinical Trial Agreements, Planning/Accounting of Funds, NIH Budgets, Billing Coverage Analysis
- **Module 5:** Recruitment, Study Start-up, Roles of Research Personnel, UNC Investigational Drug Services, UNC Device Policy
- **Module 6:** Introduction to RedCap, Investigator-Initiated Study Process, ClinicalTrials.gov, Documenting AEs & SAEs, IND and IDE studies

Week 6
Evaluation Link:
https://go.unc.edu/orientwk6

OR

If you need a certificate of attendance, please email marie_rape@med.unc.edu after completing the evaluation survey.

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THINKING OUTSIDE OF THE CLASSROOM

REDCap Coordinator Overview

~2500 and counting

Clarence W. Potter
Clinical Data Manager
cpotter@med.unc.edu

My Two Favorite Data Sayings …

"Try to Keep you from Messing up your Data"

"Just Say No …"

Easiest way I know to collect data “properly” (“gcp”)

https://go.unc.edu/redcap-consent

https://go.unc.edu/redcap-multilingual

https://tracs.unc.edu/redcap

https://tracs.unc.edu/redcap-resources

REDCap …

- ***YOU CAN DO IT – designed for non-programmers***
- Web-based data collection tool – nothing to install
- Transfer to statistics package for analysis
- **Secure, Consistent, Easy, CHEAP**
- Encrypted during transmission
- Offline solutions – MyCap and Mobile

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FDA Studies – 21CFR11

- REDCap at UNC is NOT 21CFR11 compliant for use in FDA studies
- UNC does not support
- Another solution is in the works - DocuSign

A favorite grumpy old man created of comedian Jeff Dunham

Want a Test Project?

- Put in a request for new project – https://tracs.unc.edu/redcap-request
- Practice project – fill out request, as that, with minimal info.
- Real (morph into real) project -- fill it out completely for the project
- Happy to help, but remember we charge for my time (suggest budget $75 x 4 hours / year)

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Service page:

tracs.unc.edu/redcap

Forms	1st Thur	10/8	9:30 - 11
Forms - Hands On	2nd Wed	10/14	1 - 3:00
Functions	3rd Tue	10/20	3 - 4:30
Open Session	4th Wed	10/28	3 – 4:30
Forms	1st Thur	11/5	9:30 - 11
Forms - Hands On	2nd Wed	11/11	1 - 3:00
Functions	3rd Tue	11/17	3 - 4:30
Open Session	4th Wed	11/25	3 – 4:30

Data Management Class – Dec 2020.
For those that are deeply involved in planning / execution of the data process

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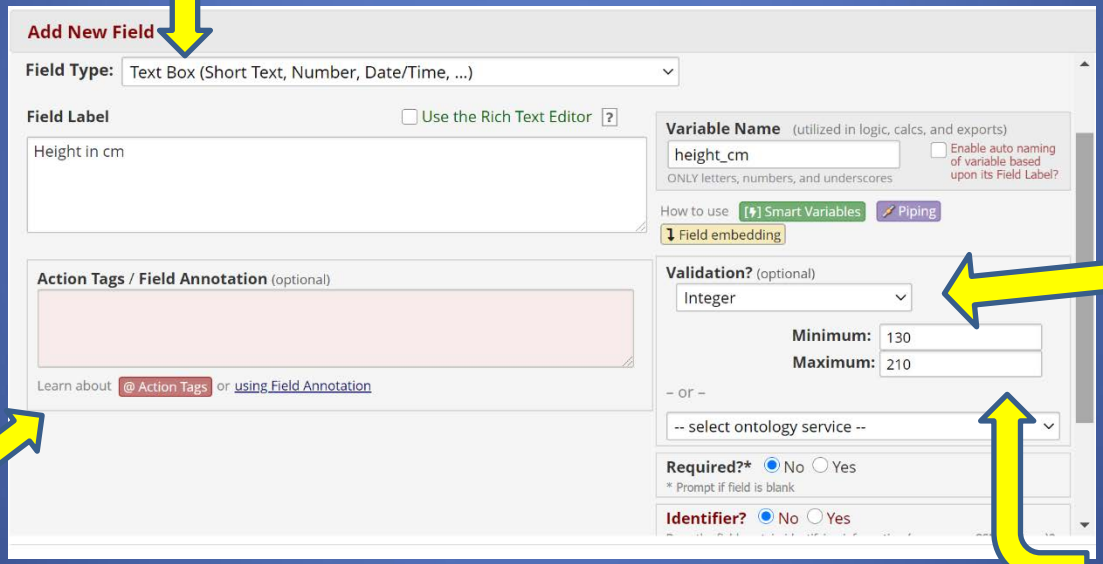
Your Easy Button

Online Designer

Like Survey Monkey

Field type – restricts the type of input (text, checkbox, radio, calculation



Validation – further restricts the type of input for text fields

Action Tags are the "magic" – set defaults, hide things

Range checks on numeric fields are "soft"

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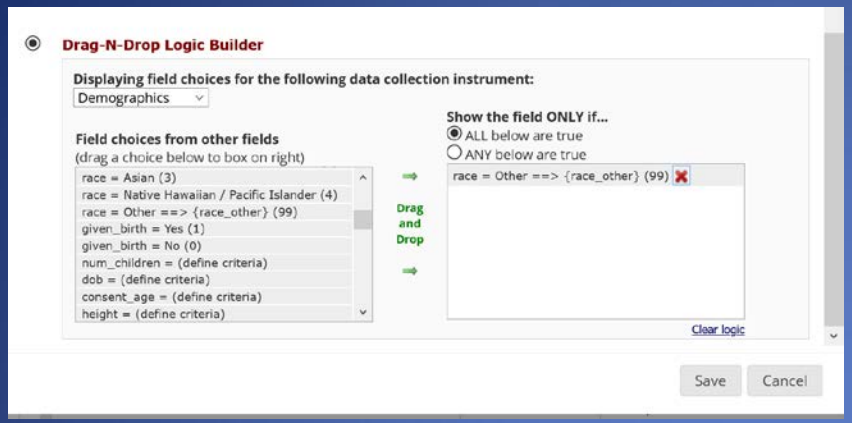
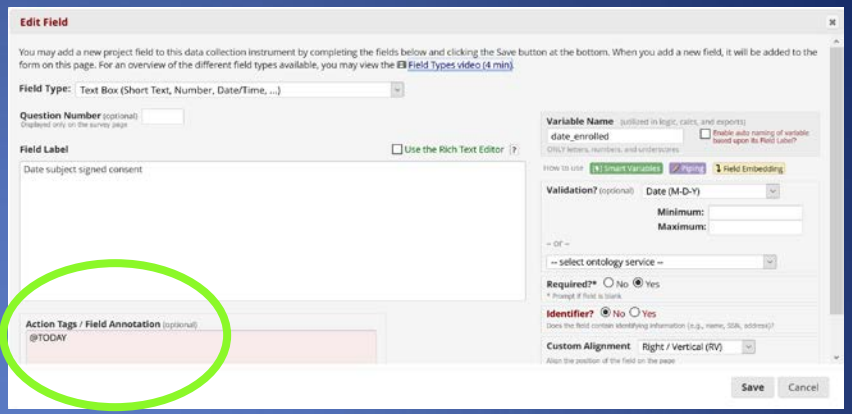
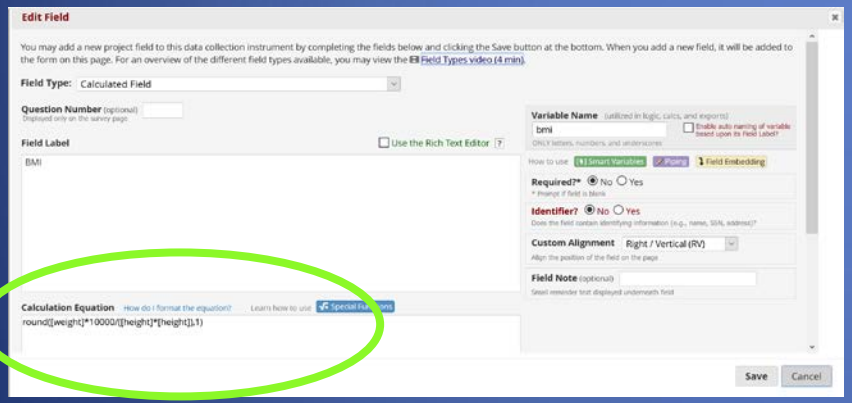
Branching logic

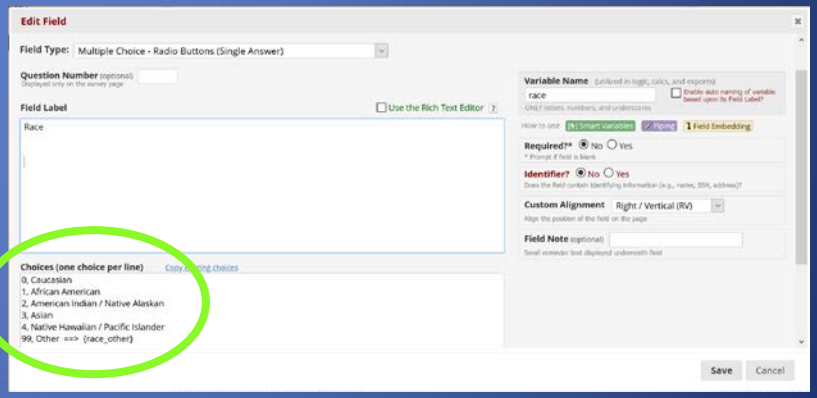


Action tags – set default





Calculate BMI



Pick list

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What ‘field type’ should I use?

- For each field (a place for every answer):
  - Fill in the blank? -> text field type
    - Validation (strict) – date, integer, number, phone, zip code, MRN, email
    - Range of values (soft check) – warning if out of range
  - Are there standard, generally acceptable answers?
    - Pick from a list?
      - Yes/No, True/False, list of symptoms?
      - Mutually exclusive -> radio / dropdown
      - Multiple selections -> checkbox
  - Calculate from existing data? -> calc
  - Upload an electronic file? -> file
  - Signature, slider, descriptive, header, yesno, truefalse, SQL

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Recruiting remotely?

REDCap Survey

- Not just data collection forms, but REDCap also has surveys.
- **Form** = Research team enters data
- **Survey** = Subjects enter data
- Survey is a form first, and then you enable it as a survey.
- Schedule those to go out at certain times

Integrated Survey Tool

- **Generic** survey link (first form only)
- **Subject-specific** links to their existing data (any other survey)
- REDCap can send up to 5 **reminders**
- Surveys can be sent **automatically**.

Qualtrix vs REDCap

- Maybe for single survey
- Rich features
- Separate surveys
- Not linked together
- Multiple exports

- Mix of research and survey data
- Multiple integrated surveys
- Linked together
- Single export

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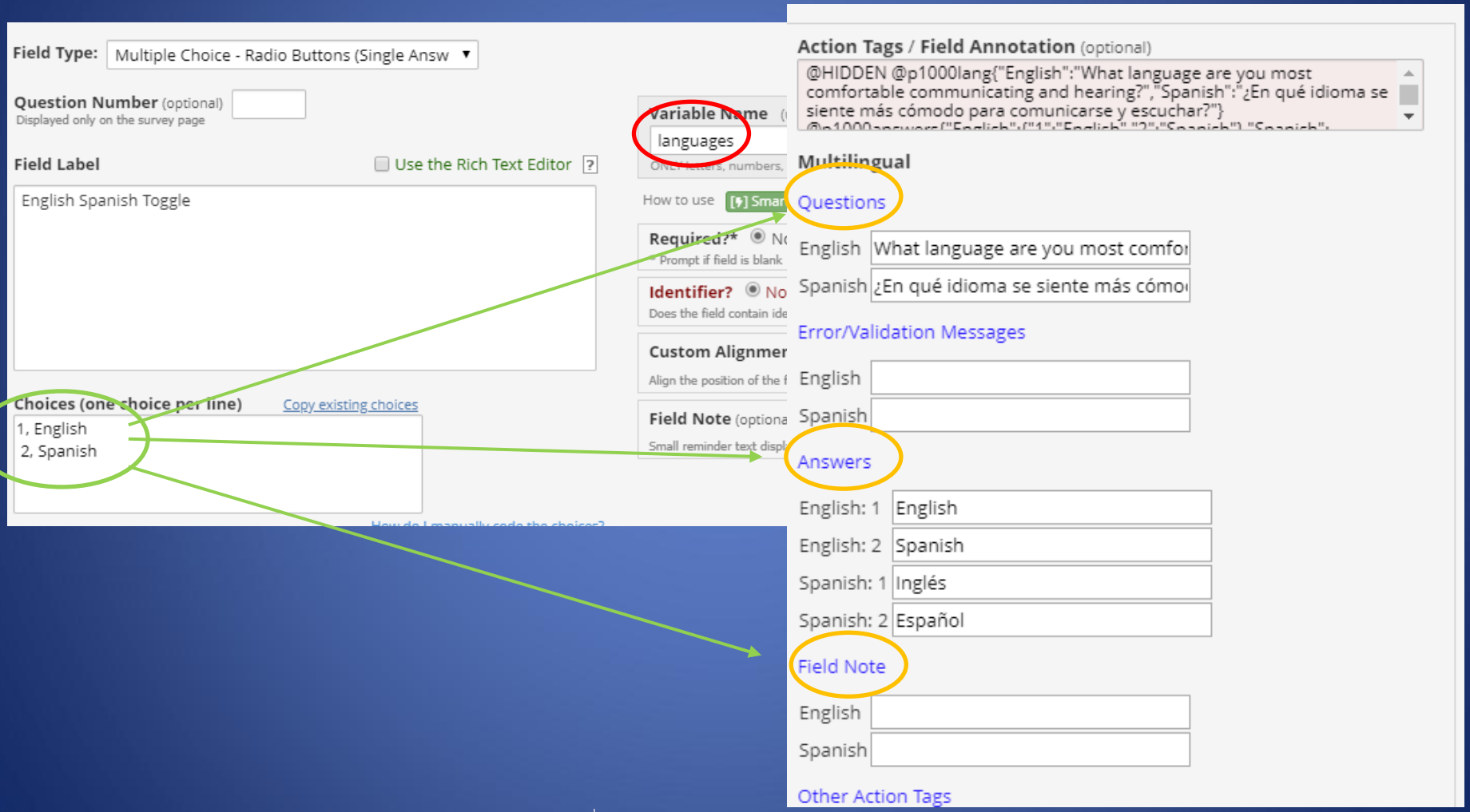
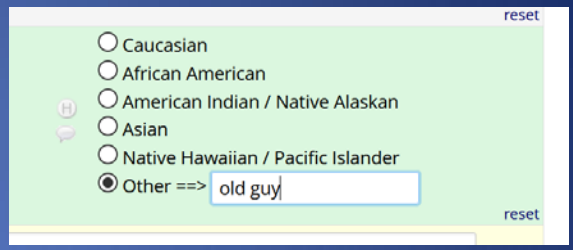
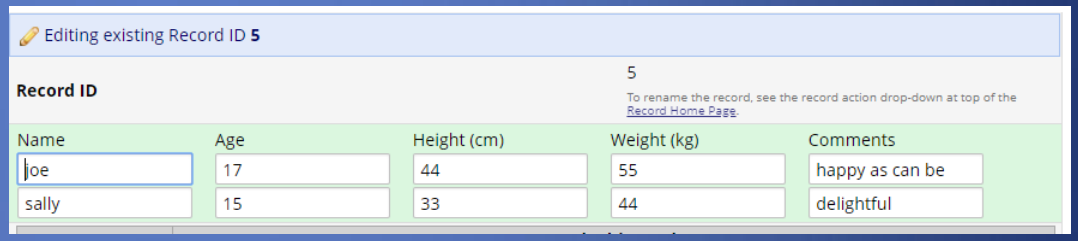
Multilingual External Module



Advanced REDCap



- DDP – pull data from Epic
- Embed – {field_other} right next to option for other. Use it to make tables.
- Smart Variables
  - [weight_kg]-[previous-event-name][weight_kg]
  - @DEFAULT="[previous-event-name][phone1]"



More Info …

- HELP -- **tracs.unc.edu/redcap-request**
- Service page -- **tracs.unc.edu/redcap**
  - Classes, FAQ, Videos from classes
- Training materials – **tracs.unc.edu/redcap-resources**
  - Slides for classes
  - REDCap Starter Guide
  - REDCap Survey Guide
  - Top 10 questions
- Working example of eConsent Survey –
  - go.unc.edu/redcap-consent
  - Grab the zip file in the tool box on training page

Check out slides for all classes

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Move to Production

- Your team: develop and test the project – all the calculations and all the branching logic
- Click move to production – We'll review and send recommendations
- Looking for –
  - consistent coding
  - Validated fields and include numeric ranges
  - branching in place and appears to work
  - proper use of checkboxes and radio/dropdown

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Next Steps

- Who ya gonna call??
- https://tracs.unc.edu/redcap-request to get your own project
- https://tracs.unc.edu/redcap to register for classes

CLICK HERE TO START

tracs.unc.edu/redcap-request


LOONEY TUNES
That's all

Sponsor-Investigator Responsibilities

Valorie Buchholz
Associate Director
Clinical Trial Quality Assurance Program

RESPONSIBILITIES OF A PI - Office of Human Research Protection (OHRP)

- obtaining and documenting informed consent of subjects or subjects' legally authorized representatives prior to the subjects' participation in the research, unless these requirements have been waived by the IRB (45 CFR 46.116; 45 CFR 46.117);
- obtaining prior approval from the IRB for any modifications of the previously approved research, including modifications to the informed consent process and document, except those necessary to eliminate apparent immediate hazards to subjects (45 CFR 46.103(b)(4)); and
- ensuring that progress reports and requests for continuing review and approval are submitted to the IRB in accordance with the policies, procedures, and actions of the IRB as referenced in the institution's OHRP-approved Federalwide assurance (45 CFR 46.103(b)(4), 45 CFR 46.109(e), 45 CFR 46.115(a)(1)). In certain circumstances, investigators also would be responsible for meeting the following additional regulatory requirements:
- providing to the IRB prompt reports of any unanticipated problems involving risks to subjects or others 45 CFR 46.103(b)(5);
- providing to the IRB prompt reports of serious or continuing noncompliance with the regulations or the requirements or determinations of the IRB (45 CFR 46.103(b)(5)); and
- keeping certain records as required by the HHS regulations for at least three years after completion of the study (45 CFR 46.115(b)).

RESPONSIBILITIES OF A PI - FDA

- Ensuring that a clinical investigation is conducted according to the signed investigator statement for clinical investigations of drugs, including biological products, or agreement for clinical investigations of medical devices, the investigational plan, and applicable regulations

- Protecting the rights, safety, and welfare of subjects under the investigator's care

- Controlling drugs, biological products, and devices under investigation (21 CFR 312.60, 21 CFR 812.100)

PI RESPONSIBILITIES – Good Clinical Practice (GCP)

- Compliance with Protocol
- Study Personnel – Adequate Resource
- Medical Care of Trial Participants
- IRB Involvement
- Investigational Product(s)/Intervention
- Informed Consent of Participants

- Participant Recruitment
- Participant Informed Consent
- Records/Recording Data
- Essential Documents
- Progress Reports
- Safety Reporting

UNC has adopted GCP as the standard by which research with human subjects is conducted.

GCP is applicable to both biomedical and social/behavioral research.

INVESTIGATOR RESPONSIBILITIES

HUMAN SUBJECTS PROTECTION

TRAINING RESEARCH STAFF

IRB SUBMISSIONS/CONTINUING REVIEW

OBTAINING & MAINTAINING INFORMED CONSENT

STUDY CONDUCT/OVERSIGHT

SUPERVISION OF STAFF TO WHOM TRIAL RELATED DUTIES ARE DELEGATED

INVESTIGATIONAL PRODUCT ACCOUNTABILITY

ASSESSMENT OF ADVERSE EVENTS

RECORD RETENTION

WHAT HAPPENS WHEN THE PRINCIPAL INVESTIGATOR IS ALSO THE SPONSOR?

Who is a Sponsor- Investigator?

GCP

- An individual who both ***initiates*** and ***conducts***, alone or with others, a clinical trial, and under whose immediate direction the investigational product is administered to, dispensed to, or used by a subject. The term does not include any person other than an individual (e.g., it does not include a corporation or an agency). **The obligations of a sponsor-investigator include both those of a sponsor and those of an investigator.**

FDA

- An individual who both ***initiates*** and ***conducts*** an investigation, and under whose immediate direction the investigational product (IP) is administered or dispensed.
  - The term does not include any person other than an individual.
  - **The requirements applicable to a sponsor-investigator include both those applicable to an investigator and a sponsor.**

[21 CFR 312.3 and 21 CFR 812.3]

RESPONSIBILITIES (Single Site)

MANAGE QUALITY THROUGHOUT THE TRIAL

SELECTING QUALIFIED MONITORS TO MONITOR THE INVESTIGATION

ENSURING THE TRIAL IS CONDUCTED ACCORDING TO THE PROTOCOL

REGISTERING TRIAL ON CLINICALTRIALS.GOV AND REPORTING RESULTS IF APPLICABLE

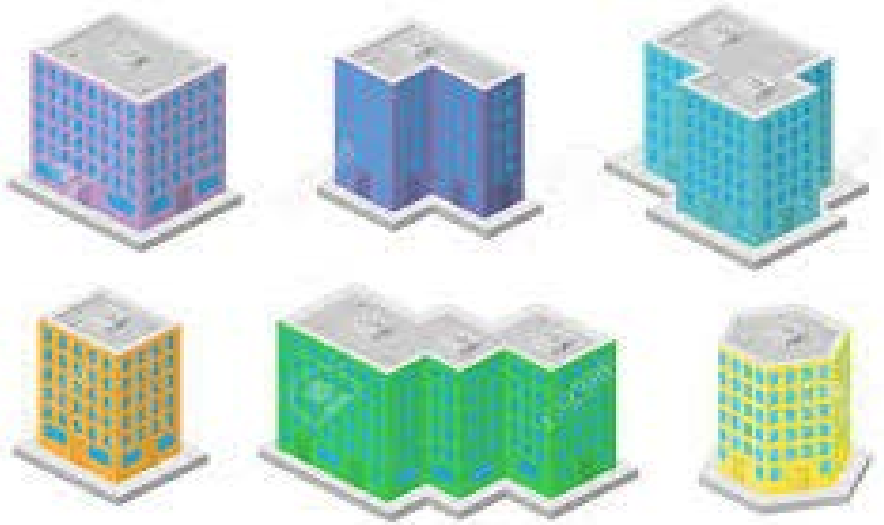
Key Responsibilities

- Monitoring of the clinical investigation
  - Risk based plan
    - Identify Critical Data Points and Processes
      - Informed Consent Obtained Properly
      - Eligibility and Protocol Compliance
      - Data Verification Related to Study End Points
      - IP Accountability (If Applicable)

- ClinicalTrials.gov
  - Timing for registration based on multiple factors – see OCT website for additional information

FDA Guidance – Risk Based Monitoringhttps://www.fda.gov/downloads/Drugs/Guidances/UCM269919.pdf

Multi-Site Trials



RESPONSIBILITIES MULTI-SITE TRIALS

MAINTAINING A TRAIL MASTER FILE INCLUSIVE OF ESSENTIAL DOCUMENTS

SELECTING QUALIFIED INVESTIGATORS

PROVIDING INFORMATION TO INVESTIGATORS TO CONDUCT THE TRIAL PROPERLY

MONITORING THE INVESTIGATORS

MAINTAINING RECORDS SHOWING RECEIPT, SHIPMENT, DISPOSTION OF THE INVESTIGATIONAL PRODUCT

INFORMING INVESTIGATORS OF SIGNIFICANT NEW ADVERSE EVENTS OR RISKS

Key Responsibilities

Collecting **Essential Documents** From Sites:

- CVs/Licenses
- IRB Approvals (inclusive of approved Informed Consent Documents)
- Signatures Pages inclusive of each amendment or version
  - (Protocol and Investigator Brochure/Device Manual if applicable)
- Lab Accreditations & Normal Ranges (if applicable)
- Trial Initiation Report
- Relevant Communications with Sites

** See ICH GCP E6(R2) Section 8 for a comprehensive listing of essential documents

Key Responsibilities

- Notification To Investigators of Any New Risks Identified or Safety Information
- Signed, Completed Case Report Forms
- Delegation/Signature Logs
- Shipping Records of Investigational Product
- Ensuring any additional sites are added to the ClinicalTrials.gov record

Studies Conducted Under an IND or IDE

- 1572s or Investigator Agreement
- Financial Disclosure Forms

As Well As…….

- Submission and maintenance of Regulatory Authority submissions (hint – FDA ☺)
  - New protocols under the same IND/IDE
  - Annual progress reports
  - Significant protocol revisions
  - Adding additional sites
  - Change in PI - FDA must be notified within 30 days
  - Safety reporting
    - Notify FDA of any unexpected fatal or life-threatening suspected adverse reactions ***within 7 calendar days***
    - Notify FDA (***and participating investigators***) via an IND safety report of potential serious risks ***within 15 calendar days***
    - Notify IRB per their reporting requirements (if using UNC IRB, see OHRE SOP 1401)

Resources offered through NC TraCS and ReGARDD.org

Risk factors for non-compliance

- Lack of knowledge (Protocol, Regulations, Processes)
- Insufficient Investigator supervision/involvement in study conduct
- Inadequate training of study staff
- Inappropriate delegation of study tasks to unqualified persons
- Overworked investigator and study staff (e.g., large number of subjects enrolled, complex study with large amount of data collection, too many concurrent studies)

Frequent Findings during CTQA Reviews

- Missing consent documents including HIPAA auths
- Missing essential documents
- Lack of training documentation
- Lack of correspondence
- Lack of database management and review

What non-compliance can lead to…..

Retraction Watch Database
(http://retractiondatabase.org/RetractionSearch.aspx?)

55 Publications Associated with UNC Researchers Retracted or Withdrawn for Corrections since 2003 (4 in 2020!!)

Results Not Reproducible

Falsification/Fabrication of Data

Investigation by Company/Institution

Concerns Issues About Data

Unreliable Results

Error in Analyses

Resources

- ICH GCP E6(R2) dated 9Novemer 2016: https://www.ich.org/page/efficacy-guidelines
- Office of Human Research Ethics- Links to internal and external resources (FDA, OHRP, NIH, Associations, Policies, etc.): https://research.unc.edu/human-research-ethics/resources/
- Office of Clinical Trials - Links to Forms/Templates (DOA log, SAE log, Start-up Checklist, Training log, etc.): https://research.unc.edu/clinical-trials/training/
- NC TraCS – Protocol development, data management, IND/IDE submissions – maintenance: https://tracs.unc.edu/

THANK YOU!!

ClinicalTrials.gov Registration Overview

Monica Coudurier

Office of Clinical Trials

m_coudurier@unc.edu

(919) 843-2333

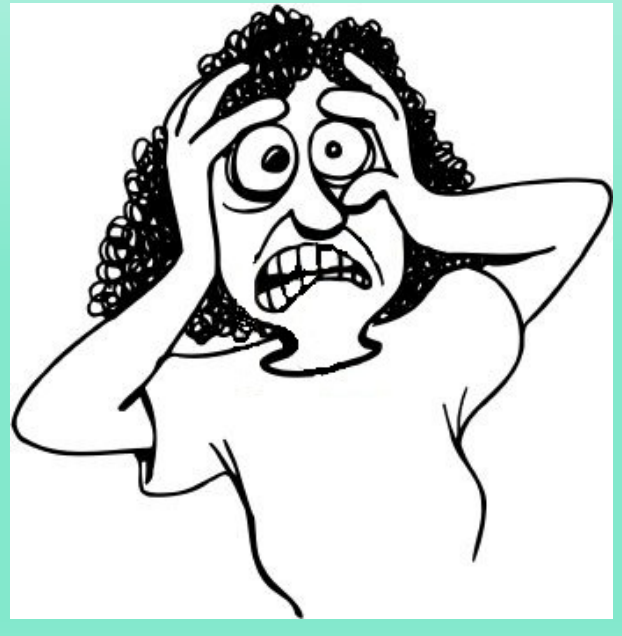
Overview

- Which trials require registry on ClinicalTrials.gov? Results reporting?
- When to: Register? Report results?
- How to get started?
- Record Upkeep/Maintenance requirements?
- Documents Required?
- Tips for Creating Outcome Measures

Background

History of ClinicalTrials.gov (CT.gov)

What is ClinicalTrials.gov?



- Web-based registry
- Includes public and privately funded clinical trials
- Maintained by National Library of Medicine (NLM)
- Mandated by FDA Modernization Act (FDAMA) 1997
- Publicly available since Feb 2000
- Expanded by FDA Amendments Act (FDAAA) 2007
- Clarified/Expanded Final Rule 2017

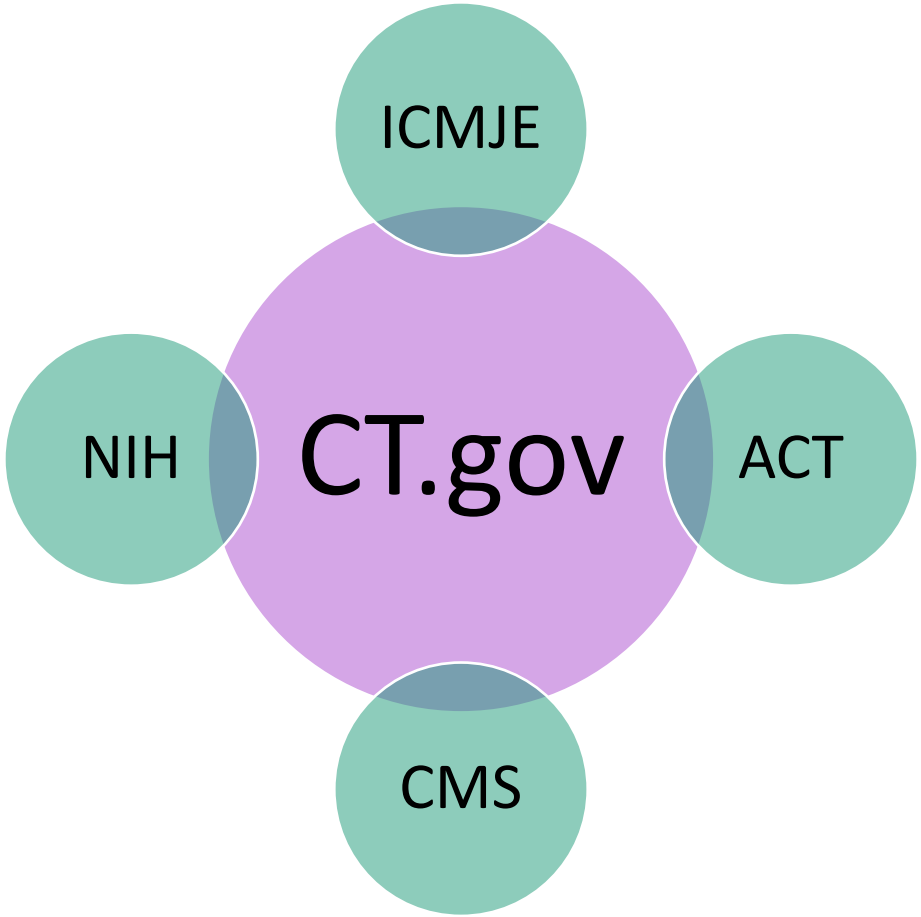
Trial Registration

Which trials need to be registered?

Organizations Requiring Trial Registration

ICMJE	International Committee of Medical Journal Editors
NIH	National Institutes of Health
ACT	Food and Drug Administration: FDAAA Section 801 Final Rule
CMS	Centers for Medicare and Medicaid Services

Rules Driving CT.gov Registration?



Trial Registration Overview Chart

	Register WHEN?	Phase 1	Phases 2-4	Device	Other Interventional *	Observational	Post Results?
ICMJE	Before enrollment of 1st subject	Yes	Yes	Yes	Yes	No	No
NIH	Within **21** days of 1st subject's enrollment	Yes	Yes	Yes	Yes	No	**Yes**
FDA	Within **21** days of 1st subject's enrollment	**No**	Yes	Yes	No	No	**Yes**
CMS	Prior to claims submission (for Qualifying Clinical Trials)	Yes	Yes	Yes	No	No	No

***Health-related or Behavioral Interventional Trials**
Patient-Centered Outcome Research Institute (PCORI) funding

International Committee of Medical Journal Editors

ICMJE

ICMJE

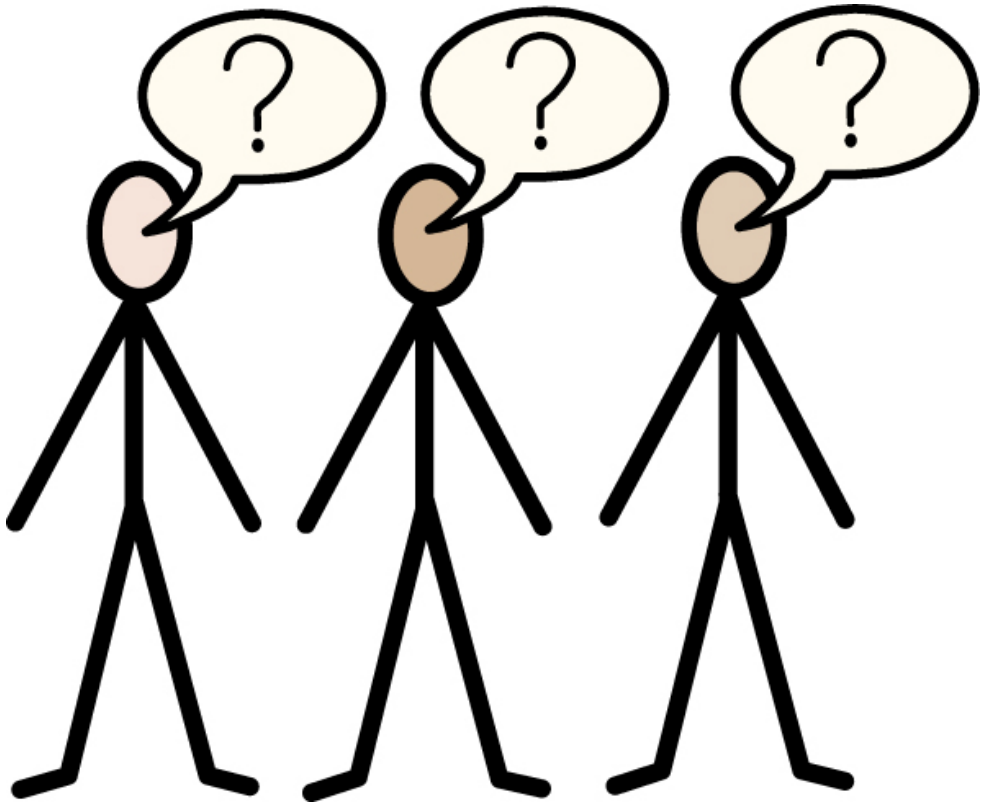
Overall

- Study must be registered *prior* to enrollment of 1st participant
- Signing Informed Consent = “Enrollment”
- NCT number assignment officially marks record registration
  - NCT assignment upon completion of CT.gov QC review process and public posting of registration record
  - Protect publication eligibility: enroll after NCT number received

Noteworthy mention

Majority of journals follow ICMJE rules

- includes non-official members



ICMJE "Clinical Trial" Definition

"any research project that prospectively assigns people or a group of people to an intervention, with or without concurrent comparison or control groups, to study the cause-and-effect relationship between a health-related intervention and a health outcome."

> ***Health-related interventions*** *are those used to modify a biomedical or health-related outcome; examples include drugs, surgical procedures, devices, behavioral treatments, educational programs, dietary interventions, quality improvement interventions, and process-of-care changes.*

> ***Health outcomes*** *are any biomedical or health-related measures obtained in patients or participants, including pharmacokinetic measures and adverse events.*

ICMJE ‘Clinical Trial’ Definition vs. Observational Trials

Purely observational studies (those in which the assignment of the medical intervention is not at the discretion of the investigator or the study protocol) will *not* require registration

- American Journal of Clinical Nutrition
- Urology
- *Some* pediatric journals

[De-Identified] Individual Participant Data (IPD) Sharing

- 2017 Editorial Annals of Internal Medicine

  (https://annals.org/aim/fullarticle/2630766/data-sharing-statements-clinical-trials-requirement-international-committee-medical-journal)

- Editors consider data sharing in making editorial decisions

- “No sharing” is considered a plan; however, may provoke consequences (i.e., not being published)

IPD Sharing (continued)

- Manuscripts must contain a data sharing statement (7/1/2018)

- CT.gov records have dedicated data sharing section
  - Trials enrolling on/after 01/01/2019 must include data sharing in trial's CT.gov registration
- Emphasis placed on the plan's presence upon registration
  - Data sharing plan changes after registration should be reflected in the statement submitted and published with the manuscript and updated in the registry record

ICMJE IPD Sharing Requirements

Data Sharing Statement must indicate:

- Will individual deidentified data will be shared?

  "Undecided" option exists--*invalid* choice

- What data will be shared?
- Which documents available (e.g., study protocol, statistical analysis plan)?
- When available and for how long?
- Criteria for obtaining the data?

IPD Sharing: UNC-recommended language

UNC has suggested language to adapt to this field:

"Deidentified individual data that supports the results will be shared beginning 9 to 36 months following publication provided the investigator who proposes to use the data has approval from an Institutional Review Board (IRB), Independent Ethics Committee (IEC), or Research Ethics Board (REB), as applicable, and executes a data use/sharing agreement with UNC."

ICMJE Data Sharing Statement Guidance - UNC Research

ICMJE

IPD Sharing: Example

IPD Sharing Statement

Plan to Share IPD: Yes

Deidentified individual data that supports the results will be shared beginning 9 to 36 months following publication provided the investigator who proposes to use the data has approval from an Institutional Review Board (IRB), Independent Ethics Committee (IEC), or Research Ethics Board (REB), as applicable, and executes a data use/sharing agreement with the University of North Carolina.

Supporting Information:

Time Frame:
9 to 36 months following publication

Access Criteria:
The investigator who proposes to use the data has IRB, IEC, or REB approval, as applicable, and an executed data use/sharing agreement with the University of North Carolina.

URL:

National Institutes of Health

NIH

NIH

Overview

Registration within *21* days of 1st participant enrollment

- Receive NIH funding of any type or amount (T-32, K awards [Research Career Development])
- Initiated on/after 1/18/2017
- Receive new funding (not disbursement from existing grant) on/after 1/18/2017
- Meet NIH “Clinical Trial” definition

See also: https://grants.nih.gov/policy/clinical-trials/definition.htm

NIH

Overview (continued)

NIH **requires Registration** and **Results reporting** of all trials funded either in whole or in part, meeting their 'clinical trial' definition, and started on/after 1/18/2017.

- Includes Phase 1 studies
- Independent of FDAAA requirements
- Applies to Extramural and Intramural award programs
- Funding applications submitted on/after 01/18/2017 requesting support for trials initiated after 01/18/2017 (not applicable to ongoing clinical trials in non-competing awards)

Clinical trials using NIH-supported infrastructure and not receiving NIH funds for conduct not subject to policy

NIH “Clinical Trial” Definition

- NOT-OD-15-015 released October 23, 2014
  - https://grants.nih.gov/grants/guide/notice-files/NOT-OD-15-015.html

- “Clinical trial” means “a research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes.”

NIH “clinical trial” definition is broader than the term Applicable Clinical Trial (ACT) defined by FDAAA in the Code of Federal Regulations

Deconstructing the NIH “Clinical Trial” Definition

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

Deconstructing the NIH “Clinical Trial” Definition

Intervention:

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

Deconstructing the NIH "Clinical Trial" Definition

Health-Related Biomedical or Behavioral Outcome:

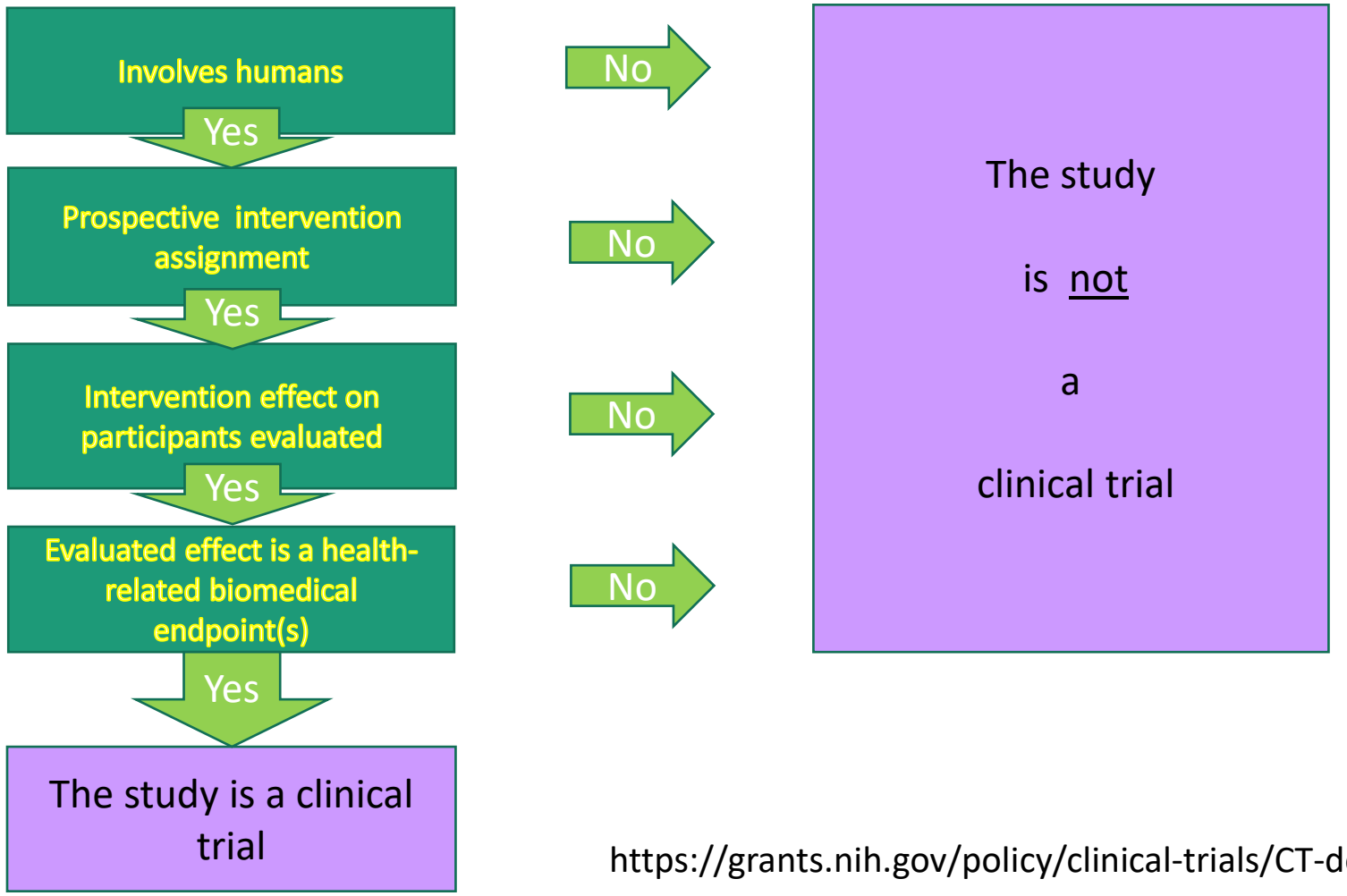
pre-specified goal(s) or condition(s) that reflect the effect of one or more interventions on human subjects' biomedical or behavioral status or quality of life. Examples include: positive or negative changes to physiological or biological parameters (e.g., improvement of lung capacity, gene expression); 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

NIH “Clinical Trial” Definition

“Clinical trial” means “a research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes.”

NIH

Clinical Trial Decision Tree



https://grants.nih.gov/policy/clinical-trials/CT-decision-tree.pdf

NIH

Your study is considered to meet the NIH ‘Clinical Trial’ definition even if:

- Using only healthy participants, or excludes a comparison group (e.g., placebo or control)
- Solely designed to assess the pharmacokinetics, safety, and/or maximum tolerated dose of an investigational drug (Phase I)
- Utilizing a behavioral intervention
- Using an intervention for the purpose of understanding fundamental aspects of a phenomenon (See guidance and FAQs about Basic Experimental Studies with Humans (BESH)).

NIH

Your study is NOT considered to meet the NIH ‘Clinical Trial’ definition if:

- Solely intended to refine measures
- Focused on secondary research with biological specimens or health information

Applicable Clinical Trial

ACT

Applicable Clinical Trial (ACT)

Registration within *21* days of 1st participant enrollment and **Results reporting** within 1 year of "Actual" Primary Completion date for all ACTs

- Interventional
- Evaluating FDA-regulated drug, biologic, or device
- At least 1 facility-U.S. or U.S. territory
- IND or IDE (includes NSR [abbreviated IDE])
- Excludes Phase 1 and Device feasibility

All single & multi-arm/group studies with prespecified outcome measures considered "controlled"

Applicable Clinical Trial (ACT)

- Includes approved & unapproved FDA-regulated products
- Excludes over-the-counter products
- ACTs require **Registration** and **Results reporting**
- All single & multi-arm/group studies with prespecified outcome measures considered “controlled”

ACT Checklist

APPLICABLE CLINICAL TRIAL (ACT)

Question	Yes	No
1. Is the study interventional (a clinical trial)? *Study Type* data element is "Interventional"	☐	☐
2. Do ANY of the following apply (is the answer "Yes" to <u>at least one</u> of the following sub-questions: 2a, 2b, OR 2c)? **a. Is at least one study facility located in the United States or a U.S. territory?** *Facility Location – Country* data element is "United States," "American Samoa," "Guam," "Northern Mariana Islands," "Puerto Rico," "U.S. Virgin Islands," or other U.S. territory. **b. Is the study conducted under a U.S. FDA Investigational New Drug application (IND) or Investigational Device Exemption (IDE)?** *U.S. Food and Drug Administration IND or IDE Number* data element is "Yes." **c. Does the study involve a drug, biological, or device product that is manufactured in and exported from the U.S. (or a U.S. territory) for study in another country?** *Product Manufactured in and Exported from the U.S.* data element is "Yes."	☐	☐
3. Does the study evaluate at least one drug, biological, or device product regulated by the United States Food and Drug Administration (U.S. FDA)? *Studies a U.S. FDA-regulated Device Product* data element is "Yes" and/or *Studies a U.S. FDA-regulated Drug Product* data element is "Yes."	☐	☐
4. Is the study <u>other than</u> a Phase 1 trial of a drug and/or biological product or is the study <u>other than</u> a device feasibility study? For drug product trials, *Study Phase* data element is NOT "Phase 1" and for device product trials, *Primary Purpose* is NOT "Device Feasibility."	☐	☐

If "Yes" is answered to all 4 questions, and the study was initiated on or after January 18, 2017, the trial would meet the definition of an ACT that is required to be registered under 42 CFR 11.22.

Centers for Medicare and Medicaid Services

CMS

Overview

NCT (National Clinical Trial) number required on all clinical trial-associated claims submitted to Medicare (01/01/2014)

-available only CT.gov

-must be entered into CRMS

-claims submitted without NCT = denied

ClinicalTrials.gov:
aka Protocol Registration and Results Reporting System (PRS)

How to get started?

Getting Started

- Is Registration required?
- Is UNC “Responsible Party”?
- Submitted to UNC IRB?
  - 118-type approval (Approval in principle) does not meet requirement
- Final, formal study protocol?
- Request CT.gov User account for each person needing ‘edit’ privileges
  - User Accounts must not be shared between users

“Responsible Party” Defined

“Responsible Party” is the individual or entity required to submit clinical trial information for an Applicable Clinical trial (ACT)

Sponsor of the clinical trial as defined in 21 CFR §50.3

“Sponsor”, “Sponsor-investigator” (*i.e.,* Principal Investigator [PI])

is responsible for conducting the trial,

- has access to and control over the data from the clinical trial,
- has the right to publish the results of the trial,
- has the ability to meet all of the requirements under this subsection for the submission of [**all**] clinical trial information.”

“Responsible Party” continued

Investigator-Initiated Studies (IITs)

UNC PI is Sponsor-Investigator

- NIH funded
- Internally funded
- Foundation or other external funding type
- Industry funded (UNC protocol, industry provides $$$)

PRS System Entry Convention

"Sponsor/Collaborators"

Responsible Party, by Official Title*

Definition: An indication of whether the responsible party is the sponsor, the sponsor-investigator, or a principal investigator designated by the sponsor to be the responsible party. Select one.

- Sponsor: The entity (for example, corporation or agency) that initiates the study
- Principal Investigator: The individual designated as responsible party by the sponsor (see Note)
- Sponsor-Investigator: The individual who both initiates and conducts the study

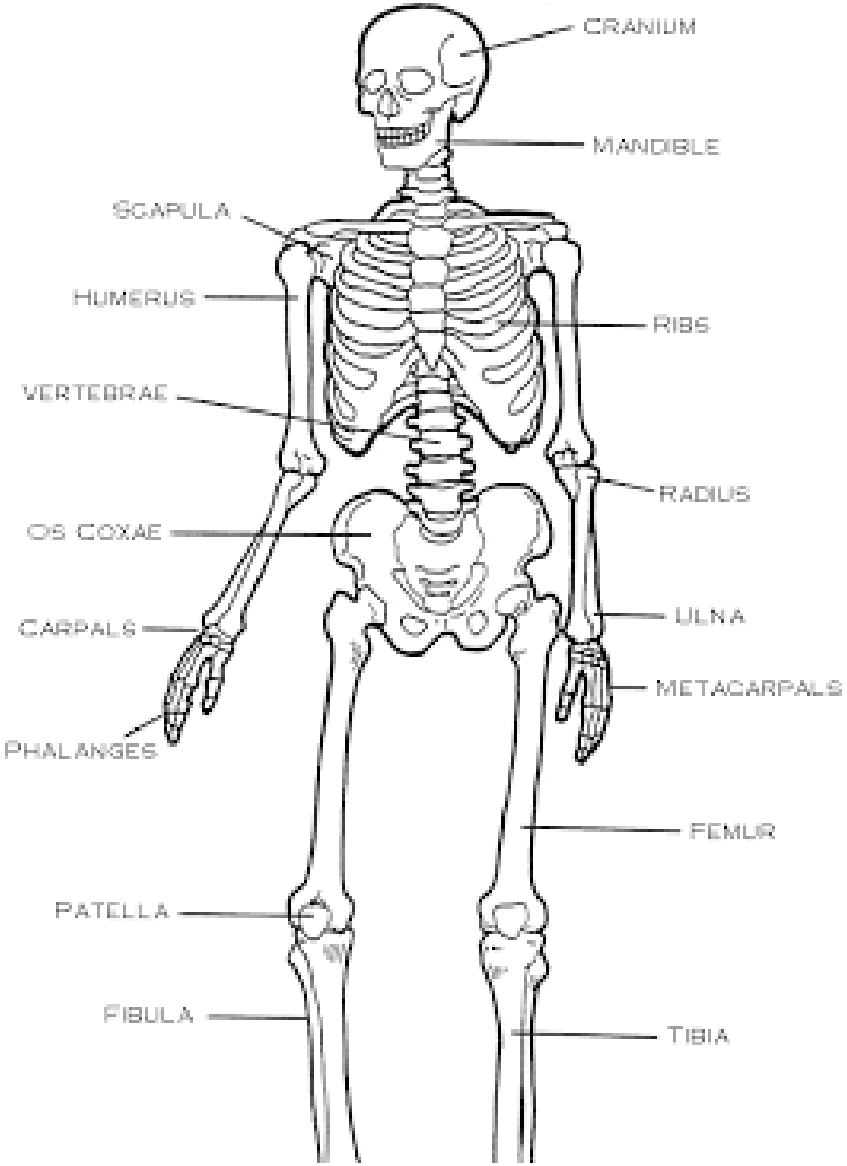
Request CT.gov User Account

Oncology	Non-Oncology
Mary O'Dwyer	Monica Coudurier
mary_odwyer@med.unc.edu	m_coudurier@unc.edu
(919) 966-7829	(919) 843-2333

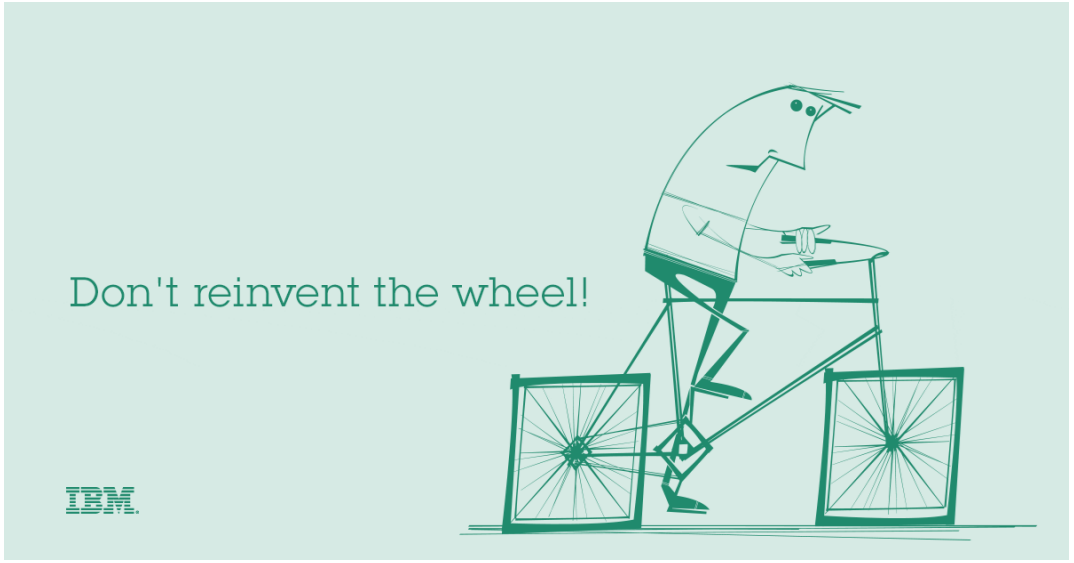
CT.gov Record Anatomy

Records consist of 3 parts:

1. Initial “Protocol” Registration
2. Results
3. Documents
   (Protocol + Statistical Analysis Plan [SAP])



Use Recent Examples for Guidance



www.clinicaltrials.gov

Use: Advanced Search

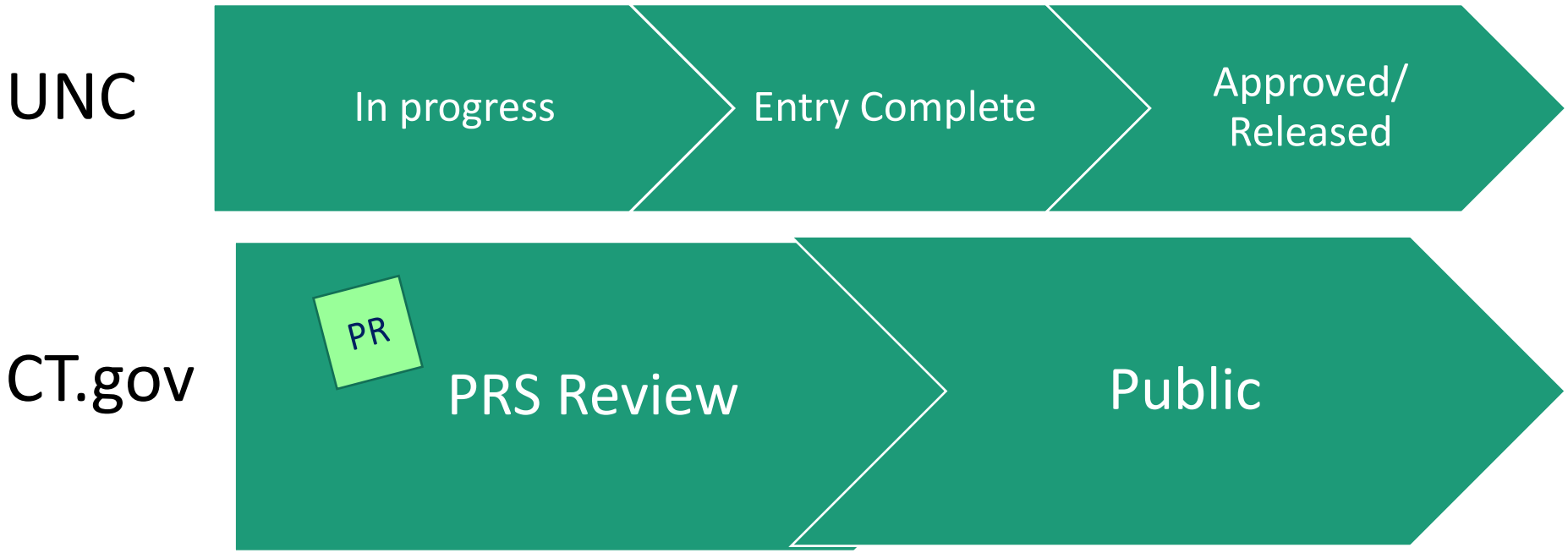
- Sort by “Newest First”
- Try limiting to “Studies with results”

Where to Find Resources?

- Login to PRS
- Help Menu: “Protocol Data Entry”
  - Quick Start Guide (basic help)
  - PRS User’s Guide (more detailed instructions)
  - Protocol Registration Data Element Definitions
- Enter Required Data Elements
- Preview and Submit

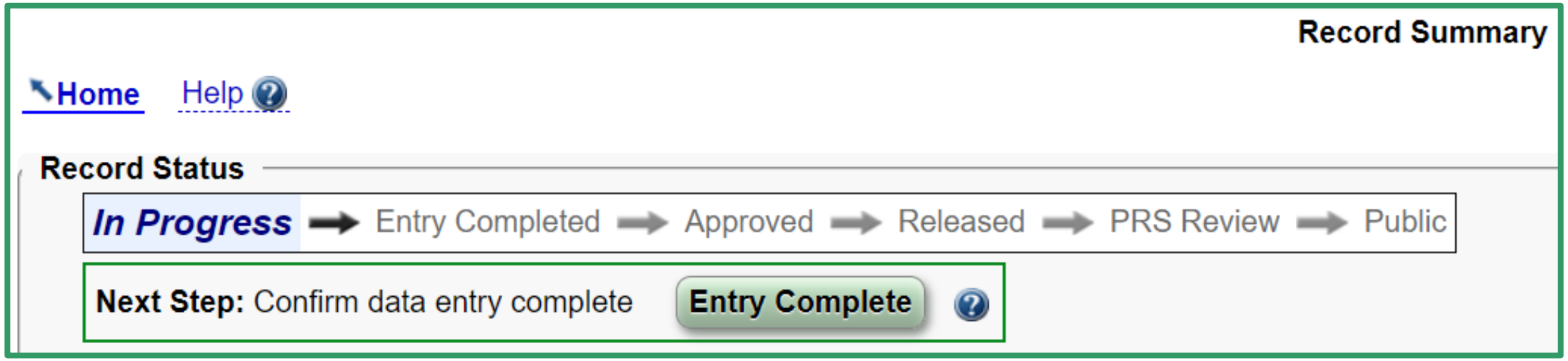
Record Creation/Release Process

No one outside UNC can see the record until released



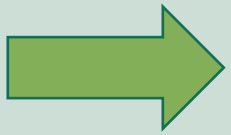
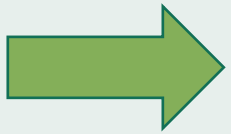
Record Release Process

- “In Progress” means record is/will be edited



Regulated QC Comment Response Time

Federal law requires all apparent errors, deficiencies, and/or inconsistencies identified during quality control review to be addressed and the record re-released to ClinicalTrials.gov

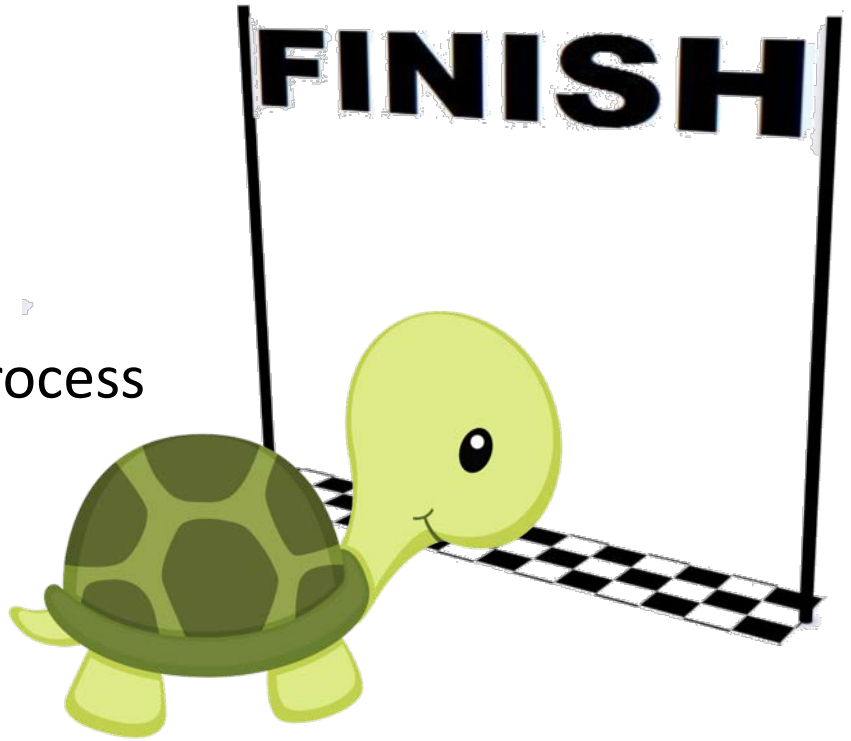
RECORD TYPE		REVIEW/RESPOND WITHIN
Registration		**15** calendar days
Results		**25** calendar days

NCT Number Assignment

Record officially registered!

NCT# provided upon completion of QC Review process

- Public posting



Ongoing Record Maintenance

- Minimally required yearly
  Always at least 1 change:
  Record Verification Date

- Certain Elements require **30-day** update
  Examples:
  - Study Start Date
  - Overall Recruitment Status
  - Individual Site Status
  - Human Subjects Protection Review Board Status
  - Primary Completion Date
  - Study Completion Date
  - Enrollment

BEYOND REGISTRATION

CT.gov Record Archives

- Every record update publicly posted by CT.gov
  - Registration records posted upon completion of QC review
  - Results record posted within 30 days of release to CT.gov

- All (time-stamped) versions publicly accessible archive
  - Readily comparably

Results Reporting

Results Reporting in CT.gov Required?

Results Reporting Req'd?	YES	NO
ICMJE *only*		✓
NIH-funded "Clinical Trial"	✓	
Applicable Clinical Trial (ACT)	✓	
Centers for Medicare & Medicaid Services (CMS)		✓

Results Reporting Req'd?

- Due by no later than 1 year of the "Actual" **Primary Completion** Date

  Definition: The date that the final participant was examined or received an intervention for the purposes of final collection of data for the primary outcome

  Unrelated to grant funding period or time for data analysis

- Multiple 30-day reviews—allow 4-6 months

- ACTs post within 30 days of release to CT.gov
  - Public disclaimer citing quality

Attaching Documents

What’s needed?

When?

Cover Page Requirement

Each document attached in CT.gov requires a cover sheet with:

- Official Study Title
- NCT number (include NCT-prefix)
- Document date

Required Document Attachments (1)

Formal Protocol

- At the time of results reporting
- Must be formal protocol (not IRB or grant application)
- Completion date on/after 01/18/2017
- Statistical Analysis Plan (SAP) if/when existing separately

Required Document Attachments (2)

Informed Consent document

Within 60 days after the last study visit, one IRB-approved informed consent document used to enroll subjects for trials

(1) meeting the NIH ‘Clinical Trial’ definition, and
(2) supported by a Common Rule (45 CFR 46) federal department or agency

must be posted on public federal website

There are currently 2 websites: Clinicaltrials.gov, regulations.gov

Monetary Penalties

What are the penalties for failing to comply with registration and/or results reporting requirements for an "Applicable Clinical Trial" or NIH-funded study?

- **ACTs**: Penalties for failure to register or providing false or misleading information in connection with ACTs may include civil monetary penalties (up to $**12,316**/day)

- **NIH-funded trials**, the withholding or recovery of grant funds for the entire University until remedied.

Questions

Outcome Measures (OM)

Avoiding QC Comments

Outcome Measures (OM): CT.gov Perspective

OM in registration records eventually become labels for results reporting data tables

CT.gov reviews initial registration records with an eye toward this end regardless of actual results reporting requirement

What do the Rules Say?
42 CFR Part 11

Results must include all:

Primary and Secondary Outcome Measures (OM). No limit on number reported

- **Primary** Outcome Measure

  The outcome measure(s) of greatest importance specified in the protocol

  — Usually the one(s) used in the power calculation

- **Secondary** Outcome Measure

  An outcome measure of lesser importance than a primary outcome measure, but is part of a pre-specified analysis plan for evaluating the intervention(s) effects and is not specified as an exploratory or other measure

  — OMs included in SAP should clearly state level of overall importance

Impact of Statistical Clarity

- Decisions regarding OM rank--PI discretion
- OM Reporting requirements tied to Statistical Analysis Plan (SAP)
- Statistical Analysis Plan (SAP) should clearly state level of overall importance for each OM
    - OM discussed in SAP ≠ Primary and ≠ tertiary/exploratory, CT.gov assumes as Secondary and must be included and results reported (when already required)
- Protocol/SAP will be attached in registry, CT.gov—use to confirm this requirement met
    - Completion Date 01/18/2017

Outcome Measure (OM) Elements

- OM Title: WHAT?
- OM Description: HOW?
- OM Time Frame: WHEN?

Creating Outcome Measures (OM)

1 UNIT OF MEASURE PER OM

VERBS SHOULD NOT BE USED IN THE OM TITLE

- ~~TO DETERMINE~~
- ~~TO ASSESS~~
- ~~TO SEEK~~

OM TITLE SHOULD NOT BE THE GOAL OR OBJECTIVE (E.G., FEASIBILITY, ADHERENCE, TOLERABILITY) BUT SHOULD RATHER REFLECT WHAT IS BEING MEASURED/REPORTED

1 TIME FRAME PER OM

EXCEPTIONS: "CHANGE FROM BASELINE IN SYSTOLIC BLOOD PRESSURE AT 6 MONTHS“

MULTIPLE TIMES OR MEASURED ITEMS ARE BEING AGGREGATED AND REPORTED AS A SINGLE VALUE

Example Outcome Measure (OM) Title
Goal or Objective

Before

OM Title: Adherence
OM Description: Evaluate adherence to MRSA eradication protocol

After

OM Title: Proportion of subjects with >80% compliance for study drug during the first 28 days
OM Description: Compliance refers to the amount of prescribed medication consumed as verified by patient diaries and drug reconciliation records.

Example Outcome Measure (OM)
Goal or Objective

Before

OM Title: Protective Immunity
OM Description: Proportion of infants in each arm with protective immunity
OM Time Frame: At 12 months of age

After

OM Title: Proportion of Infants with Protective Immunity
OM Description: Protective Immunity is defined as quantitative HBsAb ≥ 10 mIU/mL
OM Time Frame: At 12 months of age

Example Outcome Measure (OM)
Goal or Objective

Before

OM Title: Safety of the Hepatitis B Birth Dose Vaccine
OM Description: Proportion of infants with adverse reactions to the birth dose Hepatitis B Vaccine
OM Time Frame: Within 2-3 days after birth

After

OM Title: Proportion of Infants with Adverse Reactions to the Birth Dose Hepatitis B Vaccine
OM Description: Adverse reactions will include fever, fatigue and injection site soreness, as described in the Package Insert (Link). Infants will be monitored for adverse reactions for safety purposes during the time they spend with their mothers at the maternity center after birth (expected average stay of 2-3 days).
OM Time Frame: Within 2-3 days after birth

Scales and Questionnaires (OM Description)

- **Full Scale Name** (i.e., indicate what the scale measures if not clear from name alone).
- Include ALL **scale ranges** (i.e., min and max scores) required to interpret any values in the data table. For example, if a “total” score is being reported, the “total” range should be provided. If subscale scores are reported, the range for each subscale should be provided.
- **Directionality** indicate if the min or max range values reflect a better or worse outcome.

TIP: OM Title - Include the word ‘score’

Outcome Measure (OM) Description
Scale/Questionnaire

Ocular comfort was assessed on an 11-point Visual Analog Scale (VAS) ranging from 0-10 where 0 = very uncomfortable and 10 = very comfortable. Higher scores reflect more comfort.

- Answers How?
  - OM is being measured and reported
- Includes mandatory scale information
  - (Scale name, range, directionality)

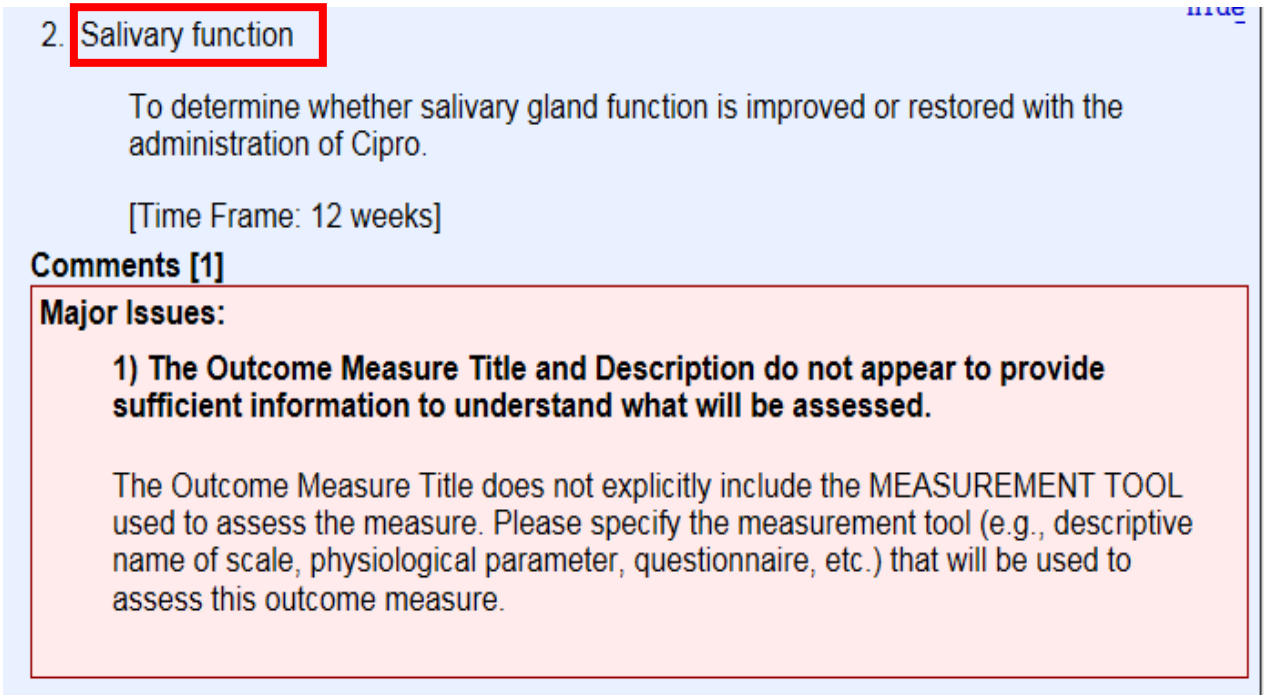
Outcome Measure (OM) Description
Scale/Questionnaire

Title:	Change in Hamilton Depression Rating Scale Score [from Baseline to V3]
Description:	The Hamilton Depression Rating Scale (**HAMD**) determines a patient's level of depression. It generally takes 15-20 minutes to complete the interview and score the results. Eight items are scored on a 5-point scale, ranging from 0 = not present to 4 = severe. Nine items are scored from 0-2. **HAMD** Scoring Instructions: 0-7 = Normal, 8-13 = Mild Depression, 14-18 = Moderate Depression, 19-22 = Severe Depression, ≥ 23 = Very Severe Depression (i.e., Minimum 0 points and maximum 50 points, the higher the score, the greater the likelihood of depression).
Time Frame:	Baseline, Visit 3 (90 +/- 3 days after randomization)

Example Outcome Measure (OM)

What? How? measured/reported?

Before



2. Salivary function

To determine whether salivary gland function is improved or restored with the administration of Cipro.

[Time Frame: 12 weeks]

Comments [1]

Major Issues:

1) The Outcome Measure Title and Description do not appear to provide sufficient information to understand what will be assessed.

The Outcome Measure Title does not explicitly include the MEASUREMENT TOOL used to assess the measure. Please specify the measurement tool (e.g., descriptive name of scale, physiological parameter, questionnaire, etc.) that will be used to assess this outcome measure.

Stimulated vs. Unstimulated

Weigh gauze, suctioning, spit into collection tubes

Example Outcome Measure (OM) cont.

- **After:**

Title:	Unstimulated Salivary Flow Rate at Week 4
Description:	After sitting at rest for 1 minute, participants collect drool using 50-mL conical tubes. The 5-minute unstimulated whole saliva flow rate recorded and collected. Salivary hypofunction is defined as unstimulated whole saliva flow rate ≤ 0.1 mL/min. Normal salivary function is defined as >0.1 mL/min.
Time Frame:	Week 4

UNC | SCHOOL OF MEDICINE
North Carolina Translational and Clinical Sciences Institute

Adverse Event Collection, Documentation and Reporting

Marie Rape, RN, BSN, CCRC
Associate Director, Regulatory Services

North Carolina Translational and
Clinical Sciences (NC TraCS) Institute

Agenda

- What defines a safety / adverse event
- Why we monitor safety events
- Where to find study specific safety event details
- How to document & track events
- Who evaluates events
- What events are reportable
- When to report events

Terms & Definitions

Multiple clinical terms often used to convey an Adverse Event (AE):

- Side Effect, Toxicity, Complication, Acute or Late Effect, Important Medical event

Research Terms:

- **Adverse Event** or Adverse Effect (AE)
- **Adverse Drug Reaction**
- **Serious Adverse Event** (SAE)
- **Suspected Unexpected Serious Adverse Reaction** (SUSAR)
- **Serious Adverse Drug Reaction** (SADR)
- **New Safety Information** (NSI)
- **Unanticipated Problem** Involving Risk to Subjects or Others **(**UPIRSO)

Adverse Event Definition (AE)

- FDA: any untoward medical occurrence associated with the use of a drug in humans **whether or not considered drug related**.

- ICH E6 (R2):
  - Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign … abnormal laboratory finding, symptom, or disease
  - Temporally associated with the use of an investigational product, **whether or not related** to the investigational product

Serious Adverse Event (SAE)

An **SAE** is any untoward medical occurrence that:

- Results in Death
- Is Life-threatening reaction
- Requires Inpatient hospitalization (> 24 hours) or prolongation
- Results in Persistent or significant disability/incapacity
  - i.e., loss of speech, fatigue so great subject can't get out of bed, loss of memory, paralysis
- Is a Congenital anomaly/birth defect (in child born to participant)
- Important medical event that may jeopardize the participant and may require intervention to prevent outcomes 1-5
  - Hemorrhaging, internal bleeding with rapid drop in B/P
  - Loss of consciousness, convulsions
  - Allergic bronchospasm → intensive treatment by paramedics

NSI and UPIRSO (per IRB SOP #1401)

New Safety Information (NSI) is information previously unknown to the IRB that **suggests new or increased risk** to subjects or others.

- Examples: adverse event, protocol deviation, non-compliance with protocol, breach of confidentiality.

Once NSI submitted, IRB determines whether event signifies an **Unanticipated Problem Involving Risk to Subjects or Others (UPIRSO)**.

A **UPIRSO** is any incident, experience, or outcome that

- is unexpected (in nature, severity, or frequency)
- is related or possibly related to a participant's participation in the research; and
- is serious or suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

TABLE 1, New Safety Information

Reporting Requirements for studies for which the UNC IRB has oversight responsibilities
Internal adverse events that are (1) unexpected, (2) related or possibly related to participation in the research, and (3) serious or suggest that there are new or increased risk(s) to subjects
External adverse events that are (1) unexpected, (2) related or possibly related to participation in the research, (3) serious or suggest that there are new or increased risk(s) to subjects, and (4) warrant a change to the protocol or consent or subject notification (See 3.3 for additional information)
Interim analysis, data and safety monitoring report, findings from other studies, findings from animal or in-vitro testing, or other finding(s) that indicate (1) there are new or increased risks to subjects or others, or (2) subjects are less likely to receive any direct benefits from the research
Unanticipated adverse device effect
Protocol deviation that harmed subject(s) or others or placed subject(s) or others at increased risk of harm. **All other protocol deviations should be documented by the investigator in a deviation log. This log is subject to review by the IRB of other agency of the UNC-CH HRPP.**
Protocol deviation that is made to eliminate an immediate hazard to a subject without IRB approval
Intentional or unintentional failure to follow applicable federal human subject protection regulations, the requirements or determinations of the IRB, the IRB-approved study protocol, or University policies when that failure adversely affects the rights or welfare of participants, such as: • Conducting human subjects research without an IRB-approved protocol or exemption • Starting research prior to meeting the conditions required by the IRB and receiving an IRB notification of approval, or conducting research during a lapse in approval • Failure to obtain informed consent • Deviating from the informed consent or recruitment process approved by the IRB • Failure to provide a participant with new information about study risks or procedures that may affect the participant's willingness to continue/participate in the study (i.e., by not reconsenting participants or by using an old version of a consent document to consent a new participant) • Initiating changes to the protocol without IRB approval, including using unapproved materials (e.g., fact or information sheets, recruitment materials, questionnaires, focus group guides, scripts, or other materials provided to participants) • Failure to complete IRB- or institutionally-required human subjects protection training prior to engaging in human subjects research • Enrollment of participants beyond what has been approved by the IRB in a study that is greater than minimal risk
Breach or potential breach of subject confidentiality or privacy.
Complaint by or on behalf of a research subject that (1) indicates that the rights, welfare, or safety of the subject have been adversely affected, or (2) cannot be resolved by the investigator. Subject complaints about payment should be resolved by the study team.
Allegation of noncompliance
Audit, inspection, or inquiry by a federal agency
Written report from a federal agency (e.g., FDA Form 483)
State board action that (1) will affect the ability to conduct or complete the research as approved by the IRB or (2) increases risks to subjects or others (e.g., suspension of professional license)
Incarceration of a subject enrolled in a research study that is not approved to involve prisoners
Institution-, investigator-, or sponsor-initiated hold or early closure as a result of safety concerns
Reporting requirements for studies ceding IRB review and oversight to an external IRB
Unanticipated Problem Involving Risk to Subjects or Others (UPIRSO) or Serious Noncompliance or Continuing Noncompliance determinations by an external IRB to which UNC cedes IRB review and oversight when the event involved UNC subjects or researchers
Suspension or termination by an external IRB to which UNC cedes IRB review and oversight

Protocol Deviations

- Per IRB SOP, a **Deviation** is “a variance from the approved study protocol.”
- In past, two terms used - **violation** and **deviation**. Now, all variances from the protocol are referred to as deviations.
- There is a special carve out for “protocol deviation that harmed subject(s) or others or placed subject(s) or others at increased risk of harm’’ which must be promptly reported to the IRB.

  – Example: Subject unable to visit clinic for labs so misses a CBC (deviation from protocol). Later find subject had low blood count and continued medication despite meeting stopping rule (potential harm).

Why do we monitor adverse events?

Monitoring adverse events is critical to the safety of subjects, overall safety of a study. The purposes of AE surveillance include:

- Identify events that may have immediate effect on the safety of the subject → stop drug or intervention
- Inform regulators, investigators, and others of new and important information about events that occur in a study or trial, identifying trends → decide if study should stop or continue
- Provide a summary of adverse experiences in order to develop a drug, regimen or device toxicity profile → FDA approval
- Collect data on events to evaluate study outcomes, conduct analyses

All events should be tracked and monitored to identify safety issues and trends. Track events even if not reportable, not related or expected to occur!

Where to find adverse event monitoring Info?

The description of the trial should include “procedures for eliciting reports of and for recording and reporting adverse events and intercurrent illnesses” (ICH GCP).

The Protocol or IRB Application should include a

- Plan on how events will be assessed and reported
- Severity scale to evaluate severity of adverse events
- To whom events are reported (PI, Sponsor, FDA, IRB, DSMB)
- Reporting timelines
- Events of special importance (outcomes)
- Events that lead to stopping the intervention or entire study

How to elicit AE Information from Subjects

- During consent process, encourage subjects to tell you everything that happens to them once in the study (e.g., car accident, catch flu, have a headache, as well as expected side effects).

- Ideally, AEs should be spontaneously reported or elicited from the subject, but you may have to help them to tell you.
  - Open ended questions: *Have you had any physical or health problems since we last spoke? Have you cut down on the things you usually do because of not feeling physically able since your last visit?*
  - During an exam or evaluation: identify medical concerns and ask questions ("I see your throat is red, has it been bothering you?")
  - Visits or telephone calls: remind them to report to you any new medical problems or concerns
  - New medications: ask why taking (e.g., on antibiotic for what?)

- To prevent bias, many studies don't ask subjects about specific events that might be anticipated in the study

Document Events Fully

- Document in **progress notes** or point to **Epic** (e.g., clinic visit or ED notes) for full details
- What to include in notes:
  - Date event began (time if relevant – e.g., infusion reaction)
  - Date you became aware of event
  - Any treatment for event
  - Actions taken with study drug - dose reduced, stopped, re-challenge
  - What happened, symptoms
    - How often or when it occurs (after eating?)
    - Interference with daily activities
    - If resolved, continuing, worsening
- Be consistent with terminology and descriptions
- Provide enough detail that PI can assign severity grade and determine relatedness
- Amend report if new information becomes available later or after PI/clinician speaks with subject

Template for Progress Notes

PROGRESS NOTES

IRB #

Study Title:

Subject ID#:

_____

_____

_____

_____

_____

_____

_____

_____

_____

_____

_____

_____

_____

Signature_____ Date _____

Telephone Contact Log

Study ID _____ Subject ID _____

Date/Time	Incoming/ Outgoing	Message/ Conversation	Comment
	Incoming Outgoing	Message Conversation	
	Incoming Outgoing	Message Conversation	
	Incoming Outgoing	Message Conversation	
	Incoming Outgoing	Message Conversation	
	Incoming Outgoing	Message Conversation	
	Incoming Outgoing	Message Conversation	

Protocol Deviation Tracking Log

IRB Study #					**Site Name/Number:**				
Protocol Title (Abbreviated):					Protocol ID/Number:				
Principal Investigator:					Page number [1]:				
Ref No.	Subject ID	Date of Deviation	Date Identified	Deviation Description	Dev. Type [2]	Resulted in AE?	Did Subject Continue in Study?	Meets IRB Reporting Req. (I.e. NSI) (Yes/No)	IRB Reporting Date
1									
2									
3									
4									
5									
6									

Investigator Signature: _____ **Date:** _____

When does AE Collection Period Begin?

- **Collection of AE info begins**
  - at initiation of study intervention in drug/device study
  - may start at placebo lead-in period or other observational period to establish a baseline for the patient if taken off usual meds
  - for studies without a drug / device, collection of AE data begins when subject first signs consent

Follow-up of Adverse Events

- **Follow AEs to resolution or stabilization**
  - Follow up required for AEs that cause interruption or discontinuation of study drug
  - If event worsens or improves in severity, collect additional details
  - Follow up events present at end of study treatment
  - Resolution does not always mean event is completely resolved (e.g. permanent disability) but is not likely to change

Are you sure you took the placebo?

UNC

Determinations - Severity & Attribution

- Severity: use of a classification scale to assess severity of event (different from a SAE)
- Attribution: determining if an event is related to participation in the study

Only PI or Sponsor can make determinations of **severity** and **relatedness (or attribution)**

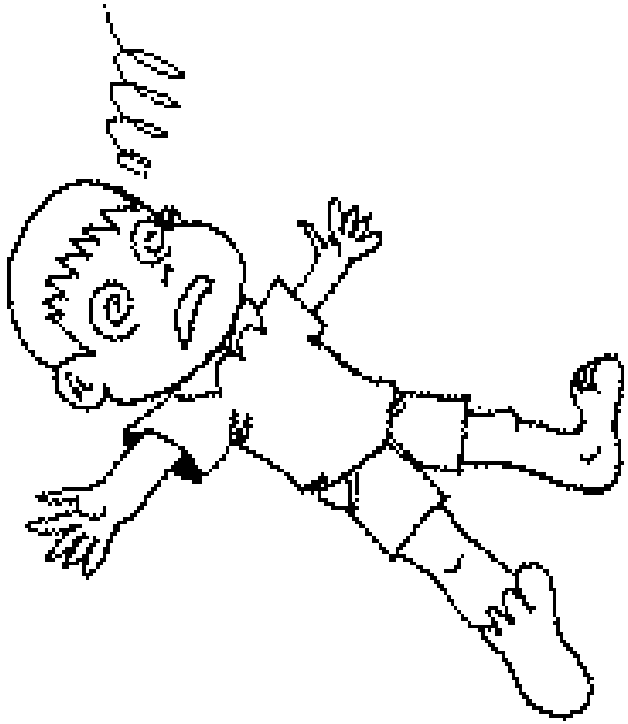
  - Medical monitor, clinician or DSMB can help the PI make the determination
  - Study Coordinator can complete part of AE/SAE report with guidance of PI and submit to IRB

Evaluating Severity of AEs

When it comes to evaluating adverse events, you should have a scale to grade the **severity**, a **classification scale.**

- Mild-Moderate-Severe Scale
- CTCAE scale (5 levels of severity)
- DAIDS AE Grading Table
- Other Specific Scale

The classification scale should be described in the protocol and used consistently for all subjects and by all investigators.



Relatedness / Attribution

- The attribution of the event (relatedness to the research intervention) is determined **by PI** with input from research team
  - Is there an obvious cause of the event (explanation for why occurred)?
  - Is it a result of an underlying medical condition?
  - What do we already know about effects of the therapy?
  - What is the temporal relationship to admin of study therapy?
  - Does the AE improve or disappear when the therapy is stopped?

It is important to identify what the AE is related to and NOT merely say it is not related

ADVERSE EVENT LOG

Protocol: _____ **PI** _____
Subject Initials: _____ **Subject ID #:** _____

ADVERSE EVENT Make a separate entry for: ➢ All new adverse events ➢ All AEs with increased severity ➢ All AEs with changes in study drug relationship ➢ All medical conditions present at study drug initiation which have worsened	√ if AE meets definition of serious*	Grade / Intensity Asymptomatic Mild Moderate Severe	Start Date	End Date	Relationship to study intervention Related Possibly Not Likely Not Related	Was Action Taken? (Circle One)	Action(s) Taken:	Outcome: Recovered Not Recovered Recovered w/Sequelae Fatal Unknown	PI Initials / Date
						Yes / No			
						Yes / No			
						Yes / No			
						Yes / No			
						Yes / No			
						Yes / No			
						Yes / No			

UNC OCT Website: https://research.unc.edu/clinical-trials/training/forms/

Tips on AE Terms for Log

- Enter separate AE on log for each event
- Make separate entry for AEs with increased severity
- Group multiple symptoms into one event
  - Running nose, cough, fever → Flu or Cold
- Separate events into 2 or more, if appropriate
  - Loss of consciousness/fall → ED visit
  - CT scan after ED visit → diagnosed with brain tumor
- Document medical conditions present at study initiation that have worsened
- Talk to sponsor about how they want AEs documented

Baseline Medical Problem vs. Adverse Event

Consider

- Does the subject have baseline symptoms or a pre-existing conditions that are ongoing during the clinical trial?
  - Hypertension
  - Diabetes
- Has the subjects baseline symptoms worsened? If so, may be an AE and needs to be documented
- Is subject on new meds to treat a condition or were they started prior to participation in the trial?
  - Anticoagulants to prevent thrombosis
  - Steroids for autoimmune condition

Is Event Expected or Unexpected

- An Event is considered "**unexpected**" if the nature, severity or frequency is not consistent with
  - procedures/risks described in the IRB approved application and protocol-related documents (consent form, IB)
  - characteristics of the participant population being studied

  Example: drug information indicates it may cause elevated LFTs; subject developed liver failure (increased severity)

- Certain events may be **expected** outcomes of the disease process or endpoints in the study (check your protocol).
- May still need to track these events or report to DSMB/Sponsor.

  Example: Death in a severely burned patient enrolled in burn study

Who Needs to Hear About Adverse Events?

- **UNC IRB:** required to report Unanticipated Problems involving risks to subjects or others.
- **Funding Agency, Sponsor:** have their own reporting requirements for AEs/SAEs.
- **FDA:** if study FDA regulated, there are special reporting requirements
- **Investigators:** if PI-initiated, required to notify other investigators (locally & other sites)
- **Data and Safety Monitoring Board**: have special requirements for when and what to report, possibly stopping rules

Reporting Timeframes Vary by Group

FDA Reporting Requirements

- Unexpected **fatal or life-threatening** suspected adverse reactions –no later than **7 calendar days** following sponsor's **initial receipt of the information**.
- Unexpected **serious suspected adverse reactions** suggesting significant risk to human subjects - no later than **15 calendar days** following sponsor's **initial receipt of the information**.

Reporting New Safety Information to the UNC IRB

- **Information previously unknown to the IRB that suggests new or increased risk** to subjects or others – report to OHRE **within 7 calendar days** of investigator becoming aware of the information.
- Other Unanticipated Problems should be reported to OHRE **within two (2)** weeks of investigator **becoming aware of the problem**.

Develop a Standard Operating Procedure (SOP)

- Describe AE processes in an SOP. Include:
  - how study team will be trained on AE / SAE process
  - how team will elicit AE information from subjects and forms used to collect data
  - forms used to document AEs and SAEs (source or progress note and AE tracking forms)
  - who will evaluate events and make determinations
  - reporting requirements (point to UNC IRB SOPs, FDA, sponsor or refer to protocol)


... AND THIS IS THE FORM YOU SEND BACK TO CONFIRM YOU'VE SENT BACK ALL THE OTHER FORMS!
FORM

Questions/Discussion

Thank you!

References

- Guidance for Industry: Investigator Responsibilities – Protecting the Rights, Safety, and Welfare of Study Subjects
- Code of Regulations Title, 21CFR50, 21CFR312, 45CFR46
- International Conference on Harmonisation Good Clinical Practice E6 - https://www.ich.org/page/efficacy-guidelines
- http://www.fda.gov
- NRP website: https://nrp.tracs.unc.edu/index.php/education/new-coordinator-orientation
- UNC IRB SOPs on NSI / Safety events - http://ohresop.web.unc.edu/
- Presentation on Documenting, Recording, and Reporting of Adverse Events and Unanticipated Problems (Sponsored by Center for Cancer Research NCI)
- UNC Office of Clinical Trials - https://research.unc.edu/clinical-trials/forms/

UNC
THE NORTH CAROLINA
TRANSLATIONAL & CLINICAL
SCIENCES INSTITUTE

Investigational New Drug (IND) and Investigational Device Exemption (IDE) Submissions and Best Practices

Amanda Wood, B.S., RAC, CCRP
IND/IDE Program Coordinator
North Carolina Translation and Clinical Sciences Institute (NC TraCS)
http://www.tracs.unc.edu/ amandawood@RTI.org

Outline

- Investigational New Drug (IND) Submission
  - Exempt Studies
  - IND submission and maintenance
- Investigational Device Exemption Submission
  - Exempt and Abbreviated IDE studies
  - IDE submission and maintenance

What is a Drug?

A drug is anything that meets the definition of a drug per the FD&C Act *(201(g)(1))*. . .

> *". . .articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals. . . "*

> *"…a substance (other than food) intended to affect the structure or any function of the body "*

> *"…compounds administered to blunt or provoke a physiological response or to study the mechanism of action or metabolism of a drug. "*

What is an Investigational Drug?

- An article that is not approved for marketing in the US as a drug
- Approved drug that is not used according to the approved label (or used in a new combination of approved drugs)

"For the purposes [of IND regulations], an experiment is any use of a drug [whether approved or unapproved] except for the use of a *marketed drug* in the course of medical practice." - 21 CFR 312.2(b)

Dietary Supplements: Drugs?

- A dietary supplement is not considered a drug if the intended use for which it is marketed is only to affect the structure or any function of the body (i.e., not intended to be used for a therapeutic purpose).
- However, if the clinical investigation is intended to evaluate the dietary supplement's ability to diagnose, cure, mitigate, treat, or prevent a disease, an IND is required

Investigational New Drug Application

An Investigational New Drug (IND) application is a request to the FDA to *provide authorization to administer*:

- an investigational drug (or biologic) to humans (always requires an IND application)
- OR a previously marketed drug in a new indication and/or patient population – i.e. Not according to approved labeling. (may be exempt from IND requirements)

Criteria for IND Exempt Studies

FIRST – The study must be the "investigation of a drug product that is **lawfully marketed in the United States**" 21 CFR 312.2(b)(1)

- If it is not marketed in the US, but approved in other countries, you will still need an IND

Criteria for IND Exempt Studies

There are 5 criteria that allow a study to be exempt from requiring an IND.

All 5 criteria must be met!

1. The study is not designed to support approval of a new indication or a change in label
2. The study is not intended to support a significant change in the advertising for the product

Criteria for IND Exempt Studies

3. If the study does not involve a route of administration, dosage level, or patient population that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug
4. The study is conducted in compliance with the IRB and informed consent regulations
5. The investigation is not intended to promote or commercialize the drug product.

21 CFR 312.2(b)

Who determines if the study is IND Exempt?

The Investigator:

- Because the assessment of risks involved in a therapeutic procedure is an everyday part of the practice of medicine, the individual investigator should usually be able to determine the applicability of the exemption."

  - FDA guidance

The IRB:

- When filling out the application in IRBIS, download the IND-Exemption checklist here: http://research.unc.edu/files/2013/04/CCM3_039765.docx you will need to justify that you meet all 5 of the exemption requirements.

The FDA:

- Submit either a Request for IND Exemption, or a full IND Submission with a statement in the cover letter requesting a determination on IND exemption. There are advantages/disadvantages to both types of submissions.

Preparing and Submitting an IND

IND Submission Template can be found at www.ReGARDD.org

Reasons for IND submissions

- **Investigator-Initiated IND** – research driven, with publication as the main goal
- **Expanded Access IND** – For single patients, including emergency settings; intermediate or large sized populations with the intent to treat, not to obtain safety information.
- **Commercial IND** – submitted with the intent to bring to market or change current labeling

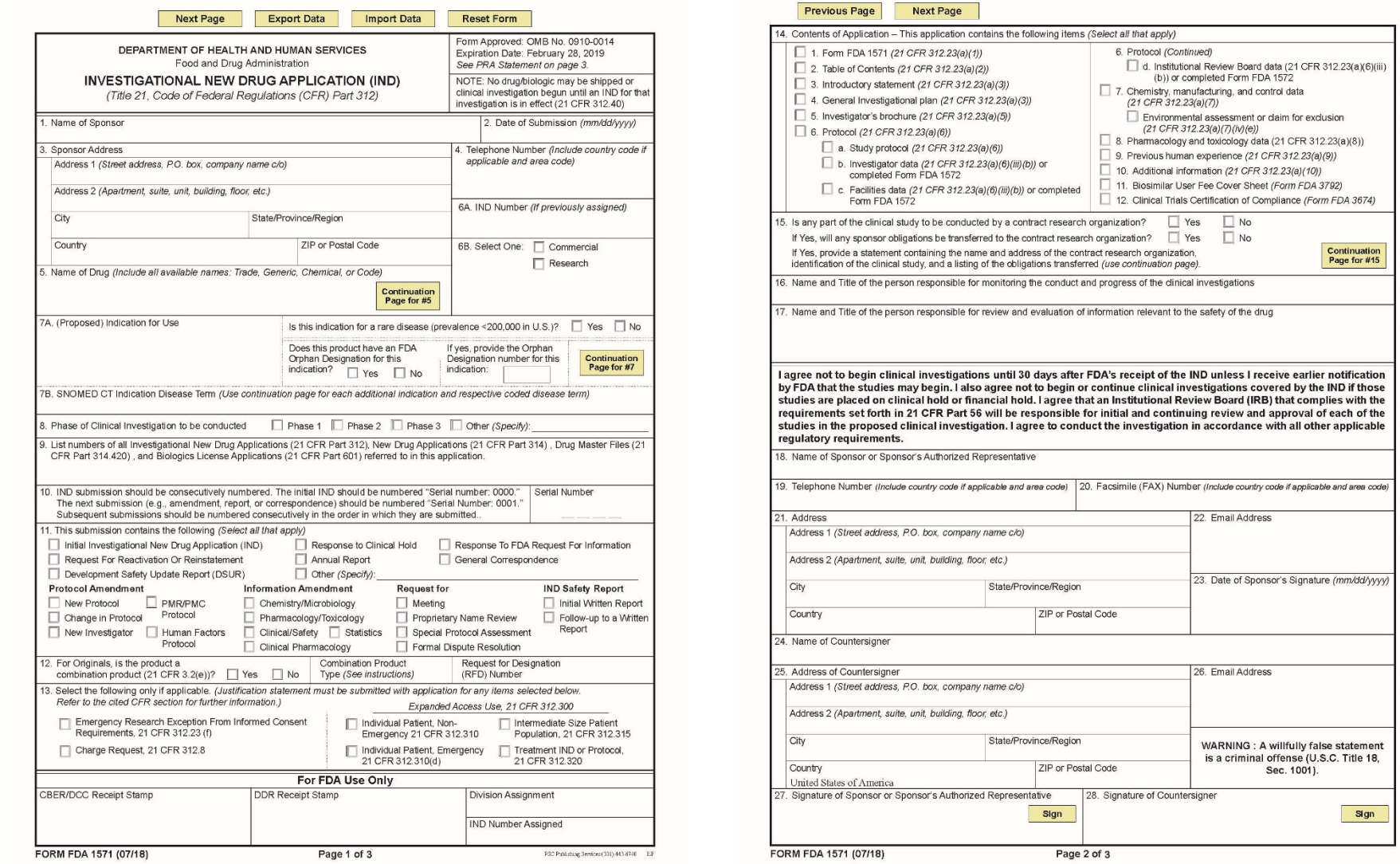
IND Submission Format and Content

1. Form 1571 (cover sheet), Form 3674
2. Table of Contents
3. Introductory Statement
4. General Investigational Plan
5. Investigator's Brochure
6. Proposed Clinical Research (Includes forms 1572, 3454, 3455)
7. Chemistry, Manufacturing and Control Data (CMC)
8. Pharmacology and Toxicology Data
9. Previous Human Experience
10. Additional Information
11. Relevant Informations

IND Submission Format and Content - FORMS

1. **Form 1571 (cover sheet), Form 3674**
2. Table of Contents
3. Introductory Statement
4. General Investigational Plan
5. Investigator's Brochure
6. **Proposed Clinical Research (Includes forms 1572, 3454, 3455)**
7. Chemistry, Manufacturing and Control Data (CMC)
8. Pharmacology and Toxicology Data
9. Previous Human Experience
10. Additional Information
11. Relevant Informations

FDA form 1571 - 1) to obtain agreement from the sponsor (or sponsor-investigator) to conduct research according to all appropriate FDA regulations; and 2) to serve as a cover sheet for all submissions to the FDA on behalf of a particular IND.



Next Page | Export Data | Import Data | Reset Form

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

INVESTIGATIONAL NEW DRUG APPLICATION (IND)
(Title 21, Code of Federal Regulations (CFR) Part 312)

Form Approved: OMB No. 0910-0014
Expiration Date: February 28, 2019
See PRA Statement on page 3.

NOTE: No drug/biologic may be shipped or clinical investigation begun until an IND for that investigation is in effect (21 CFR 312.40)

1. Name of Sponsor
2. Date of Submission *(mm/dd/yyyy)*
3. Sponsor Address
Address 1 *(Street address, P.O. box, company name c/o)*
Address 2 *(Apartment, suite, unit, building, floor, etc.)*
City | State/Province/Region
Country | ZIP or Postal Code
4. Telephone Number *(Include country code if applicable and area code)*
6A. IND Number *(If previously assigned)*
6B. Select One: ☐ Commercial ☐ Research
5. Name of Drug *(Include all available names: Trade, Generic, Chemical, or Code)*
Continuation Page for #5
7A. (Proposed) Indication for Use
Is this indication for a rare disease (prevalence <200,000 in U.S.)? ☐ Yes ☐ No
Does this product have an FDA Orphan Designation for this indication? ☐ Yes ☐ No
If yes, provide the Orphan Designation number for this indication:
Continuation Page for #7
7B. SNOMED CT Indication Disease Term *(Use continuation page for each additional indication and respective coded disease term)*
8. Phase of Clinical Investigation to be conducted ☐ Phase 1 ☐ Phase 2 ☐ Phase 3 ☐ Other *(Specify)*:
9. List numbers of all Investigational New Drug Applications (21 CFR Part 312), New Drug Applications (21 CFR Part 314) , Drug Master Files (21 CFR Part 314.420) , and Biologics License Applications (21 CFR Part 601) referred to in this application.
10. IND submission should be consecutively numbered. The initial IND should be numbered "Serial number: 0000." The next submission (e.g., amendment, report, or correspondence) should be numbered "Serial Number: 0001." Subsequent submissions should be numbered consecutively in the order in which they are submitted..
Serial Number
11. This submission contains the following *(Select all that apply)*
☐ Initial Investigational New Drug Application (IND) ☐ Response to Clinical Hold ☐ Response To FDA Request For Information
☐ Request For Reactivation Or Reinstatement ☐ Annual Report ☐ General Correspondence
☐ Development Safety Update Report (DSUR) ☐ Other *(Specify)*:

Protocol Amendment	Information Amendment	Request for	IND Safety Report
☐ New Protocol	☐ Chemistry/Microbiology	☐ Meeting	☐ Initial Written Report
☐ Change in Protocol	☐ Pharmacology/Toxicology	☐ Proprietary Name Review	☐ Follow-up to a Written Report
☐ New Investigator	☐ Clinical/Safety ☐ Statistics	☐ Special Protocol Assessment	
☐ PMR/PMC Protocol	☐ Clinical Pharmacology	☐ Formal Dispute Resolution	
☐ Human Factors Protocol			

12. For Originals, is the product a combination product (21 CFR 3.2(e))? ☐ Yes ☐ No
Combination Product Type *(See instructions)*
Request for Designation (RFD) Number
13. Select the following only if applicable. *(Justification statement must be submitted with application for any items selected below. Refer to the cited CFR section for further information.)*
☐ Emergency Research Exception From Informed Consent Requirements, 21 CFR 312.23 (f)
☐ Charge Request, 21 CFR 312.8
Expanded Access Use, 21 CFR 312.300
☐ Individual Patient, Non-Emergency 21 CFR 312.310
☐ Individual Patient, Emergency 21 CFR 312.310(d)
☐ Intermediate Size Patient Population, 21 CFR 312.315
☐ Treatment IND or Protocol, 21 CFR 312.320

For FDA Use Only

CBER/DCC Receipt Stamp	DDR Receipt Stamp	Division Assignment
		IND Number Assigned

FORM FDA 1571 (07/18) Page 1 of 3

Previous Page | Next Page

14. Contents of Application – This application contains the following items *(Select all that apply)*
☐ 1. Form FDA 1571 *(21 CFR 312.23(a)(1))*
☐ 2. Table of Contents *(21 CFR 312.23(a)(2))*
☐ 3. Introductory statement *(21 CFR 312.23(a)(3))*
☐ 4. General Investigational plan *(21 CFR 312.23(a)(3))*
☐ 5. Investigator's brochure *(21 CFR 312.23(a)(5))*
☐ 6. Protocol *(21 CFR 312.23(a)(6))*
☐ a. Study protocol *(21 CFR 312.23(a)(6))*
☐ b. Investigator data *(21 CFR 312.23(a)(6)(iii)(b))* or completed Form FDA 1572
☐ c. Facilities data *(21 CFR 312.23(a)(6)(iii)(b))* or completed Form FDA 1572
☐ 6. Protocol *(Continued)*
☐ d. Institutional Review Board data (21 CFR 312.23(a)(6)(iii)(b)) or completed Form FDA 1572
☐ 7. Chemistry, manufacturing, and control data *(21 CFR 312.23(a)(7))*
☐ Environmental assessment or claim for exclusion *(21 CFR 312.23(a)(7)(iv)(e))*
☐ 8. Pharmacology and toxicology data (21 CFR 312.23(a)(8))
☐ 9. Previous human experience *(21 CFR 312.23(a)(9))*
☐ 10. Additional information *(21 CFR 312.23(a)(10))*
☐ 11. Biosimilar User Fee Cover Sheet *(Form FDA 3792)*
☐ 12. Clinical Trials Certification of Compliance *(Form FDA 3674)*
15. Is any part of the clinical study to be conducted by a contract research organization? ☐ Yes ☐ No
If Yes, will any sponsor obligations be transferred to the contract research organization? ☐ Yes ☐ No
If Yes, provide a statement containing the name and address of the contract research organization, identification of the clinical study, and a listing of the obligations transferred *(use continuation page)*.
Continuation Page for #15
16. Name and Title of the person responsible for monitoring the conduct and progress of the clinical investigations
17. Name and Title of the person responsible for review and evaluation of information relevant to the safety of the drug

I agree not to begin clinical investigations until 30 days after FDA's receipt of the IND unless I receive earlier notification by FDA that the studies may begin. I also agree not to begin or continue clinical investigations covered by the IND if those studies are placed on clinical hold or financial hold. I agree that an Institutional Review Board (IRB) that complies with the requirements set forth in 21 CFR Part 56 will be responsible for initial and continuing review and approval of each of the studies in the proposed clinical investigation. I agree to conduct the investigation in accordance with all other applicable regulatory requirements.

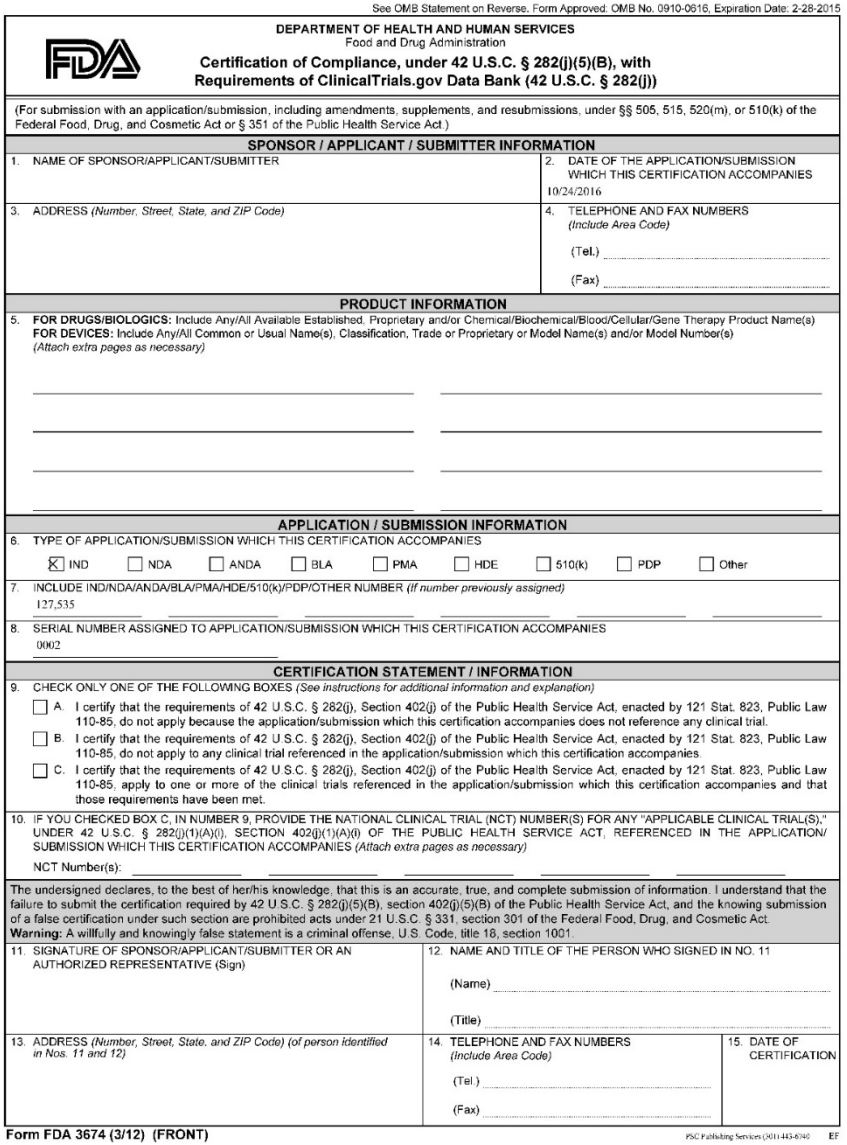
18. Name of Sponsor or Sponsor's Authorized Representative
19. Telephone Number *(Include country code if applicable and area code)*
20. Facsimile (FAX) Number *(Include country code if applicable and area code)*
21. Address
Address 1 *(Street address, P.O. box, company name c/o)*
Address 2 *(Apartment, suite, unit, building, floor, etc.)*
City | State/Province/Region
Country | ZIP or Postal Code
22. Email Address
23. Date of Sponsor's Signature *(mm/dd/yyyy)*
24. Name of Countersigner
25. Address of Countersigner
Address 1 *(Street address, P.O. box, company name c/o)*
Address 2 *(Apartment, suite, unit, building, floor, etc.)*
City | State/Province/Region
Country: United States of America | ZIP or Postal Code
26. Email Address

WARNING : A willfully false statement is a criminal offense (U.S.C. Title 18, Sec. 1001).

27. Signature of Sponsor or Sponsor's Authorized Representative — Sign
28. Signature of Countersigner — Sign

FORM FDA 1571 (07/18) Page 2 of 3

FDA form 3674 - Signed statement from the sponsor/investigator that they will comply with clinicaltrials.gov requirements concerning their investigation.



See OMB Statement on Reverse. Form Approved: OMB No. 0910-0616, Expiration Date: 2-28-2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

Certification of Compliance, under 42 U.S.C. § 282(j)(5)(B), with Requirements of ClinicalTrials.gov Data Bank (42 U.S.C. § 282(j))

(For submission with an application/submission, including amendments, supplements, and resubmissions, under §§ 505, 515, 520(m), or 510(k) of the Federal Food, Drug, and Cosmetic Act or § 351 of the Public Health Service Act.)

SPONSOR / APPLICANT / SUBMITTER INFORMATION

1. NAME OF SPONSOR/APPLICANT/SUBMITTER
2. DATE OF THE APPLICATION/SUBMISSION WHICH THIS CERTIFICATION ACCOMPANIES
   10/24/2016
3. ADDRESS *(Number, Street, State, and ZIP Code)*
4. TELEPHONE AND FAX NUMBERS *(Include Area Code)*
   (Tel.)
   (Fax)

PRODUCT INFORMATION

5. **FOR DRUGS/BIOLOGICS:** Include Any/All Available Established, Proprietary and/or Chemical/Biochemical/Blood/Cellular/Gene Therapy Product Name(s) **FOR DEVICES:** Include Any/All Common or Usual Name(s), Classification, Trade or Proprietary or Model Name(s) and/or Model Number(s) *(Attach extra pages as necessary)*

APPLICATION / SUBMISSION INFORMATION

6. TYPE OF APPLICATION/SUBMISSION WHICH THIS CERTIFICATION ACCOMPANIES
   ☒ IND ☐ NDA ☐ ANDA ☐ BLA ☐ PMA ☐ HDE ☐ 510(k) ☐ PDP ☐ Other
7. INCLUDE IND/NDA/ANDA/BLA/PMA/HDE/510(k)/PDP/OTHER NUMBER *(If number previously assigned)*
   127,535
8. SERIAL NUMBER ASSIGNED TO APPLICATION/SUBMISSION WHICH THIS CERTIFICATION ACCOMPANIES
   0002

CERTIFICATION STATEMENT / INFORMATION

9. CHECK ONLY ONE OF THE FOLLOWING BOXES *(See instructions for additional information and explanation)*
   - ☐ A. I certify that the requirements of 42 U.S.C. § 282(j), Section 402(j) of the Public Health Service Act, enacted by 121 Stat. 823, Public Law 110-85, do not apply because the application/submission which this certification accompanies does not reference any clinical trial.
   - ☐ B. I certify that the requirements of 42 U.S.C. § 282(j), Section 402(j) of the Public Health Service Act, enacted by 121 Stat. 823, Public Law 110-85, do not apply to any clinical trial referenced in the application/submission which this certification accompanies.
   - ☐ C. I certify that the requirements of 42 U.S.C. § 282(j), Section 402(j) of the Public Health Service Act, enacted by 121 Stat. 823, Public Law 110-85, apply to one or more of the clinical trials referenced in the application/submission which this certification accompanies and that those requirements have been met.
10. IF YOU CHECKED BOX C, IN NUMBER 9, PROVIDE THE NATIONAL CLINICAL TRIAL (NCT) NUMBER(S) FOR ANY "APPLICABLE CLINICAL TRIAL(S)," UNDER 42 U.S.C. § 282(j)(1)(A)(i), SECTION 402(j)(1)(A)(i) OF THE PUBLIC HEALTH SERVICE ACT, REFERENCED IN THE APPLICATION/SUBMISSION WHICH THIS CERTIFICATION ACCOMPANIES *(Attach extra pages as necessary)*
    NCT Number(s):

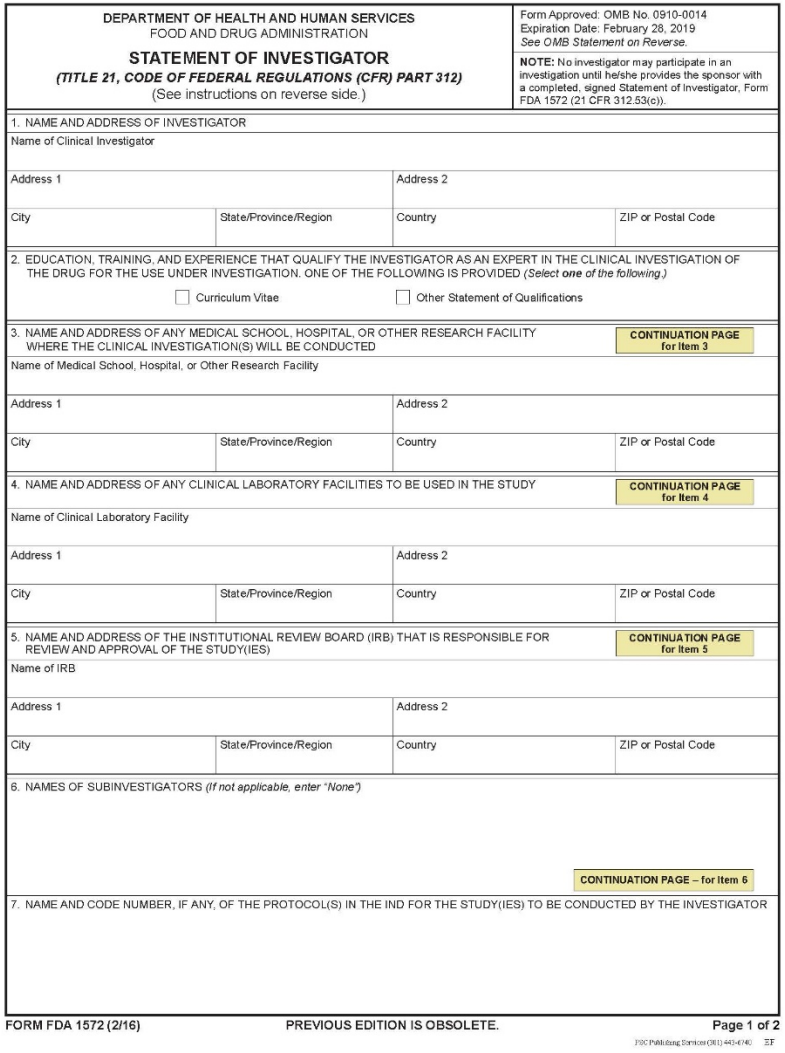
The undersigned declares, to the best of her/his knowledge, that this is an accurate, true, and complete submission of information. I understand that the failure to submit the certification required by 42 U.S.C. § 282(j)(5)(B), section 402(j)(5)(B) of the Public Health Service Act, and the knowing submission of a false certification under such section are prohibited acts under 21 U.S.C. § 331, section 301 of the Federal Food, Drug, and Cosmetic Act. **Warning:** A willfully and knowingly false statement is a criminal offense, U.S. Code, title 18, section 1001.

11. SIGNATURE OF SPONSOR/APPLICANT/SUBMITTER OR AN AUTHORIZED REPRESENTATIVE (Sign)
12. NAME AND TITLE OF THE PERSON WHO SIGNED IN NO. 11
    (Name)
    (Title)
13. ADDRESS *(Number, Street, State, and ZIP Code) (of person identified in Nos. 11 and 12)*
14. TELEPHONE AND FAX NUMBERS *(Include Area Code)*
    (Tel.)
    (Fax)
15. DATE OF CERTIFICATION

Form FDA 3674 (3/12) (FRONT)

PSC Publishing Services (301) 443-6740 EF

FDA form 1572 - Agreement from the Investigator that research will be compliant with FDA regulations. Contains clinical site and investigator info to assure the FDA that all investigators have the experience/background needed to conduct the trial.



DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

STATEMENT OF INVESTIGATOR
(TITLE 21, CODE OF FEDERAL REGULATIONS (CFR) PART 312)
(See instructions on reverse side.)

Form Approved: OMB No. 0910-0014
Expiration Date: February 28, 2019
See OMB Statement on Reverse.

NOTE: No investigator may participate in an investigation until he/she provides the sponsor with a completed, signed Statement of Investigator, Form FDA 1572 (21 CFR 312.53(c)).

1. NAME AND ADDRESS OF INVESTIGATOR

Name of Clinical Investigator

Address 1		Address 2	
City	State/Province/Region	Country	ZIP or Postal Code

2. EDUCATION, TRAINING, AND EXPERIENCE THAT QUALIFY THE INVESTIGATOR AS AN EXPERT IN THE CLINICAL INVESTIGATION OF THE DRUG FOR THE USE UNDER INVESTIGATION. ONE OF THE FOLLOWING IS PROVIDED *(Select **one** of the following.)*

☐ Curriculum Vitae ☐ Other Statement of Qualifications

3. NAME AND ADDRESS OF ANY MEDICAL SCHOOL, HOSPITAL, OR OTHER RESEARCH FACILITY WHERE THE CLINICAL INVESTIGATION(S) WILL BE CONDUCTED — CONTINUATION PAGE for Item 3

Name of Medical School, Hospital, or Other Research Facility

Address 1		Address 2	
City	State/Province/Region	Country	ZIP or Postal Code

4. NAME AND ADDRESS OF ANY CLINICAL LABORATORY FACILITIES TO BE USED IN THE STUDY — CONTINUATION PAGE for Item 4

Name of Clinical Laboratory Facility

Address 1		Address 2	
City	State/Province/Region	Country	ZIP or Postal Code

5. NAME AND ADDRESS OF THE INSTITUTIONAL REVIEW BOARD (IRB) THAT IS RESPONSIBLE FOR REVIEW AND APPROVAL OF THE STUDY(IES) — CONTINUATION PAGE for Item 5

Name of IRB

Address 1		Address 2	
City	State/Province/Region	Country	ZIP or Postal Code

6. NAMES OF SUBINVESTIGATORS *(If not applicable, enter "None")*

CONTINUATION PAGE – for Item 6

7. NAME AND CODE NUMBER, IF ANY, OF THE PROTOCOL(S) IN THE IND FOR THE STUDY(IES) TO BE CONDUCTED BY THE INVESTIGATOR

FORM FDA 1572 (2/16) PREVIOUS EDITION IS OBSOLETE. Page 1 of 2

8. PROVIDE THE FOLLOWING CLINICAL PROTOCOL INFORMATION. *(Select **one** of the following.)*

☐ For Phase 1 investigations, a general outline of the planned investigation including the estimated duration of the study and the maximum number of subjects that will be involved.

☐ For Phase 2 or 3 investigations, an outline of the study protocol including an approximation of the number of subjects to be treated with the drug and the number to be employed as controls, if any; the clinical uses to be investigated; characteristics of subjects by age, sex, and condition; the kind of clinical observations and laboratory tests to be conducted; the estimated duration of the study; and copies or a description of case report forms to be used.

9. COMMITMENTS

I agree to conduct the study(ies) in accordance with the relevant, current protocol(s) and will only make changes in a protocol after notifying the sponsor, except when necessary to protect the safety, rights, or welfare of subjects.

I agree to personally conduct or supervise the described investigation(s).

I agree to inform any patients, or any persons used as controls, that the drugs are being used for investigational purposes and I will ensure that the requirements relating to obtaining informed consent in 21 CFR Part 50 and institutional review board (IRB) review and approval in 21 CFR Part 56 are met.

I agree to report to the sponsor adverse experiences that occur in the course of the investigation(s) in accordance with 21 CFR 312.64. I have read and understand the information in the investigator's brochure, including the potential risks and side effects of the drug.

I agree to ensure that all associates, colleagues, and employees assisting in the conduct of the study(ies) are informed about their obligations in meeting the above commitments.

I agree to maintain adequate and accurate records in accordance with 21 CFR 312.62 and to make those records available for inspection in accordance with 21 CFR 312.68.

I will ensure that an IRB that complies with the requirements of 21 CFR Part 56 will be responsible for the initial and continuing review and approval of the clinical investigation. I also agree to promptly report to the IRB all changes in the research activity and all unanticipated problems involving risks to human subjects or others. Additionally, I will not make any changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazards to human subjects.

I agree to comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements in 21 CFR Part 312.

INSTRUCTIONS FOR COMPLETING FORM FDA 1572
STATEMENT OF INVESTIGATOR

1. Complete all sections. Provide a separate page if additional space is needed.
2. Provide curriculum vitae or other statement of qualifications as described in Section 2.
3. Provide protocol outline as described in Section 8.
4. Sign and date below.
5. FORWARD THE COMPLETED FORM AND OTHER DOCUMENTS BEING PROVIDED TO THE SPONSOR. The sponsor will incorporate this information along with other technical data into an Investigational New Drug Application (IND). INVESTIGATORS SHOULD NOT SEND THIS FORM DIRECTLY TO THE FOOD AND DRUG ADMINISTRATION.

10. DATE *(mm/dd/yyyy)*	11. SIGNATURE OF INVESTIGATOR — Sign

(**WARNING**: A willfully false statement is a criminal offense. U.S.C. Title 18, Sec. 1001.)

The information below applies only to requirements of the Paperwork Reduction Act of 1995.

The burden time for this collection of information is estimated to average 100 hours per response, including the time to review instructions, search existing data sources, gather and maintain the data needed and complete and review the collection of information. Send comments regarding this burden estimate or any other aspect of this information collection, including suggestions for reducing this burden to the address to the right:

Department of Health and Human Services
Food and Drug Administration
Office of Operations
Paperwork Reduction Act (PRA) Staff
PRAStaff@fda.hhs.gov

"An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB number."

DO NOT SEND YOUR COMPLETED FORM TO THIS PRA STAFF EMAIL ADDRESS.

FORM FDA 1572 (2/16) PREVIOUS EDITION IS OBSOLETE. Page 2 of 2

Form 3454 and 3455 Certification and Disclosure of Financial Interests

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

Form Approved: OMB No. 0910-0396
Expiration Date: March 31, 2019

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable check box.

☐ (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators		

☐ (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

☐ (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME	TITLE
FIRM/ORGANIZATION	
SIGNATURE	DATE *(mm/dd/yyyy)*

This section applies only to the requirements of the Paperwork Reduction Act of 1995.

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Do NOT send your completed form to the PRA Staff email address below.

Department of Health and Human Services
Food and Drug Administration
Office of Operations
PRAStaff@fda.hhs.gov

"An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB number."

FORM FDA 3454 (3/16)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

DISCLOSURE: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

Form Approved: OMB No. 0910-0396
Expiration Date: March 31, 2019

TO BE COMPLETED BY APPLICANT

The following information concerning _____ *Name of clinical investigator*, who participated as a clinical investigator in the submitted study _____ *Name of clinical study* is submitted in accordance with 21 CFR part 54. The named individual has participated in financial arrangements or holds financial interests that are required to be disclosed as follows:

Please mark the applicable check boxes.

☐ any financial arrangement entered into between the sponsor of the covered study and the clinical investigator involved in the conduct of the covered study, whereby the value of the compensation to the clinical investigator for conducting the study could be influenced by the outcome of the study;

☐ any significant payments of other sorts made on or after February 2, 1999, from the sponsor of the covered study, such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria;

☐ any proprietary interest in the product tested in the covered study held by the clinical investigator;

☐ any significant equity interest, as defined in 21 CFR 54.2(b), held by the clinical investigator in the sponsor of the covered study.

Details of the individual's disclosable financial arrangements and interests are attached, along with a description of steps taken to minimize the potential bias of clinical study results by any of the disclosed arrangements or interests.

NAME	TITLE
FIRM/ORGANIZATION	
SIGNATURE	Date *(mm/dd/yyyy)*

This section applies only to the requirements of the Paperwork Reduction Act of 1995.

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 5 hours per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Do NOT send your completed form to the PRA Staff email address below.

Department of Health and Human Services
Food and Drug Administration
Office of Operations
PRAStaff@fda.hhs.gov

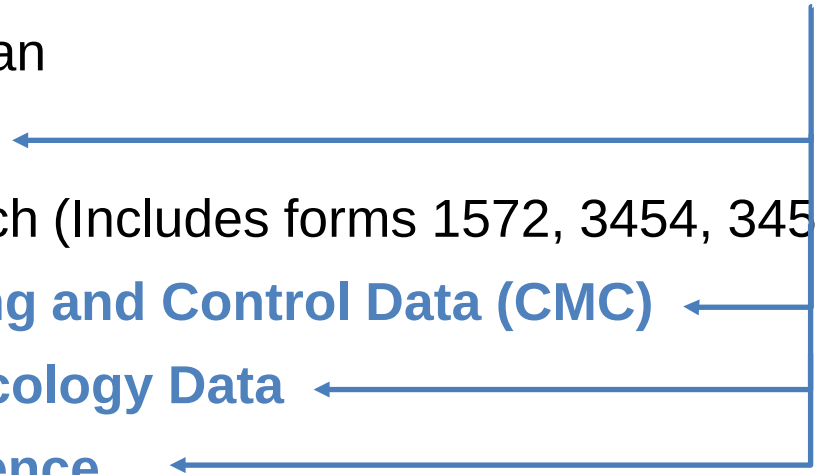
"An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB number."

FORM FDA 3455 (3/16)

IND Submission Format and Content

1. Form 1571 (cover sheet), Form 3674
2. Table of Contents
3. Introductory Statement
4. General Investigational Plan
5. **Investigator's Brochure**
6. Proposed Clinical Research (Includes forms 1572, 3454, 3455)
7. **Chemistry, Manufacturing and Control Data (CMC)**
8. **Pharmacology and Toxicology Data**
9. **Previous Human Experience**
10. Additional Information
11. Relevant Informations

Can refer to drug labeling or to letter of authorization (cross reference letter) for these sections



Approved Labeling vs. Letter of Authorization

Approved Labeling: Use when investigating an approved, marketed drug.

- Contains all pertinent info on safety, manufacturing, and previous human experience that the FDA needs to consider. http://dailymed.nlm.nih.gov/dailymed/about.cfm
- Include a copy of the labeling in your submission

Letter of Authorization: Use when investigating a new drug that has an existing IND elsewhere.

- This is a letter from a sponsor (company) providing their permission to the FDA to reference the named materials in support of your IND submission. Don't re-invent the wheel!
- Include a copy of the letter in your submission

5 – Investigator's Brochure

- Investigator's brochures are not mandatory for investigator initiated trials, but are very useful for multi-center studies.
- If not including an IB, you may state the following "In accordance with 21 CFR Part 312.55(a), an Investigator's Brochure is not required for a sponsor-investigator IND."

  OR

- Refer to the approved drug labeling (Often included as an appendix at the end of the submission)

6 – Proposed Clinical Research

- Includes the complete study protocol. We highly encourage using the NIH-FDA Protocol Template.
- Can include the informed consent document, although this is not required. The FDA may request to see the informed consent document if not included, however.
- FDA form 1572, Sponsor-Investigator CV, Medical License, and Financial Disclosure forms (FDA Forms 3454 and 3455). Sub-investigator documents do not need to be submitted, but must be kept current in the regulatory binder.

7 – Chemistry, Manufacturing, and Control

- If the investigational drug has been marketed, this section may be covered by referring to the product labeling. Alternatively, it might be appropriate to refer to a 'Letter of Authorization' if using a drug provided by a commercial company.
- If you are manufacturing your own compound, highly detailed information regarding the chemical characteristics and processing must be included here, highlighting adherence to Good Manufacturing Practices (GMP)

8 – Pharmacology and Toxicology

- Similar to section 7, if the investigational drug has been marketed, this section may be covered by referring to the product labeling. Alternatively, it might be appropriate to refer to a 'Letter of Authorization' if using a drug provided by a commercial company.

- If you are manufacturing your own compound, include information about pharmacological and toxicological (laboratory animals or in vitro) studies on the basis of which the sponsor of the IND application has concluded that it is reasonably safe to conduct the proposed clinical investigations

9 – Previous Human Experience

- Similar to section 7 and 8, if the investigational drug has been marketed, this section may be covered by referring to the product labeling. Alternatively, it might be appropriate to refer to a 'Letter of Authorization' if using a drug provided by a commercial company.

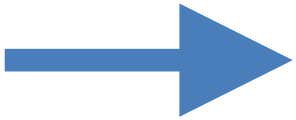
- It is also beneficial to include summaries (if known) of prior clinical research experience for the drug.

Appendices

- Appendices may help to organize the submission, and include information that the FDA may use as a reference when reviewing the presented information.

- Package inserts, LOAs, reprints of publications, investigator CVs, etc

IND Submission Formatting and Instructions



IND Submission Formatting and Instructions

- Submission should be in 12 point Times New Roman
- Include a brief cover letter signed by Sponsor
- Three copies (original and 2 exact copies) must be sent to the FDA at the address below:

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
5901-B Ammendale Rd.
Beltsville, Md. 20705-1266

(use this address for drugs)

Food and Drug Administration
Center for Biologics Evaluation and Research
Document Control Center
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

(use this address for biologics (i.e. vaccines, blood components, etc.)

IND Submission Formatting and Instructions

- **A "courtesy e-copy" may be sent as well**. The e-copy should be an exact copy of the original, in PDF format. If use of multimedia is necessary for the submission (i.e. large detailed images, or videos), then the submission cover letter should indicate the additional information contained on the e-copy. The e-copy is submitted on a CD, DVD, or thumb drive. Make sure that the information is not encrypted (especially common on thumb drives).

- **The paper submissions should be bound individually in 3-hole punch ACCO-style folders**. The original submission should be in a gray folder. The other two copies may be in different colors. Submissions that are inadequately bound will not be reviewed.

IND Submission Formatting and Instructions

- A label should be attached to the front of each folder. The e-copy should also have a label.

INITIAL IND APPLICATION
Serial No. 0000

<Sponsor Name>
<Date of Submission>
Original Copy (or Duplicate Copy 1 of 2)

What Next?

- Upon receipt of an IND application, FDA will notify the sponsor of the date it receives the application through an IND acknowledgment letter. The acknowledgment letter will also contain the IND number, the FDA review division assigned to review the IND, and the FDA point of contact.

- **The study may proceed 30 days after FDA receives the IND**, unless FDA notifies the sponsor that the investigations described in the IND are subject to a clinical hold. In the absence of hearing from FDA, the sponsor is encouraged to contact FDA to ensure the study may proceed.

Clinical Hold ?!

If an IND has been placed on clinical hold, the study may not be initiated until the Agency has contacted you telling you that the study may proceed.

- **Complete Clinical Hold:** A delay or suspension of all clinical work requested under an IND.
- **Partial Clinical Hold:** A delay or suspension of only part of the clinical work requested under the IND (e.g., a specific protocol or part of a protocol is not allowed to proceed; however, other protocols or parts of the protocol are allowed to proceed under the IND).

Maintaining an IND

IND Templates can be found at

www.ReGARDD.org

Annual Reporting

- IND application sponsors are expected to submit brief reports of the progress of the investigations conducted under their respective IND application within 60 days of the anniversary date that the application went into effect.
- Information in report should include: Summary Information, Protocol Updates, Update to General Investigational plan, etc. (refer to template for guidance)
- Submit in triplicate, and include signed Form 1571

Protocol Amendments

- **New Protocol Amendment**: INDs can include multiple protocols that study the same drug and indication. Include a brief summary and rationale of the new study, and a complete protocol.
- **Change in Protocol**: include a brief summary of the differences between revised protocol and previous protocol(s), rationale for the proposed change, a copy of the revised/updated protocol, and a track-changes version of the protocol.
- **New Investigator/New Site**: FDA must be notified within 30 days. Include new 1572 and CV/Med License
- **Information Amendment**: Anything that doesn't fall under the above topics, or safety reporting. Usually for manufacturing or toxicology updates, or for study closure.

Safety Reporting

IND application sponsors are required to notify FDA (and all participating investigators) in a written safety report of any adverse experience (AE) associated with the use of the drug that is both serious and unexpected.

Safety Reporting

There are two kinds of Safety Report submissions:

- **Initial Written Report** - IND sponsor must report any adverse reaction or suspected adverse reaction to study treatment that is both serious and unexpected to FDA as soon as possible but no later than 7 calendar days following the sponsor's initial receipt of the information

- **Follow-Up to the Written Report** - Any relevant additional information obtained by the sponsor during investigation of the AE that pertains to a previously submitted IND safety report must be submitted as a Follow-up IND Safety Report. Such reports should be submitted without delay, as soon as the information is available but no later than 15 calendar days after the sponsor receives the information

Safety Report Submission Format

- Form FDA 3500A (Mandatory MedWatch)
  - For clinical trial safety reports, for use by IND reporters, manufacturers, distributors, importers, user facilities personnel
  - **Do not use:** Form FDA 3500 (Voluntary MedWatch), which is used by healthcare professionals, consumers, and patients

Investigational Device Exemptions (IDEs)

What is a Medical Device?

Its an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent or other similar or related article or component part or accessory which:

- is intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease
- is intended to affect the structure or any function of the body
- **achieve its primary intended purposes through physical action and NOT chemical or metabolic action**

What Is A Medical Device?

What else can be classified as a Device?

Devices don't need to be applied to or implanted in someone to be considered a device.

Novel blood tests, diagnostic algorithms, and software can all be classified as a device if they meet the federal definition: "**Is intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease**"

Section 201(h) of the FD&C Act

In Vitro Diagnostics and Software as Devices.

- IVDs are those reagents, instruments, and systems intended for use in diagnosis of disease or other conditions. Such products are intended for use in the collection, preparation, and examination of specimens taken from the human body.

- Apps and software intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease can be classified as devices. However, the FDA is selective in regulating software and apps. (21st Century Cures Act)

FDA's new focus on APPS

"Intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease"

MULTIPLE DEVICES

MULTIPLE DATA SOURCES INCLUDING:

- EMR
- HIE
- Monitors & Body Sensors
- Messaging Platforms
- Medical Devices

AIRSTRIP ONE BRINGS IT ALL TOGETHER

MULTIPLE CARE SETTINGS INCLUDING:

- Pre-Hospital
- Hospital
- Post-Acute
- Community-based Care

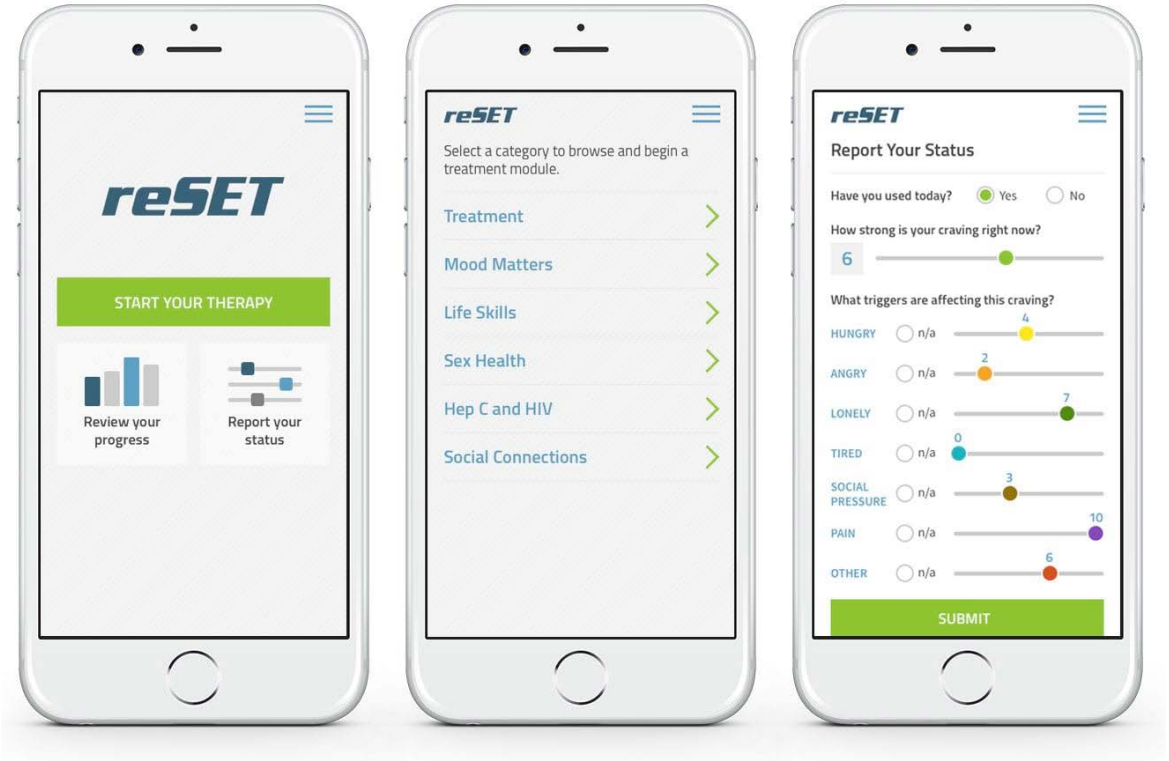
MULTIPLE DATA TYPES INCLUDING:

- Monitoring Data
- Medical History
- Waveforms
- Clinical Notes
- Lab Results
- Radiographic Images*

MULTIPLE VENDORS

FDA's new focus on APPS

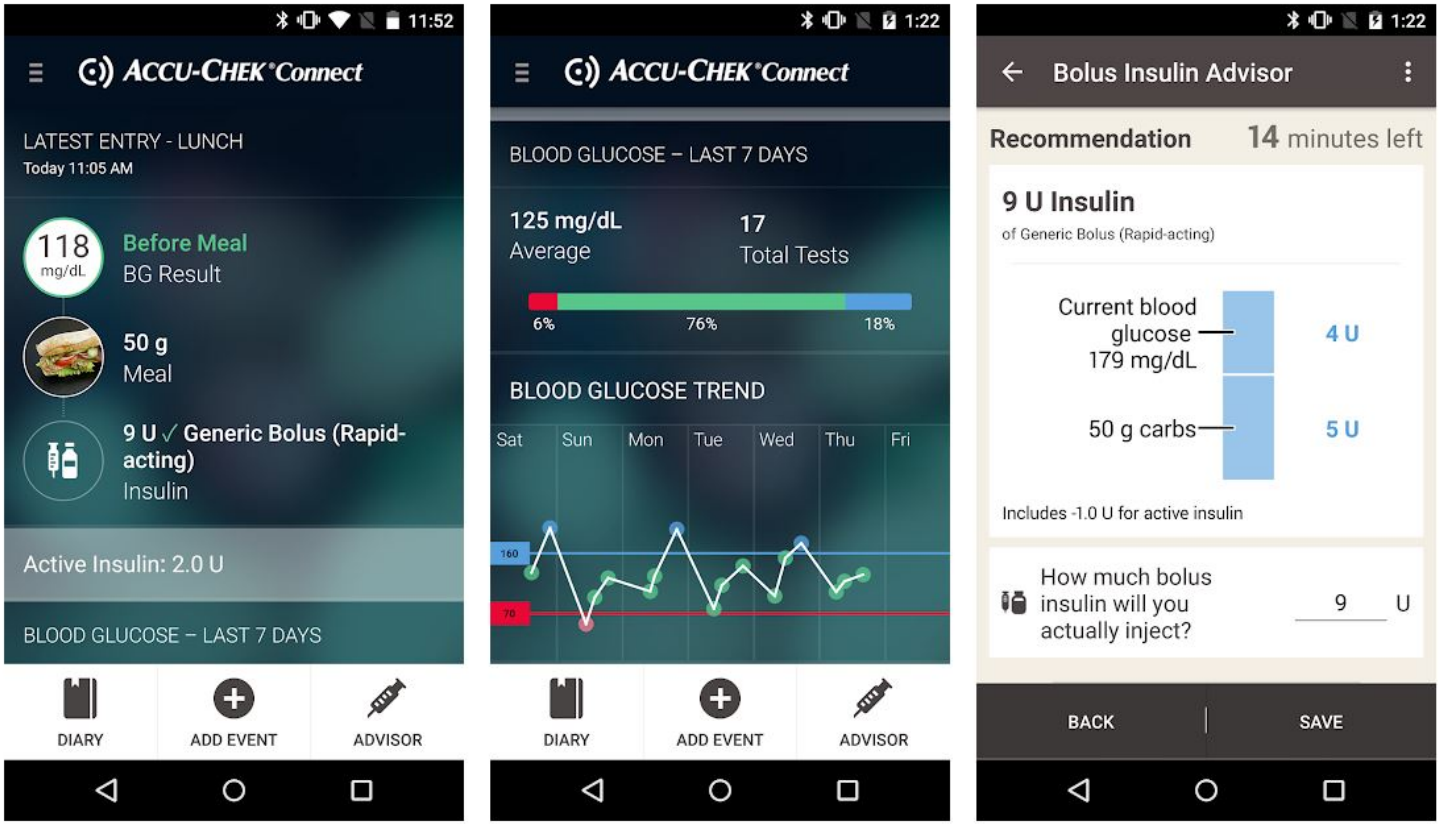
"Intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease"



reSET® : a prescription digital therapeutic to be used in conjunction with standard outpatient treatment for substance use disorder (SUD)

FDA's new focus on APPS

"Intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease"



Investigational Device Exemption (IDE)?

- An IDE is a regulatory submission that permits clinical investigation of devices to determine safety and effectiveness.
- An FDA-approved Investigational Device Exemption Application (IDE) permits a device that otherwise would be required to comply with a performance standard or to have premarket approval to be shipped lawfully for the purpose of conducting investigations of that device

(21 CFR 812.1).

What Studies are IDE-Exempt?

- If the objective of the study is not to test the safety or effectiveness of the device, then the study would not fall within the scope of IDE Regulations. (Devices used as “tools”)
- A diagnostic device that is noninvasive, non-significant risk, does not introduce energy, and is confirmed by another established procedure.
- A device undergoing a consumer preference testing, or testing that is not for the purpose of determining safety or effectiveness.
- A legally marketed device when used in accordance with its labeling. (Comparative effectiveness)

Abbreviated IDE vs IDE Requirements

In order to decide which type of IDE is needed, an SR/NSR determination is required. That determination can be made by the IRB or the FDA

- **A non-significant risk (NSR)** study requires an Abbreviated IDE and is solely overseen by an IRB.
- **A significant risk (SR)** study requires an IDE that is reviewed by the FDA.

Abbreviated IDE Regulations

- Investigator and IRB determine that the study is non-significant risk. Oversight is provided by the IRB. FDA does not have direct oversight.

- When filling out the application in IRBIS, download the Investigational Device Worksheet here: https://research.unc.edu/files/2016/04/Investigational-Device-Worksheet-ver.10-05-2016.pdf you will need to justify that you meet all of the exemption or abbreviated IDE requirements.

Significant Risk Investigations = IDE submission.

- A **significant risk** device is one that:
  - Is intended as an implant and presents a potential for serious risk to the health, safety, and welfare of a subject.
  - Is used to support or sustain human life.
  - Is of substantial importance in diagnosing, curing, mitigating, or treating disease and/or otherwise preventing impairment of human health.
  - Otherwise presents a potential for serious risk to the health, safety, or welfare of a subject.
- The study risk determination is based on the proposed use of a device in an investigation, and not on the device alone.

Preparing and Submitting an IDE

IDE Submission Template can be found at www.ReGARDD.org

IDE Submission

1. Cover Sheet
2. Name and Address of the Sponsor
3. Report of Prior Investigations
4. Investigational Plan
5. Manufacturing Information
6. Investigators Agreement
7. Investigators Certification
8. IRB Information
9. Name and Address of Investigators Institution
10. Financial Claims
11. Environmental Assessment
12. Labeling
13. Informed Consent
14. Additional Information

4 - Investigational Plan

Includes several sections:

- Description of the purpose of the device and the objectives of the study
- Study Protocol – Again, the NIH-FDA template is recommended.
- Risk Analysis
- Description of Device
- Monitoring Procedures

5 – Manufacturing Information

If you are using a marketed device, then it is appropriate to **refer to the product label** and provide copy or a URL to the most current product label. If any modifications have been made, provide details on all changes.

If you have a Letter of Authorization (LoA) from another sponsor referencing their FDA submission (IND, NDA, BLA, IDE, DMF, etc), **include the LoA** in this section.

If you are manufacturing the device, include a description of the methods, facilities, and controls used for the manufacture, processing, packing, storage, and, where appropriate, installation of the device.

6 – Investigator's Agreement

The investigators agreement must include:

- The investigator's CV;
- If the investigator was involved in an investigation or other research that was terminated, an explanation of the circumstances that led to termination;
- Investigator's commitment to provide sufficient and accurate financial disclosure information.
- A statement of the investigator's commitment to:
  - Conduct the investigation in accordance with the agreement, the investigational plan, Part 812 and other applicable FDA regulations, and conditions of approval imposed by the reviewing IRB and FDA;
  - Supervise all testing of the device involving human subjects;
  - Ensure that the requirements for obtaining informed consent are met

IDE Formatting and Submission

Preface with a cover letter and include **three Copies:**

- One original hard copy in ACCO-like grey report cover, and
- Two electronic copies with a single cover letter that contains a signature and an adequate eCopy statement "the eCopy is an exact duplicate of the paper copy“ Or, "the eCopy is an exact duplicate of the paper copy, with the exception of..."

E-Copy details

An electronic copy (eCopy) is a PDF version of your medical device submission stored on a CD, DVD, or a flash drive. Make sure they are not ‘mastered’ or encrypted.

A submission with an eCopy that does not meet the technical standards outlined in the eCopy guidance will be placed on eCopy hold until a valid eCopy is received. E-Copy Guidance

Shipping Information

For devices regulated by the Center for Devices and Radiological Health (CDRH):

U.S. Food and Drug Administration
Center for Devices and Radiological Health
Document Mail Center - WO66-G609
10903 New Hampshire Avenue
Silver Spring, Maryland 20993-0002

For devices regulated by the Center for Biologics Evaluation and Research (CBER):

U.S. Food and Drug Administration
Center for Biologics Evaluation and Research
Document Control Center - WO71-G112
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

FDA Review

Once the initial IDE submission has been sent to the FDA, a team of staff reviews the IDE and provides one of several standard responses within 30 days of receipt.

- Acknowledgement
- Approval
- Approval with Conditions (Sponsor must reply)
- Disapproval (Sponsor must reply)

Maintaining an IDE

IDE Templates can be found at www.ReGARDD.org

Supplements / Reports / Amendments

- **Supplement -** A written response from the sponsor-investigator while IDE is under review or approved (trial is ongoing) regarding changes to the protocol or the device. Supplements are intended to seek FDA's approval for something new or different.

- **Report –** A written response from the sponsor-investigator while IDE is in effect regarding study progress and unanticipated events. Reports are intended to provide notification or updates for FDA's routine monitoring of a clinical investigation.

- **Amendment -** A written response from the sponsor-investigator in response to the FDA's request for more information regarding a previous submission.

Supplements – Prior Approval

Changes requiring prior approval - most of the time, changes that are made in the Investigational Plan, need to be pre-approved by FDA. Examples of these changes are:

- Changes in the Investigational Plan or Protocol
  - Affecting the validity of data/information,
  - Patient risk to benefit relationship,
  - Scientific soundness of investigational plan,
  - Right, safety or welfare of subjects.
- Developmental Changes in the device (including manufacturing changes) that present a significant change in design or basic principle of operation

Supplements – 5 Day Notice

Changes requiring 5-day notice - these changes do not require prior approval, but notice must be provided to FDA within 5 working days of making the change:

- Changes Effected for Emergency Use: changes in the investigational plan to protect the life or well-being of the subject in the case of emergency. However, these changes must be reported to the FDA within 5 working days.
- Non-significant changes in design or manufacturing should also be reported to the FDA within 5 working days.
- Other changes to protocol that do not fit the criteria for prior approval such as:
  - Modification to inclusion/exclusion criteria to better define the target patient population, increasing the frequency at which data or information is gathered, modifying secondary endpoints

Reports

- **Annual Progress Report**
  - Template available on www.ReGARDD.org
- **Current Investigators list**
  - Report every 6 months.
- **Unanticipated Adverse Device Effects:**
  - Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device if that effect, problem or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (21 CFR 812.3 (s)). Report to the FDA within 10 working days.
- **Deviation from the investigational plan**
  - The investigator must notify the sponsor and the reviewing IRB of any deviation from the investigational plan to protect the life or physical well-being of a subject in an emergency. Report to the FDA within 5 working days.

Questions?