Stroke Trials:

Reminders and Tips for Good Clinical Practices and Study Quality

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University of California, San Diego

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GCP Training

Background

Effective January 1, 2017 – NIH expects all NIH-funded clinical investigators and clinical trial staff who are involved in the design, conduct, oversight, or management of clinical trials to be trained in Good Clinical Practice (GCP). Recipients of GCP training are expected to retain documentation of their training. GCP training should be refreshed at least every three years in order to stay up to date with regulations, standards, and guidelines.

Disclaimer - All personnel are required to upload to WebDCU evidence of GCP certification (this training does not satisfy this requirement)

Today's Agenda

- Review GCP and Study Quality Tips and Reminders:
  - Investigator Responsibilities
    - What is a 1572 and why?
  - Control of Investigational Product
  - Protection of Human Subjects - Informed Consent
    - Requirements and Reminders
  - Good Documentation Practices
    - Eligibility / Consent / Enrollment / Daily Progress Notes
    - ALCOA-C
    - Making corrections
  - Study Organization
    - Trial Master File (TMF) vs. Local site file
    - Training and Communication
    - CIRB Event Reporting
  - Quality Assurance

What is Good Clinical Practice and Why is it Important?

Definition and Purpose:

- GCP is defined as a standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials or studies

- It provides assurance that the data and the reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected

GCP is established in:

- FDA Regulations (21CFR)
- FDA Guidance Documents
- International Standards (ICH)
- StrokeNet and Local SOPs
- Local Law (Institutional and IRB Policies)
- State Law

Who is responsible for GCP compliance in research?

- Sponsors
- Clinical investigators
- Institutional Review Boards (IRBs)
- Contract Research Organizations (CROs)
- Research nurses
- Clinical Research Coordinators (CRCs)
- Clinical Research Associates (CRAs)
- Medical monitors
- Data entry personnel
- Data Managers
- Others

Who is responsible for GCP compliance in research?

- Sponsors –Prime PI of the Study (and NINDS)
- Clinical investigators – YOU, the PI, the subinvestigators
- Institutional Review Boards (IRBs) – Univ of Cin /Advarra
- Contract Research Organizations (CROs) – NCC @ Univ of Cin
- Research nurses - YOU
- Clinical Research Coordinators (CRCs) - YOU
- Clinical Research Associates (CRAs) – DMC @ MUSC
- Medical monitors – Identified by the Prime PI
- Data entry personnel – YOU
- Data Managers - DMC @ MUSC
- Others - eg. Local Compliance Office, Local IRB

What constitutes GCP in research?

The Basics:

- Current Standard Operating Procedures
- **Sponsor / Monitor / Investigator responsibilities**
- **Informed Consent process**
- Institutional Review Board approval
- **Compliance with study protocol and related procedures**
- *Controls of investigational supplies*
- Adequate safety surveillance
- *Quality Assurance*
- *Financial Disclosure*

Responsibilities of Investigators

21 CFR 312.60
21 CFR 812

Investigator responsibilities

21 CFR 312 - Drugs	21 CFR 812 - Devices
312.60:… Ensuring that an investigation is conducted according to the **signed investigator statement, the investigational plan,** and **applicable regulations…**	812.110: An investigator shall conduct an investigation in accordance with the **signed agreement with the sponsor, the investigational plan, this part and other applicable FDA regulations, and any conditions of approval imposed by an IRB or FDA.**

Investigator Responsibilities

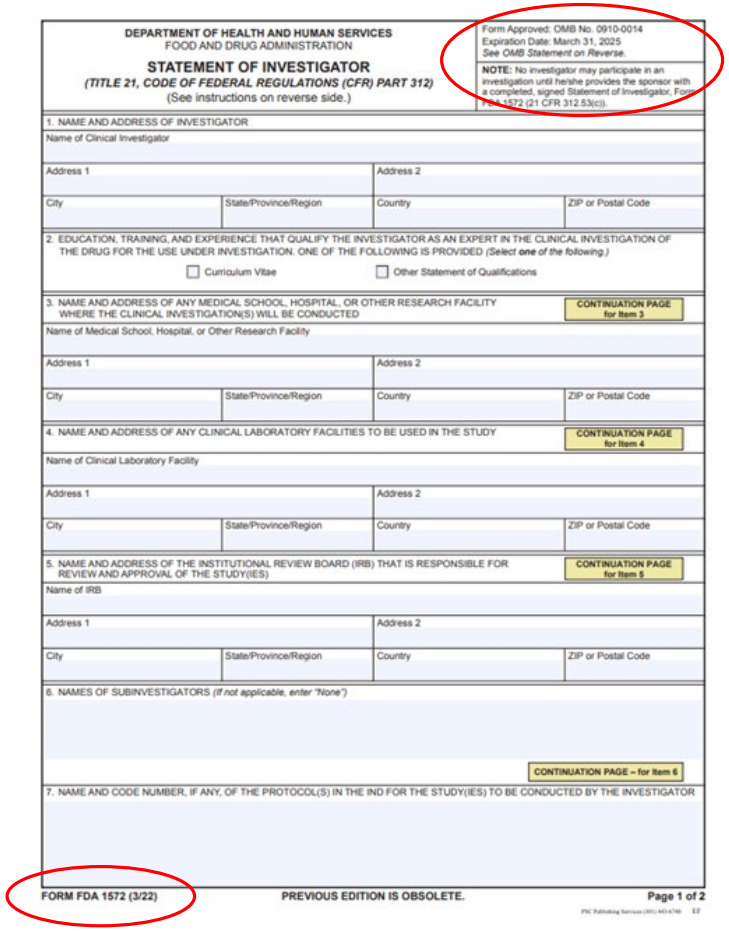
Investigator Statement - 1572

21 CFR 312 - Drugs

312.60:… Ensuring that an investigation is conducted according to the **signed investigator statement,** the investigational plan, and applicable regulations…

FORM 1572

- Provides the sponsor information about the investigator and the clinical site
- **Contract between the PI and the FDA**
- Investigator's commitment to follow pertinent FDA regulations.



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: March 31, 2025
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 (3/22) PREVIOUS EDITION IS OBSOLETE. Page 1 of 2

Page 1

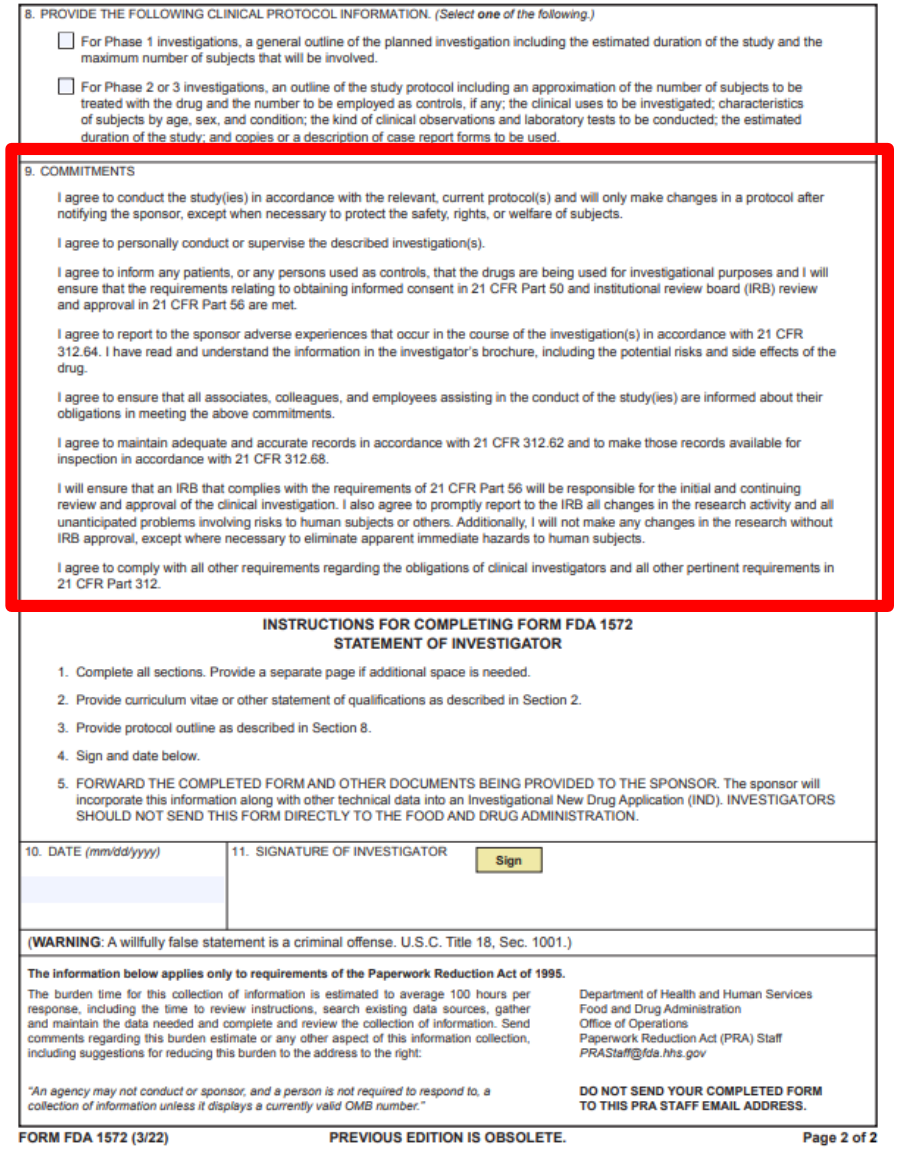
Investigator Responsibilities

1572 Commitments

The PI agrees to:

1. Conduct the study according to the protocol.
2. Personally conduct or supervise all research.
3. Fully inform participating patients and obtain IRB approval for the protocol and informed consent.
4. Report all adverse experiences.
5. Acknowledge that he/she has read the investigator's drug brochure, including sections on risks and side effects to patients.
6. Ensure that the study staff assisting in the study are informed of its obligation.
7. Keep adequate records and have them available for inspection.
8. Utilize an IRB that complies with FDA requirements.
9. Compliance with all other federal requirements.

Page 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 (3/22) **PREVIOUS EDITION IS OBSOLETE.** **Page 2 of 2**

Statement of Investigator - Agreement

Device Studies

- No formal form (ie.1572)

  Signed agreement from each investigator that includes:

  - statement of commitment to protocol, IDE, FDA regs, IRB and GCP
  - supervise all testing of device
  - ensure that requirements of ICF are met

- Qualified by CV, relevant experience, note if any study has ever been terminated
- Provide accurate financial disclosure

Control of Investigational Product

21 CFR 312.57 and 312.61

Control of Investigational Supplies

- Investigator is responsible
- May delegate to another (pharmacy, SC, etc)
  - but see first bullet
- Maintain records:
  - Dates, quantities, batch/serial numbers, expiration dates, and any unique codes assigned to the product
  - Maintain records on which subjects received product and reconcile against records
  - Return unused product as directed by sponsor

Protection of Human Subjects (ICF)

21 CFR 50 and 45 CFR 46

Requirements of: Informed Consent

45 CFR.46
21CFR Part 50

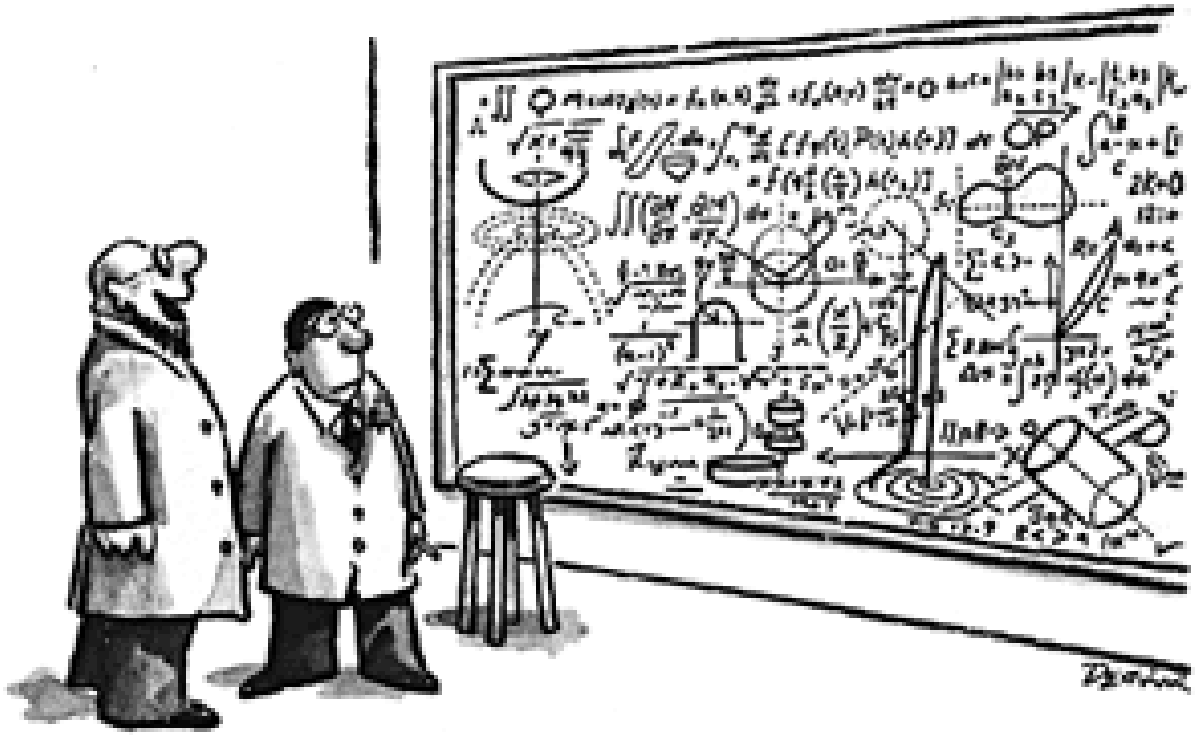
An investigator must obtain (45 CFR.46) the legally effective informed consent of the subject or the subject's legally authorized representative

Consent Process involves:

- giving a subject adequate information concerning the study
- providing adequate opportunity for the subject to consider all options
- responding to the subject's questions
- ensuring that the subject has comprehended this information
- obtaining the subject's voluntary agreement to participate
- continuing to provide information as the subject or situation requires

This is challenging in the acute treatment window

Reading Consents



"Hey, no problem!"

Average Reading Time

of words in ICF

CAPTIVA~8,149

SleepSMART~6,436

SATURN~5,834

FASTEST~4,198

SISTER ~6,078

Table #2: Minutes to read a consent form

Consent Form Length (Words)	Very Slow Reading Speed (100 words/min)	Average Reading Speed (200 - 250 words/ min)	Fast Reading Speed (300 words/ min)
2,000	20 minutes	8 - 10 minutes	7 minutes
3,000	30	12 - 15	10
4,000	40	16 - 20	13
5,000	50	20 - 25	17
6,000	60	24 - 30	20
7,000	70	28 - 35	23
8,000	80	32 - 40	27
9,000	90	36 - 45	30
10,000	100	40 - 50	33
11,000	110	44 - 55	37
12,000	120	48 - 60	40

SoCRA *SOURCE* © - November 2008 - 64

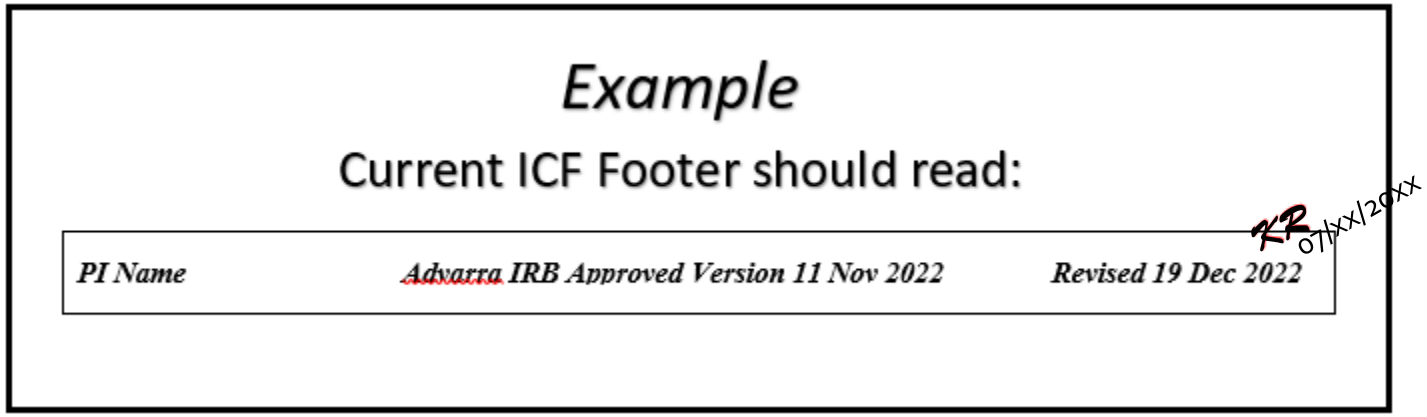
Informed Consent: Christine Grady, Department of Bioethics, NIH Clinical Center

Are you using the correct version of the ICF?

- Informed consents are often revised over the course of a study
- Consenting on the wrong version of the ICF is an FDA audit finding
- How do you prevent this?
  - Use eCONSENT (version is managed centrally)
  - Verify you are using the correct version at time of use

When using a paper ICF the study team personnel should verify the version in hand is correct. (eg. thru central file verification, ClinOne app, etc).

Best Practice Idea: After confirming you are using the correct version of the ICF, initial the date stamp information, to demonstrate this was verified prior to consent.



Informed Consent – Witness

Must a witness observe the entire consent interview or only the signature of the subject?

Informed Consent – Witness

Must a witness observe the entire consent interview or only the signature of the subject?

FDA does not require the signature of a witness when the subject reads and is capable of understanding the consent document, as outlined in 21 CFR 50.27(b)(1). The intended purpose is to have the witness present during the entire consent interview and to attest to the accuracy of the presentation and the apparent understanding of the subject. If the intent of the regulation were only to attest to the validity of the subject's signature, witnessing would also be required when the subject reads the consent.

21 CFR Part 50

https://www.fda.gov/regulatory-information/search-fda-guidance-documents/institutional-review-boards-frequently-asked-questions#GeneralQuestions
Guidance for Institutional Review Boards and Clinical Investigators (1998 Update)

Informed Consent – Witness

- Attests to the fact informed consent was provided, not that the signature belongs to the subject.
- In the prevention setting where the ICF is often read independently by the subject, or in the hospital setting where you leave the consent for the patient to read, and then you return later to answer questions, a witness is NOT needed
- If the ICF is read to them because they are illiterate, or visually impaired, or physically unable to sign due to limb impairment, a witness is needed.
- A witness needs to be a impartial bystander. Members of the research team do NOT qualify as impartial.

Informed Consent – Witness

How do I know if I need a witness?

Ask yourself: Can the participant/LAR **read** and **sign** the ICD?

Yes – no witness needed

No – witness needed

Reasons a participant/LAR can not read or sign the ICD:

1. They are non-English speaking therefore can not read an English ICD
2. They are illiterate therefore can not read or sign the ICD
3. They are visually impaired therefore can not read the ICD
4. They are physically unable to sign the consent form

SOP ADM 26

NIH StrokeNet
PREVENTION | TREATMENT | RECOVERY

Informed Consent – Witness

Who can be my witness?

- **Impartial Witness** - A person who is independent of the trial, cannot be unduly influenced by the people involved with the trial, who is present during the entire informed consent process and who attests to the adequacy of the consent process and to the participant's/LAR's voluntary consent.
- A **non-research staff member** or the **participant's adult relative** if there is no reasonable concern that the proposed witness is not acting in the best interest of the individual.
  - Sites may have different policy on who can be a witness. Sites should follow any local policy.

SOP ADM 26

NIH StrokeNet
PREVENTION | TREATMENT | RECOVERY

Regaining Capacity to Consent

Initial consent by LAR/surrogate

Consenting is an ongoing process:

- For patients where consent was initially given by an LAR/surrogate, the patient's capacity to provide consent should be assessed at every visit.
- A subject who regains the cognitive ability to consent must be reconsented using standard consenting procedures.

Informed Consent – Documentation

Reminders and Tips

- **DATE**
  - **DO NOT** fill in the dates for subject/LAR/witness.
  - **MUST BE** in same handwriting as signature line
- **DO NOT** leave any lines unaddressed (strike through or write N/A)
- **TIME** (if present on ICF)
  - Ensure consent obtained **PRIOR** to research procedures
- **RECONSENT** – Once a subject regains capacity
- **Medical Record**: Document the consent process in your study note and place a copy of the signed ICF in the patient's medical record.

Best Practices:

- Instead of paper, obtain consent using the REDCap eConsent provided by the study
- If a LAR is used at enrollment, evaluate a patient's capacity to consent daily while hospitalized and at each visit post-discharge; document the outcome of the evaluation in the medical record.

Informed Consent

REMINDER

ALL consents (100%) will be reviewed in:

- Sponsor audits
- IRB audits
- Compliance audits
- OHRP audits
- FDA audits

GET IT RIGHT!!

Good Documentation Practices

Good Documentation Practices

Eligibility and Consent

Progress Note in Medical Record

- At a minimum, it should include:
  - the name of the study
  - documentation that the subject met all eligibility criteria
  - the name of the person consenting the subject
  - a statement that the study was explained to the subject or the subject's representative
  - a statement that the subject was given the opportunity to ask questions
  - documentation that consent was obtained before any subject procedures were performed

Best Practice:

Use a template in your medical record system to capture all of the elements identified above *(see example for SISTER)*

Good Documentation Practices

Eligibility and Consent

Use a template or dot phrase in your EMR

Example

CLINICAL RESEARCH TRIALS: SISTER IRB# XXXXXX

@NAME@ is a candidate for the SISTER clinical protocol (IRB#XXXXXX). SISTER (STRATEGY FOR IMPROVING STROKE TREATMENT RESPONSE (SISTER) TRIAL) is a Phase-2, prospective, randomized, placebo-controlled, blinded, dose-finding trial that aims to determine the safety and preliminary efficacy of TS23, a monoclonal antibody against the alpha-2 antiplasmin (a2-AP), in acute ischemic stroke. This study is being performed in coordination with the NIH StrokeNet to identify a dose of TS23 that is safe and more efficacious than placebo for the treatment of patients from 4.5 to 24 hours of ischemic stroke onset (or last known well) who have evidence of core-penumbra mismatch on perfusion imaging and are not a candidate for the standard of care reperfusion therapies. Randomized subjects will receive one of five doses of TS23 or placebo being evaluated in this study (placebo, 3.0 mg/kg TS23, 5.0 mg/kg TS23, 7.0 mg/kg TS23, or 10.0 mg/kg TS23). The study medication will be given as a one-time IV infusion over 15 minutes. Patients and bedside clinicians are blinded to the treatment assignment.

All acute ischemic stroke patients with a last known well time of 4.5 hours to 24 hours are considered for this protocol.

I have reviewed the inclusion/exclusion, and the patient is eligible for the study. The patient has no contraindications to receive TS23, such as a history of significant bleeding issues, history of stroke or penetrating head injury in the past 90 days, acute intracranial hemorrhage, subarachnoid hemorrhage, intracranial neoplasm, or arteriovenous malformation. Before the stroke, the patient had no prior significant disability and was able to perform basic activities of daily living (dressing, eating, walking, bathing, toileting) without assistance. Consideration for this protocol did not delay the standard of care management. No clinical trial procedures were performed before consent was obtained unless it was part of routine care.

After determining through my assessment of the patient on whether or not they had the capacity to provide informed consent, I reviewed the details of the protocol with the patient (or surrogate if appropriate) and discussed all relevant risks, benefits, and alternatives to this protocol. The patient (or surrogate) was given time to ask questions and have all questions answered by the investigator. Based on the discussion, the patient (or surrogate) reported that the patient would want to be enrolled into the clinical trial. If the patient was determined to have capacity, the patient completed the consent. If it was determined the patient did not have the capacity to provide consent, consent was obtained by a surrogate. The consent form was signed and dated by the consenter (patient or surrogate), and witnessed if required.

Per the protocol, the patient will receive one dose of TS23 or placebo. This will be given after the consent is signed, all required imaging is completed, and the patient is deemed eligible. All investigators and participants are blinded throughout the study, except the research pharmacist. Neither the patient nor the clinical team will know which group the patient was assigned to, and the team has no influence on this assignment.

In summary, the patient was enrolled in this clinical trial after obtaining informed consent. After determining the stroke onset time to be *** on ***, the patient was randomized at *** on ***. The study medication was administered at *** on ***. I was at the patient's bedside and oversaw the patient receiving the study medication.

Good Documentation Practices

Eligibility and Consent

Use a template or dot phrase in your EMR

Example

SISTER (IRB #XXXXXX)
Did the patient have capacity to provide consent?
YES – No surrogate needed
NO – Surrogate needed for consent

Did the patient and/or surrogate indicate, either verbally or non-verbally, any hesitation or unwillingness to participate?
NO

Does the patient meet all eligibility criteria?
YES

Were all study procedures, the consequences of participating, and the option not to participate explained to the patient and/or surrogate?
YES

Was the patient or surrogate given the opportunity to ask questions?
YES

Did the patient/surrogate sign the consent form?
YES

Was consent obtained before any study specific procedure?
YES

Investigator Obtaining Consent @MEWITHCREDENTIAL@
Date of consent ***
Time of consent ***

Was a copy of the form given to the person providing consent?
YES

Was the decision re-reviewed after a "time out?"
YES

Note Author: @MEWITHCREDENTIAL@

Good Documentation Practices

Daily Progress Note

Use a template or dot phrase in your EMR

Example

DAILY CLINICAL TRIAL RESEARCH NOTE – SISTER (IRB#809375):

Demographics
Date: @FDATE@
Age: @AGE@
Sex: @SEX@
DOA: @ADMITDT@

@NAME@ was consented and enrolled into the SISTER clinical trial protocol which is a Phase-2, prospective, randomized, placebo-controlled, blinded, dose finding trial that aims to determine the safety and preliminary efficacy of TS23, a monoclonal antibody against the alpha-2 antiplasmin (a2-AP), in acute ischemic stroke. This clinical trial is being performed in coordination with the NIH StrokeNet to identify a dose of TS23 that is safe and more efficacious than placebo for the treatment of patients from 4.5 to 24 hours of ischemic stroke onset (or last known well), who have evidence of core-penumbra mismatch on perfusion imaging, and are not a candidate for standard of care reperfusion therapies. In summary, this patient has received a treatment of one infusion of either TS23 or placebo.

Interval events since last research note (including significant laboratory or imaging results):
***

Summary of study medication administration:
The study medication was administered at *** on ***.

Summary of adverse events since last research note (write "N/A" if no adverse events since last research note)**:**
***

Vitals:
@VS@

Neurological Examination:
***

Overview of NIHSS
Randomization NIHSS:***
Last NIHSS: *** (provide date/time and total score)

Today's NIHSS Breakdown (insert NIHSS template score entered
Item Q1a. LOC Code (X/3): ***
Item Q1b. LOCQ (X/2): ***
Item Q1c. LOCC (X/2): ***
Item Q2. Best Gaze (X/2): ***
Item Q3. Visual Fields (X/3): ***
Item Q4. Facial Palsy (X/3): ***
Item Q5a. Left Arm Code (X/4): ***
Item Q5b. Right Arm Code (X/4): ***
Item Q6a. Left Leg Code (X/4): ***
Item Q6b. Right Leg Code (X/4): ***
Item Q7. Limb Ataxia (X/2): ***
Item Q8. Sensory Loss (X/2): ***
Item Q9. Aphasia (X/3): ***
Item Q10. Dysarthria (X/2): ***
Item Q11. Extinction/ Neglect (X/2):***
NIHSS Total Score (Date): ***
Time NIHSS Score Performed:***
Study Investigator Name Performing NIHSS:***

Total Change in NIHSS since Randomization:***
Total Change in NIHSS since last assessment:***
If neuroworsening noted (>= 4pts), presumed cause (write "N/A" if no neuroworsening): ***

Today's Clinical Assessment and Plan:
***

Note Author:
@SIGNATURE@, @TITLE@

Good Documentation Practices

Daily Progress Note

Use a template or dot phrase in your EMR

Example

DAILY CLINICAL TRIAL RESEARCH NOTE – SISTER (IRB#809375):

Demographics
Date: @FDATE@
Age: @AGE@
Sex: @SEX@
DOA: @ADMITDT@

@NAME@ was consented and enrolled into the SISTER clinical trial protocol which is a Phase-2, prospective, randomized, placebo-controlled, blinded, dose finding trial that aims to determine the safety and preliminary efficacy of TS23, a monoclonal antibody against the alpha-2 antiplasmin (a2-AP), in acute ischemic stroke. This clinical trial is being performed in coordination with the NIH StrokeNet to identify a dose of TS23 that is safe and more efficacious than placebo for the treatment of patients from 4.5 to 24 hours of ischemic stroke onset (or last known well), who have evidence of core-penumbra mismatch on perfusion imaging, and are not a candidate for standard of care reperfusion therapies. In summary, this patient has received a treatment of one infusion of either TS23 or placebo.

Interval events since last research note (including significant laboratory or imaging results):
***

Summary of study medication administration:
The study medication was administered at *** on ***.

Summary of adverse events since last research note (write "N/A" if no adverse events since last research note)**:**
***

Vitals:
@VS@

Neurological Examination:
***

Overview of NIHSS
Randomization NIHSS:***
Last NIHSS: *** (provide date/time and total score)

Today's NIHSS Breakdown (insert NIHSS template score entered
Item Q1a. LOC Code (X/3): ***
Item Q1b. LOCQ (X/2): ***
Item Q1c. LOCC (X/2): ***
Item Q2. Best Gaze (X/2): ***
Item Q3. Visual Fields (X/3): ***
Item Q4. Facial Palsy (X/3): ***
Item Q5a. Left Arm Code (X/4): ***
Item Q5b. Right Arm Code (X/4): ***
Item Q6a. Left Leg Code (X/4): ***
Item Q6b. Right Leg Code (X/4): ***
Item Q7. Limb Ataxia (X/2): ***
Item Q8. Sensory Loss (X/2): ***
Item Q9. Aphasia (X/3): ***
Item Q10. Dysarthria (X/2): ***
Item Q11. Extinction/ Neglect (X/2):***
NIHSS Total Score (Date): ***
Time NIHSS Score Performed:***
Study Investigator Name Performing NIHSS:***

Total Change in NIHSS since Randomization:***
Total Change in NIHSS since last assessment:***
If neuroworsening noted (>= 4pts), presumed cause (write "N/A" if no neuroworsening): ***

Today's Clinical Assessment and Plan:
***

Note Author:
@SIGNATURE@, @TITLE@

Daily Research Note: This is often a secondary note to the clinical progress note. It should include a summary of interval events, dosing, toleration, adverse events, assessment of neuroworsening, and plan as it relates to research (eg. reassess capacity for consent).

Good Documentation Practices

ALCOA - C

Remember –
"If isn't documented, it didn't happen"

Good Documentation Practices:

Attributable – It should be obvious who documented or did what; traceable to a person, date, and subject visit

Legible – the record should be easy to read and signatures identifiable

Contemporaneous – The info should be documented as it happens. If a clinical observation cannot be entered when made, chronology should be recorded. All signatures or initials should be attached to a date indicating when the signature was added to the document.

Original – First record of the information or certified copy. The investigator should have the original source document.

Accurate – Accurate, consistent, and real representation of facts.

Complete - The information should be complete (e.g., to answer who, what, when, where, why, and how).

Good Documentation Practices

Reminders and Tips

ALCOA - C

- Any change or correction to a CRF should be dated, initialed, and explained (if necessary) and should not obscure the original entry (ICH 4.9.3)
- The completer must sign ALL source documents. FDA guidance specifies that data should be “attributable”.

Good Documentation Practices

Reminders and Tips

ALCOA - C

- Review the following CRF data and select the most appropriate method to correct the date to 01/10/2024. Identify the mistake in each of the others.

A.

CXR Findings

01/10/24

Date of Report: ~~01/10/23~~

07/22/24 KR

B.

CXR Findings

01/10/24

Date of Report: [redacted]

07/22/2024 KR

C.

CXR Findings

01/10/24

Date of Report: ~~01/10/23~~ KR

D.

CXR Findings

01/10/24

Date of Report: ~~01/10/23~~

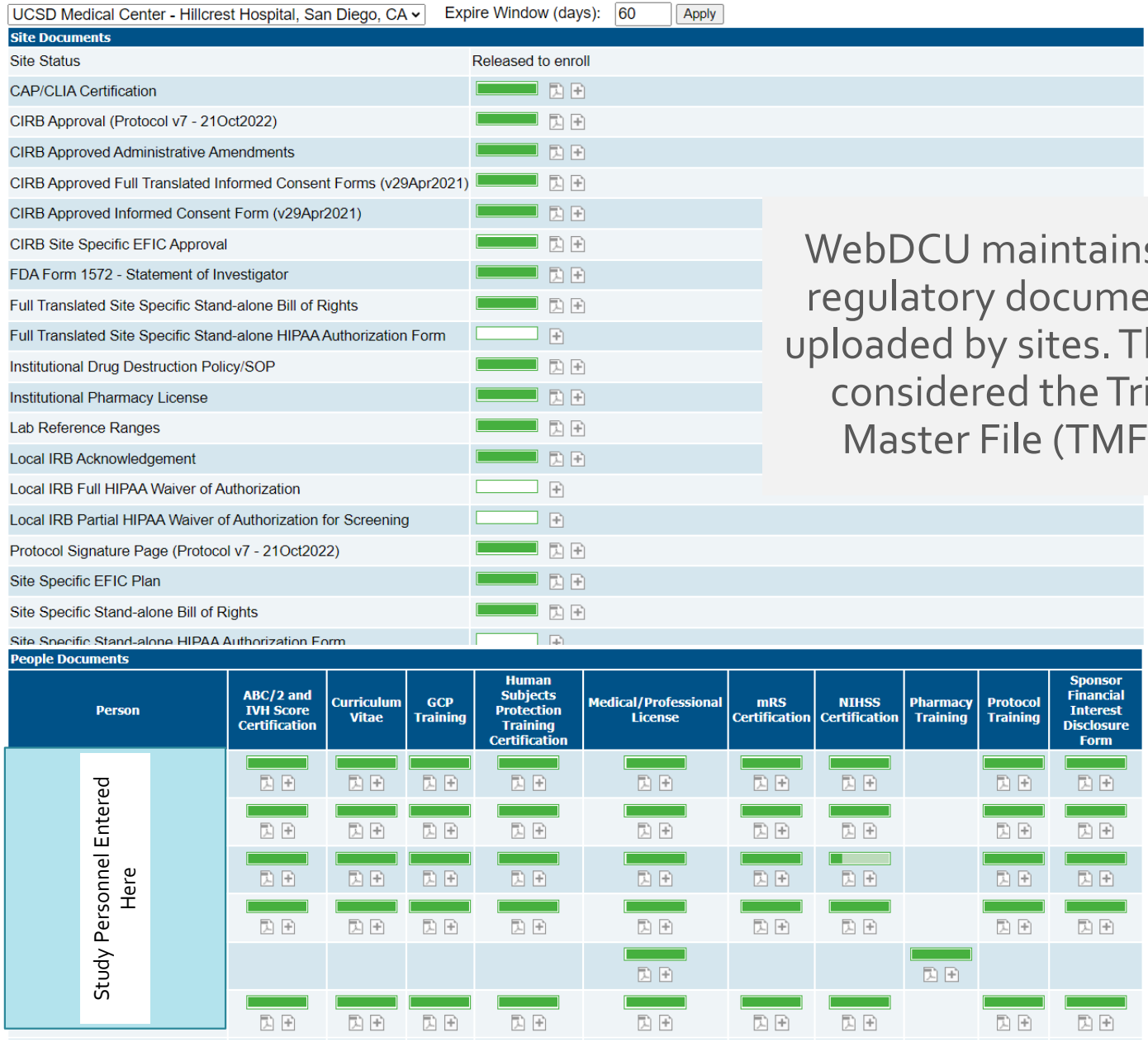
07/22/2024 KR

Study Organization

Regulatory Reminders and Tips

Study Organization

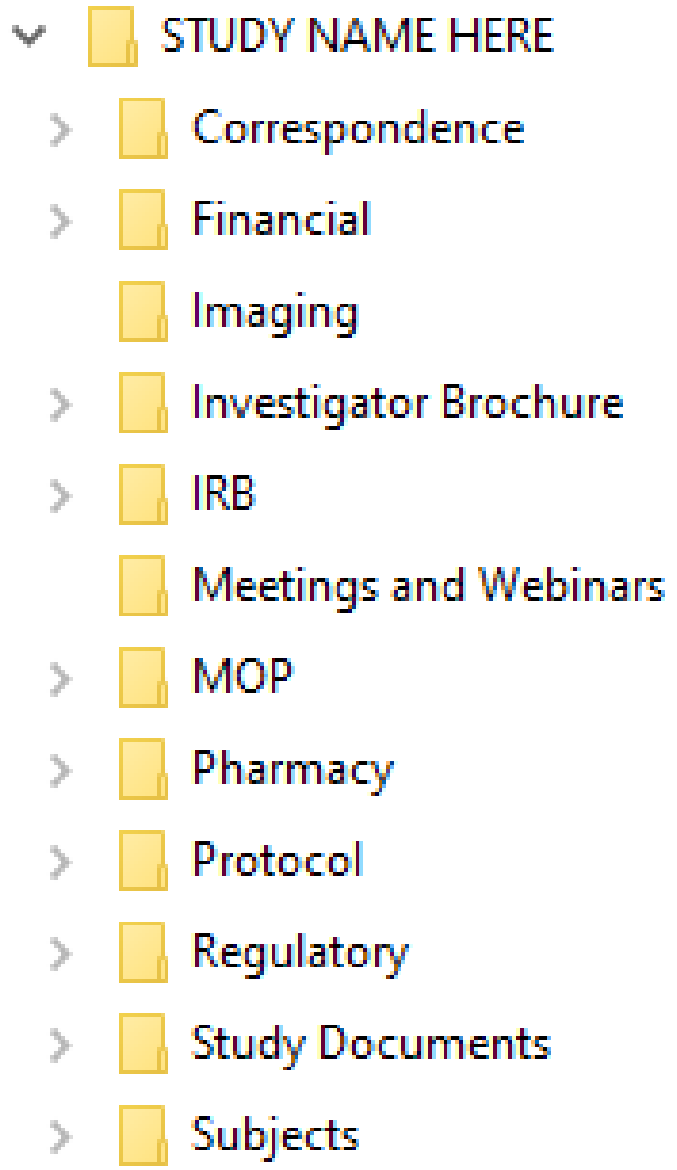
Central



WebDCU maintains all regulatory documents uploaded by sites. This is considered the Trial Master File (TMF).

Study Organization

Local



Every Site MUST maintain a file of the documents in WebDCU and MORE

(eg. items from Toolbox)

EXAMPLE FILE STRUCTURE

Example – Local Site Study File - expanded

- STUDY NAME HERE
  - Correspondence
    - DSMB
    - Local Study Team
    - NCC
    - Newletters
  - Financial
    - CTA
      - Amendments
      - Initial
    - Invoices
    - WebDCU Payments
  - Imaging
  - Investigator Brochure
    - IB Receipt of Acknowledgement
- IRB
  - CIRB
    - Approval Letters - Prime
    - Approved Submissions - Site
    - ICF
      - 1_Current ICF - combined
      - Bill of Rights
      - E Consent Email Script
      - Main ICF_word versions
      - Stand Alone HIPAA
      - Verification Dates
    - IRB Roster
    - Issues
      - Protocol Deviations_Exceptions_Violations
      - SAEs
      - Serious Non Compliance
      - Unanticipated Problems
  - Local IRB
    - Local Site Approval Letters
    - Local Site Submissions
      - 2022 10 XX Initial Application
  - Meetings and Webinars
- MOP
  - Imaging
  - Lab
  - Pharmacy
  - Study
- Pharmacy
  - Drug Destruction Policy
  - Orders
  - Pharmacy License
- Protocol
  - Protocol Sig Page
- Regulatory
  - 1572
  - CV
  - DOA Log
  - Financial Disclosure
  - GCP
  - Human Subjects
  - Lab Documents
    - CAP_CLIA Certs
    - Lab License
    - Lab Ref Ranges
- Monitoring
  - Data Quality Reports
  - Visits
- mRS
- NIHSS
- Prof License
- Training
  - Local Trainings
  - Pharmacist
  - Protocol
  - Study Coordinator
- Study Documents
  - Templates
  - Tools
- Subjects
  - 2001
  - 2002
  - 2003

Reminders of specific regulatory items that could be OVERLOOKED

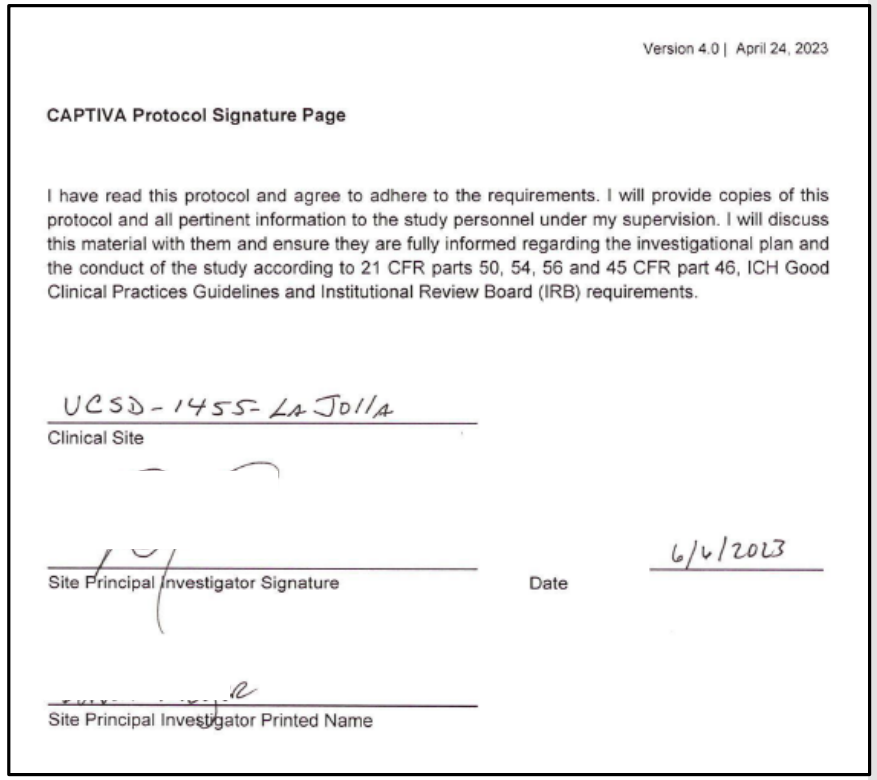
Training and Communication

Study Organization

Regulatory Reminders/Tips

Training and Communication

- **Receipt, review and/or training of new protocols, amendments, IBs, MOPs, and study guidance provided on webinars**
  - **How is this disseminated? Documented? and where is it filed?**



Version 4.0 | April 24, 2023

CAPTIVA Protocol Signature Page

I have read this protocol and agree to adhere to the requirements. I will provide copies of this protocol and all pertinent information to the study personnel under my supervision. I will discuss this material with them and ensure they are fully informed regarding the investigational plan and the conduct of the study according to 21 CFR parts 50, 54, 56 and 45 CFR part 46, ICH Good Clinical Practices Guidelines and Institutional Review Board (IRB) requirements.

UCSD - 1455 - La Jolla

Clinical Site

Site Principal Investigator Signature

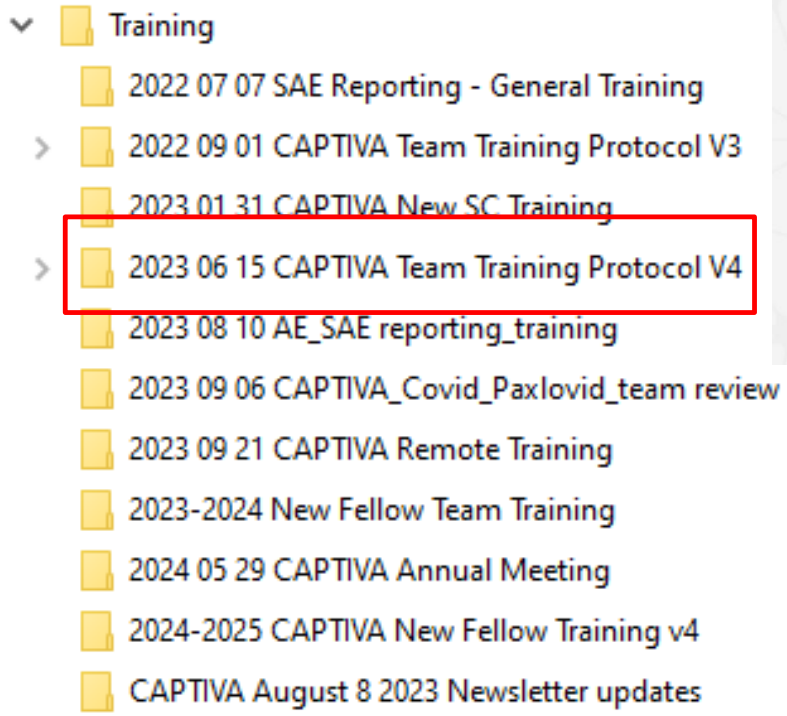
Date 6/6/2023

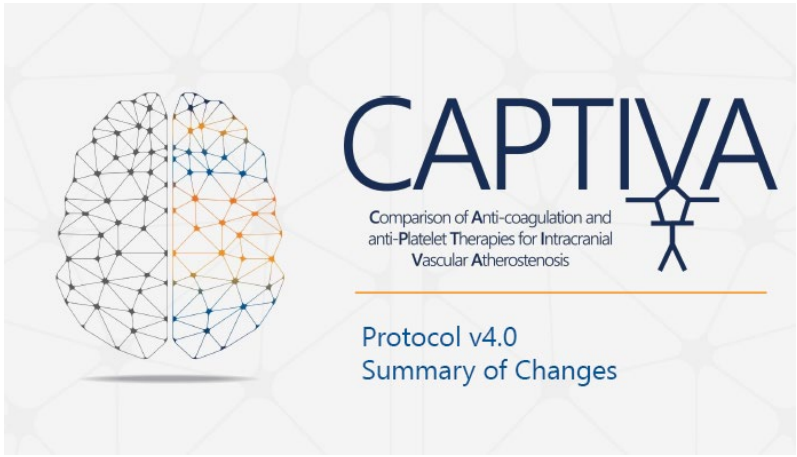
Site Principal Investigator Printed Name

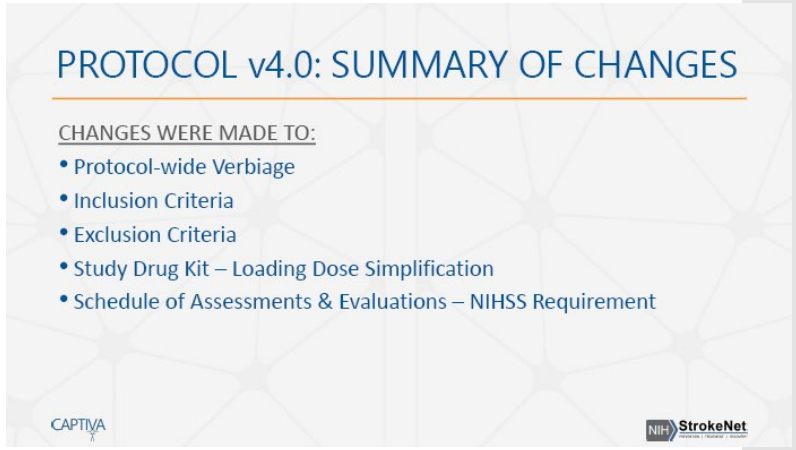
Study Organization

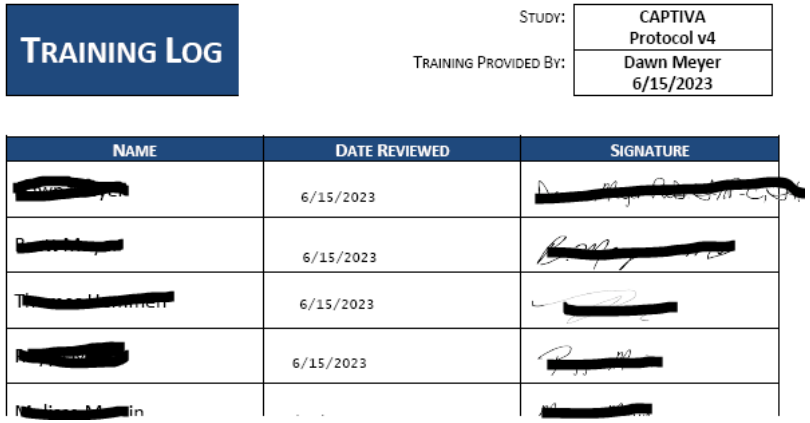
Regulatory Reminders/Tips

Training and Communication









Reminders of specific regulatory items that could be OVERLOOKED

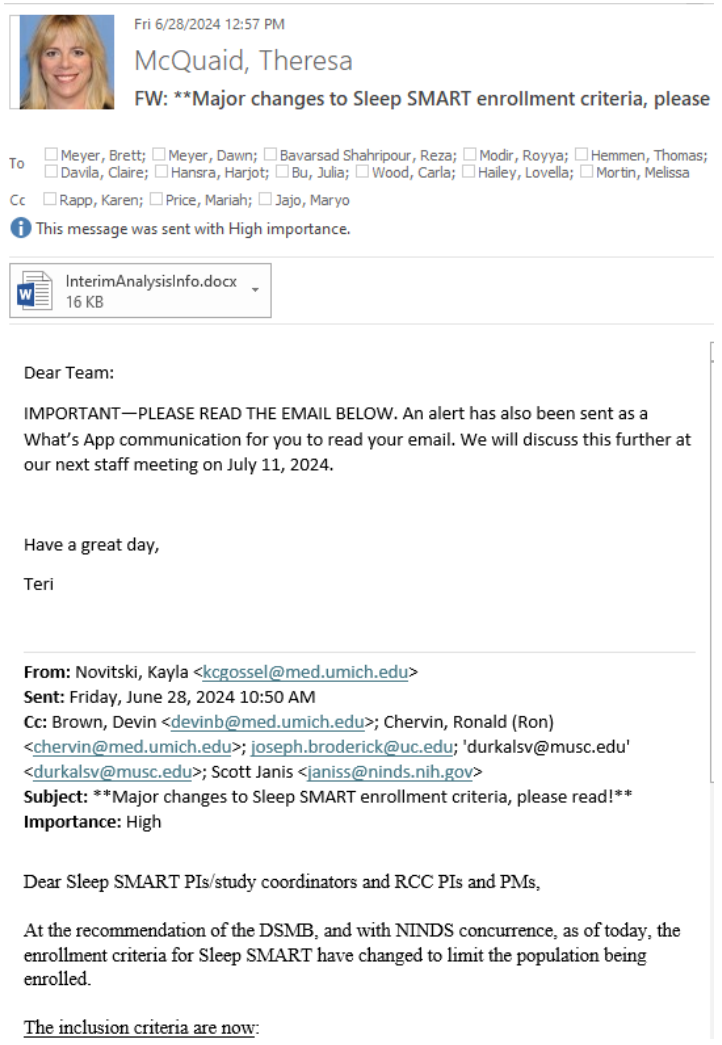
Training and Communication

Study Organization

Regulatory Reminders/Tips

Training and Communication

- Ongoing Communication with the Study Team
  - How is this documented and where is it filed?



Fri 6/28/2024 12:57 PM

McQuaid, Theresa

FW: **Major changes to Sleep SMART enrollment criteria, please

To Meyer, Brett; Meyer, Dawn; Bavarsad Shahripour, Reza; Modir, Royya; Hemmen, Thomas; Davila, Claire; Hansra, Harjot; Bu, Julia; Wood, Carla; Hailey, Lovella; Mortin, Melissa

Cc Rapp, Karen; Price, Mariah; Jajo, Maryo

This message was sent with High importance.

InterimAnalysisInfo.docx
16 KB

Dear Team:

IMPORTANT—PLEASE READ THE EMAIL BELOW. An alert has also been sent as a What's App communication for you to read your email. We will discuss this further at our next staff meeting on July 11, 2024.

Have a great day,

Teri

From: Novitski, Kayla <kcgossel@med.umich.edu>
Sent: Friday, June 28, 2024 10:50 AM
Cc: Brown, Devin <devinb@med.umich.edu>; Chervin, Ronald (Ron) <chervin@med.umich.edu>; joseph.broderick@uc.edu; 'durkalsv@musc.edu' <durkalsv@musc.edu>; Scott Janis <janiss@ninds.nih.gov>
Subject: **Major changes to Sleep SMART enrollment criteria, please read!**
Importance: High

Dear Sleep SMART PIs/study coordinators and RCC PIs and PMs,

At the recommendation of the DSMB, and with NINDS concurrence, as of today, the enrollment criteria for Sleep SMART have changed to limit the population being enrolled.

The inclusion criteria are now:

Reminders of specific regulatory items that could be OVERLOOKED

CIRB Reporting

Study Organization

Regulatory Reminders/Tips

Miscellaneous – CIRB Reporting

- SAE and UAE Reporting to CIRB
  - University of Cincinnati (UC) IRB Studies –
    - You (the site) are responsible for submitting the report to WebDCU per the study reporting requirements.
    - The NCC submits to the UC CIRB on your behalf.
  - Advarra IRB Studies –
    - You (the site) are responsible for submitting the report to WebDCU per the study reporting requirements.
    - After the central review of the event, if it meets the reporting requirements to Advarra, the NCC Project Manager will send you an alert to submit it to Advarra.

Reminders of specific regulatory items that could be OVERLOOKED

Study Organization

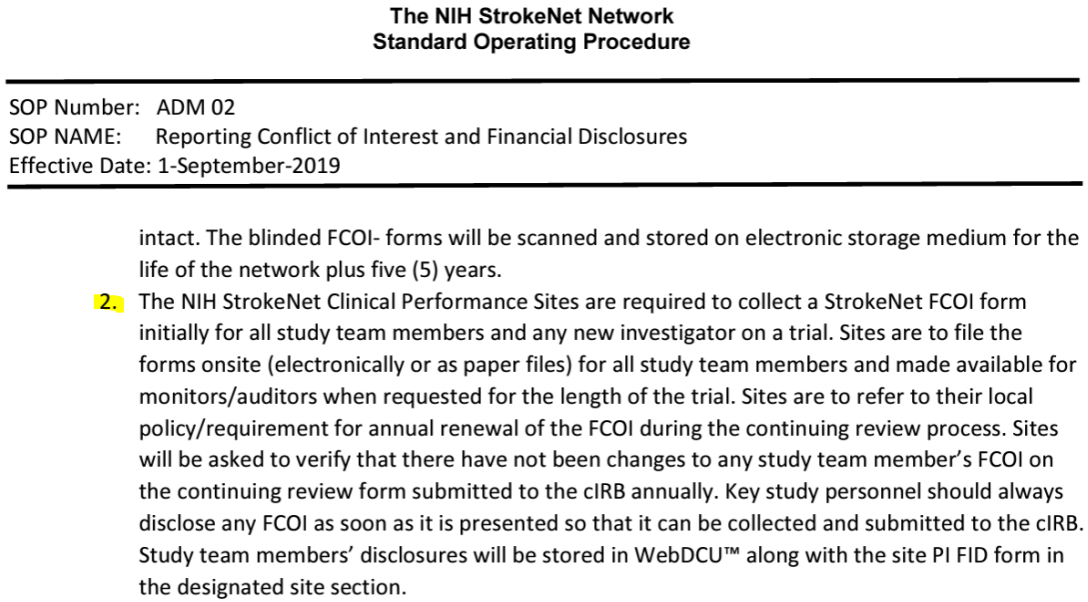
Regulatory Reminders/Tips

Financial Disclosure Local

Financial Disclosure

- **<u>At the time of award</u>** sub recipients must indicate they are compliant with PHS COI policy (CTA)

- At the time of Continuing Review (CR) - Assessment of Financial Disclosure must occur on <u>all</u> Study Personnel
  - Only the site PI is required to be uploaded in WebDCU and therefore other team members could be easily missed
  - Your site PI must attest that no study team member has any ***new*** reported conflict at CR. This is difficult to attest to without evidence.



The NIH StrokeNet Network
Standard Operating Procedure

SOP Number: ADM 02
SOP NAME: Reporting Conflict of Interest and Financial Disclosures
Effective Date: 1-September-2019

intact. The blinded FCOI- forms will be scanned and stored on electronic storage medium for the life of the network plus five (5) years.

2. The NIH StrokeNet Clinical Performance Sites are required to collect a StrokeNet FCOI form initially for all study team members and any new investigator on a trial. Sites are to file the forms onsite (electronically or as paper files) for all study team members and made available for monitors/auditors when requested for the length of the trial. Sites are to refer to their local policy/requirement for annual renewal of the FCOI during the continuing review process. Sites will be asked to verify that there have not been changes to any study team member's FCOI on the continuing review form submitted to the cIRB annually. Key study personnel should always disclose any FCOI as soon as it is presented so that it can be collected and submitted to the cIRB. Study team members' disclosures will be stored in WebDCU™ along with the site PI FID form in the designated site section.

Quality Assurance

Quality Assurance

- Training
  - Initiation
  - Study Updates - Inservices
  - Correspondence to study team
  - Certifications
- Standard Operating Procedures
- Database logic/queries
- Data Entry Audits
- Appropriate Delegation of Authority

IF you do it,
DOCUMENT
it in your study file

Good Clinical Practice

Basic Philosophy

Quality cannot be built in at the end of a study

Quality has to be built in at the BEGINNING

Questions?

Thank you!