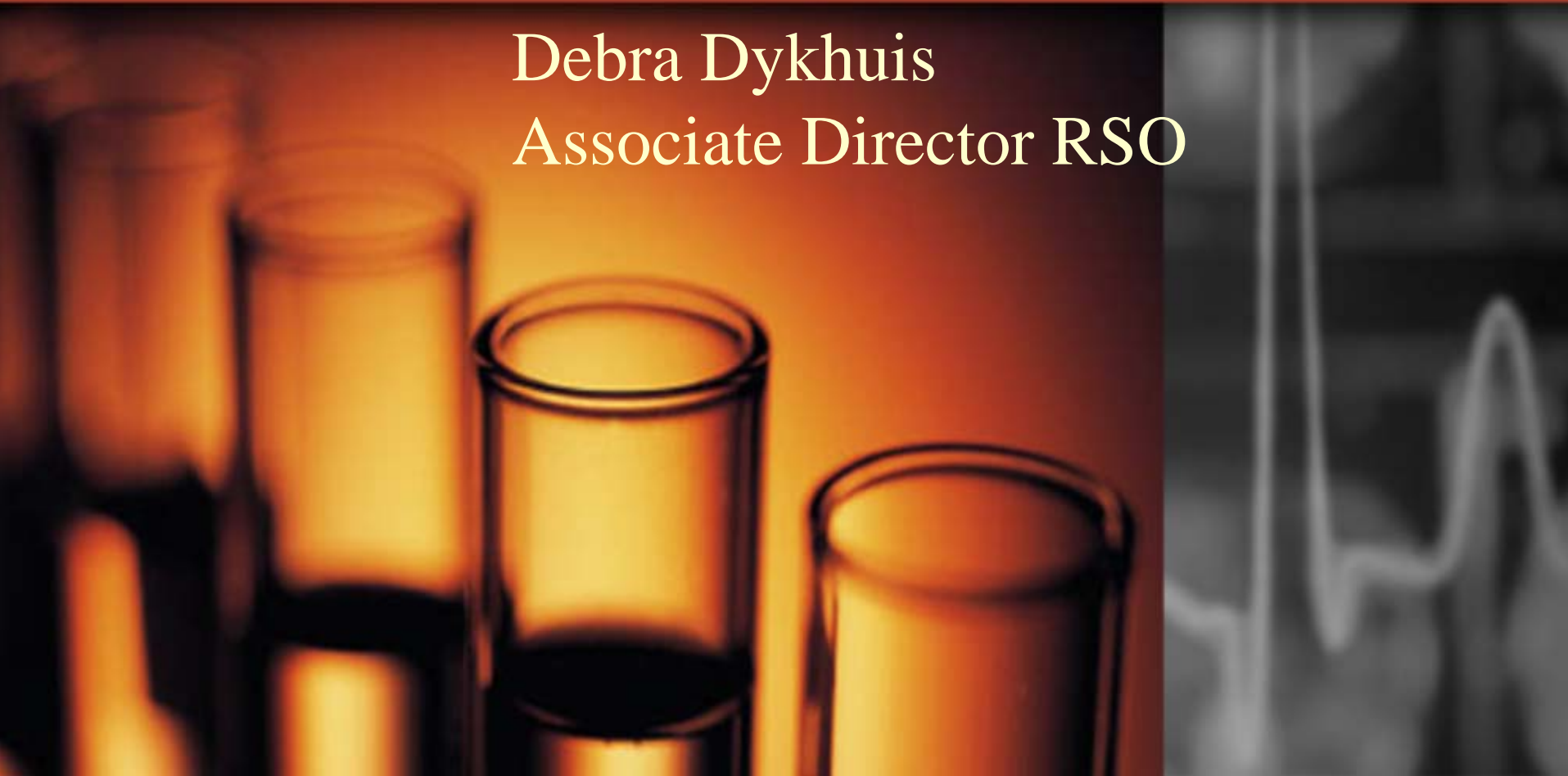


Essential Documents for the Conduct of a Clinical Trial

Debra Dykhuis
Associate Director RSO





Introduction

- Rationale for choosing this topic
 - AHC movement toward setting GCP (Good Clinical Practice) guidelines as the minimum standard for conduct of clinical research
 - Outside the AHC – the FDA and industry endorse GCP; and the NIH recognizes GCP as a standard for clinical trials

Introduction

- One way to find a copy of the GCP Guidelines:

<http://www.history.nih.gov/01Docs/historical/2020b.htm>

GCP Part 8 – Essential Documents for
the Conduct of a Clinical Trial

Introduction

- Outline for the presentation
 - Pre-study
 - During the study
 - Post study
 - Some documents are listed in each section
 - Q/A

Introduction

- Essential documents serve to demonstrate compliance with:
 - GCP standards
 - Applicable regulatory requirements
 - Collectively allow sponsor, regulatory authorities, & FDA to evaluate:
 - Conduct of a trial
 - Quality of data produced
- ❖ Keep in mind: Sponsor & regulatory authorities will look for these documents during an audit

Introduction

- Document retention required for
 - Study site
 - Sponsor
 - Both study site & sponsor

Reminder:

- ❖ In a study involving an IND or IDE – the person or company who holds the IND/IDE is the sponsor - Novartis, Medtronic, NIH, Dr. Kildare.
- ❖ As a sponsor, Dr. Kildare has same responsibilities as any industry sponsor.

Introduction

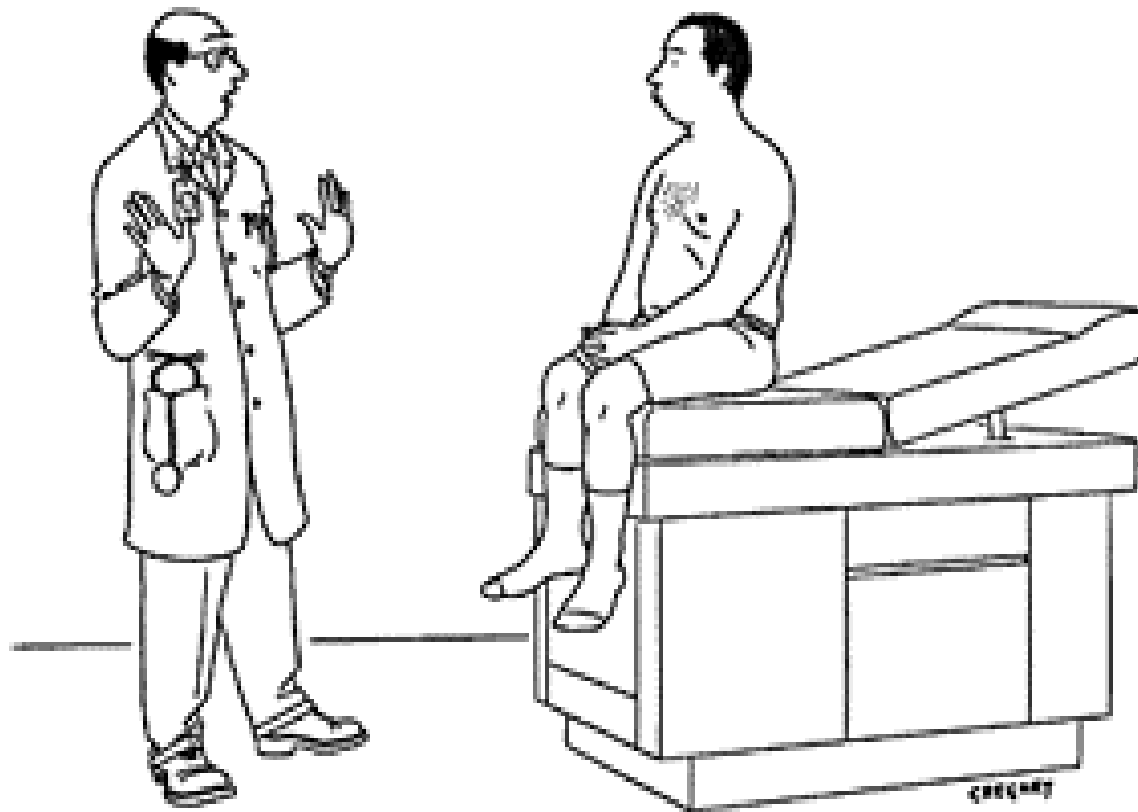
- How you apply GCP guidelines for essential documents will be affected by:
 - the role you are helping to support
 - the type of study you are working on

Introduction

- If the material presented today is brand new to you – don't panic
- The AHC has a *goal* of bringing all clinical research into compliance with GCP (and it won't be accomplished in a day)

Introduction

- Organization and consistency is the key
 - GCP does not provide a guide to organizing essential documents
 - You may be able to create your own way of organizing documents that works best for you and your team
 - Once you have created your plan for organizing documents – be consistent



"Whoa—way too much information!"

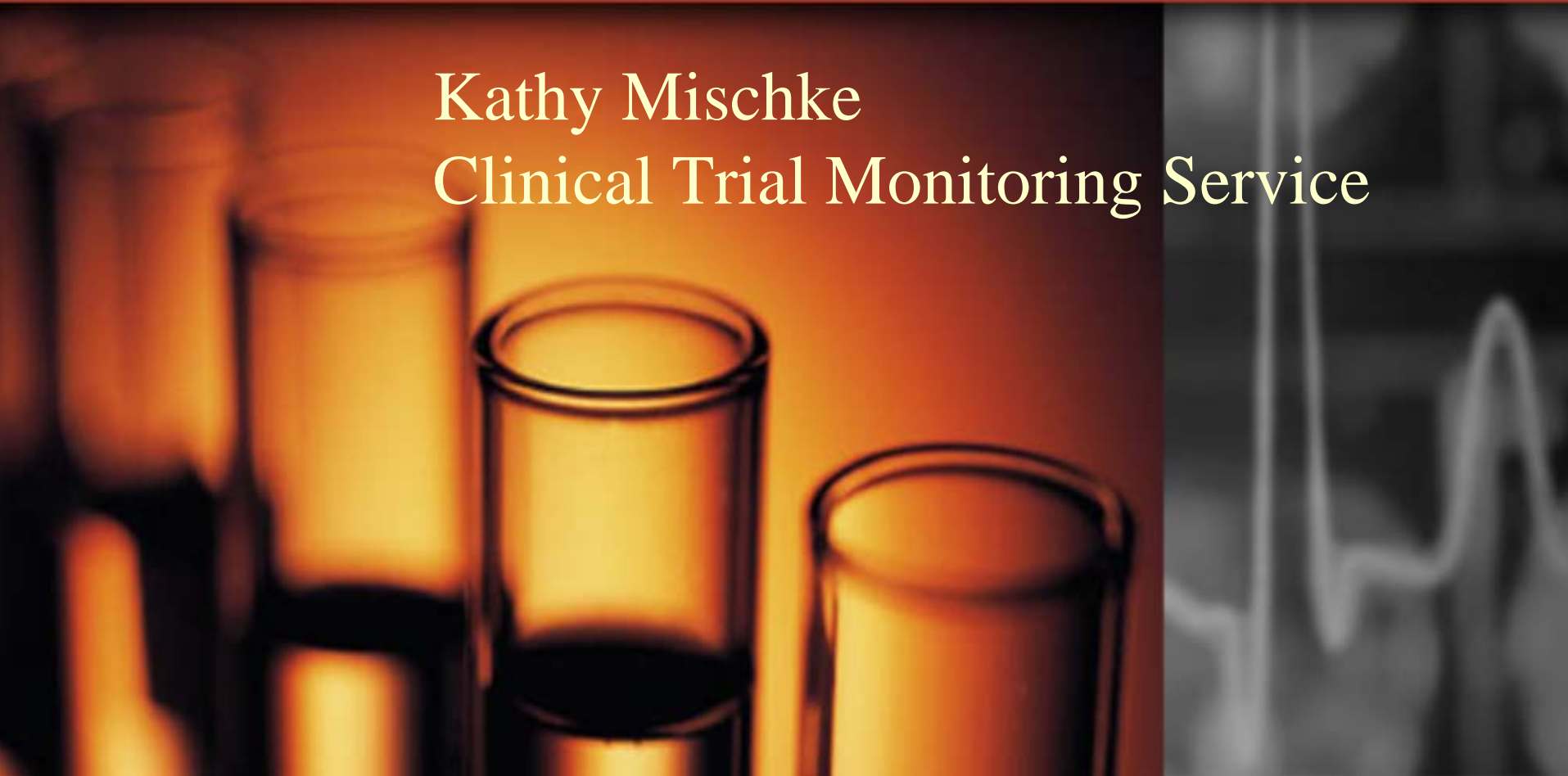
Introduction

How to get help.....

- Debbie Dykhuis 612-624-9154
- Jessy Thomas 612-624-2431
- Valerie O'Brien 612-625-8220
- Kathy Mischke 612-625-8904
- Janet Sauers 612-624-3238

Before Study Begins

Kathy Mischke
Clinical Trial Monitoring Service



Before Study Begins

- Investigator Brochure –To document that relevant and current scientific information about the investigational product has been provided to all investigators.
 - All study personnel are familiar with investigational product (package insert or other preprinted information)
- Located in the investigator/institution files and sponsor file.

Before Study Begins

- Signed protocol and amendments, if any, and sample case report forms (CRF).
- To document investigator and sponsor agreement to the protocol and amendment(s) and CRF
- Located in the investigator/institution files sponsor file.

Before Study Begins

- Information given to trial subject
 - Informed consent form (including all applicable translation)
 - To document informed consent
- Located in the Investigator/Institution and also Sponsor files
- Any other written information
 - To document that subjects will be given appropriate written information (content and wording) to support their ability to give fully informed consent
- Located in the Investigator/Institution and also Sponsor files
- Advertisement for subject recruitment (if used)
 - To document that recruitment measures are appropriate and not coercive
- Located in the investigator/institution files only

Before Study Begins

- Financial Aspects of the Trial
 - To document the financial agreement between the investigator/institution and the sponsor for the trial
 - This needs to be completed for all sites involved in the trial.
 - This includes all financial disclosures regarding the investigator and the manufacturer of the product being studied.
- Located in the investigator/institution and sponsor file

Before Study Begins

- Insurance statement (where required)
 - To document that compensation to subject(s) for trial related injury will be available.
 - Certificate of Assurance
- Located in the investigator/institution and sponsor file.

Before Study Begins

- Signed agreement between involved parties, e.g.
 - Investigator/institution and sponsor
 - Located in the investigator/institution and sponsor file
 - Investigator/institution and CRO
 - Located in the investigator/institution file and where required the sponsor file
 - CRO and sponsor
 - Located in the sponsor file only
 - Investigator/institution and authorities where required
 - Located in the investigator/institution and sponsor file

Before Study Begins

- Dated, documented approval/favorable opinion of IRB/IEC of the following:
 - Protocol and any amendments
 - CRF (if applicable)
 - Informed consent form(s)
 - Any other written information to be provided to subject
 - Advertisement for subject recruitment (if any)
 - Subject compensation (if any)
 - Any other documentation given approval/favorable opinion
- To document that the trial has been subject to the IRB/IEC review and given approval/favorable opinion. To identify the version number and date of the document(s)
- Located in the investigator/institution and sponsor file

Before Study Begins

- Institutional review board/independent ethics committee composition
 - To document the IRB/IEC is constituted in agreement with GCP
- Located in investigator/institution and where required in the sponsor file

Before Study Begins

- Regulatory authority authorization/approval/notification of protocol (if required)
 - To document appropriate authorization/approval/notification by the regulatory authority has been obtained prior to initiation of the trial in compliance with the applicable regulatory requirements
- Located when required in the investigator/institution and sponsor file

Before Study Begins

- Curriculum vitae or other relevant document evidencing qualifications of investigators and sub investigator
 - To document qualifications and eligibility to conduct trial and provide medical supervision of subjects.
- Located in investigator/institution and sponsor file

Essential Documents Required Before the Trial

Valerie O'Brien
Clinical Trial Monitoring Service

The background of the slide is split into two vertical panels. The left panel shows several glass test tubes in a rack, illuminated with a warm, orange glow. The right panel shows a white ECG (heart rate) line on a dark background.

Before the Trial Begins

- Normal values/ranges for lab tests & medical procedures
 - Document it! Many lab reports include normal ranges. If so, document this in a memo to file for the regulatory binder
 - Who must have a copy? Investigator & Sponsor
 - Recommended location: Regulatory binder
- ❖ Reminder: Sponsor (including sponsor-investigator) is responsible for obtaining normal values for all tests at all sites.

Before the Trial Begins

- Certification, accreditation, or other validation of lab/facility to perform tests & procedures
 - Document it! Demonstrates site competence to perform protocol-required tests, and supports reliability of results
 - Who must have a copy? Site & Sponsor

Before the Trial Begins

- Sample of label attached to investigational product container
 - Document it! Demonstrates compliance with labeling regulations & appropriateness of instructions provided to subjects
 - Who must have a copy? Sponsor
- ❖ Reminder: Sponsor-Investigator using IDS should file a copy of the label in the regulatory binder.

Before the Trial Begins

- Instructions for handling investigational products & trial-related materials
 - Document it! Demonstrate that instructions given to investigators ensure proper storage, packaging, dispensing, and disposition of investigational products and trial-related materials
 - Who must have a copy? Site & Sponsor
- ❖ Note: Not required if already included in protocol or Investigator Brochure

Before the Trial Begins

- Shipment records for investigational products and trial-related materials
 - Document it!
 - Shipment dates, batch #, shipping method, shipping & storage conditions
 - Allows tracking of batches of drugs/product
 - Demonstrates oversight & accountability of product
 - Who must have a copy? Site & Sponsor
- ❖ Reminder: More accountability records are needed once trial begins

Before the Trial Begins

- Certificates of analysis of investigational products shipped
 - Document it! Identity, purity, and strength of products to be used
 - Who must have a copy? Sponsor

Before the Trial Begins

- Decoding procedures for blinded trials
 - Document it! In an emergency, allows identification of product to be revealed without breaking blind for remaining subjects
 - Who must have a copy? Site, Sponsor, & 3rd party if applicable
 - Recommended location: Someplace accessible at 3:15 a.m. when subject shows up in ER. Not in a locked cabinet at site.
- ❖ Reminder: If using IDS, usually the telephone # is for the Fairview inpatient pharmacy (which needs the unblinding procedure).

Before the Trial Begins

- Master randomization list
 - Document it! Demonstrates the integrity of the process used to assign subjects to treatment or control groups. Supports reliability of unbiased results.
 - Who must have a copy? Sponsor, & 3rd party if applicable

Before the Trial Begins

- Pretrial monitoring report
 - Document it! Shows site is suitable to conduct trial
 - Review protocol requirements
 - Assess subject pool
 - Evaluate experience of site
 - Evaluate facilities (lab, equipment required, exam area, pharmacy, etc.)
 - Review responsibilities of the research team in obtaining consent and CRFs, etc.
 - Who must have a copy? Sponsor
- ❖ Note: The sponsor uses pretrial visits to determine which sites qualify to conduct the trial. May be combined with Trial Initiation visit

Before the Trial Begins

- Trial initiation monitoring report
 - Document it! Demonstrate that protocol requirements were reviewed and site trained:
 - Subject selection & consent processes
 - Protocol requirements
 - CRF completion
 - Essential documents
 - Identification of source documents
 - AE reporting requirements & other trial-related issues
 - Who must have a copy? Site & Sponsor
- ❖ Note: Investigator Mtg. may take place of this visit. May be combined with the pre-trial visit.

Before the Trial Begins

Remember:

If it isn't documented, it didn't happen!

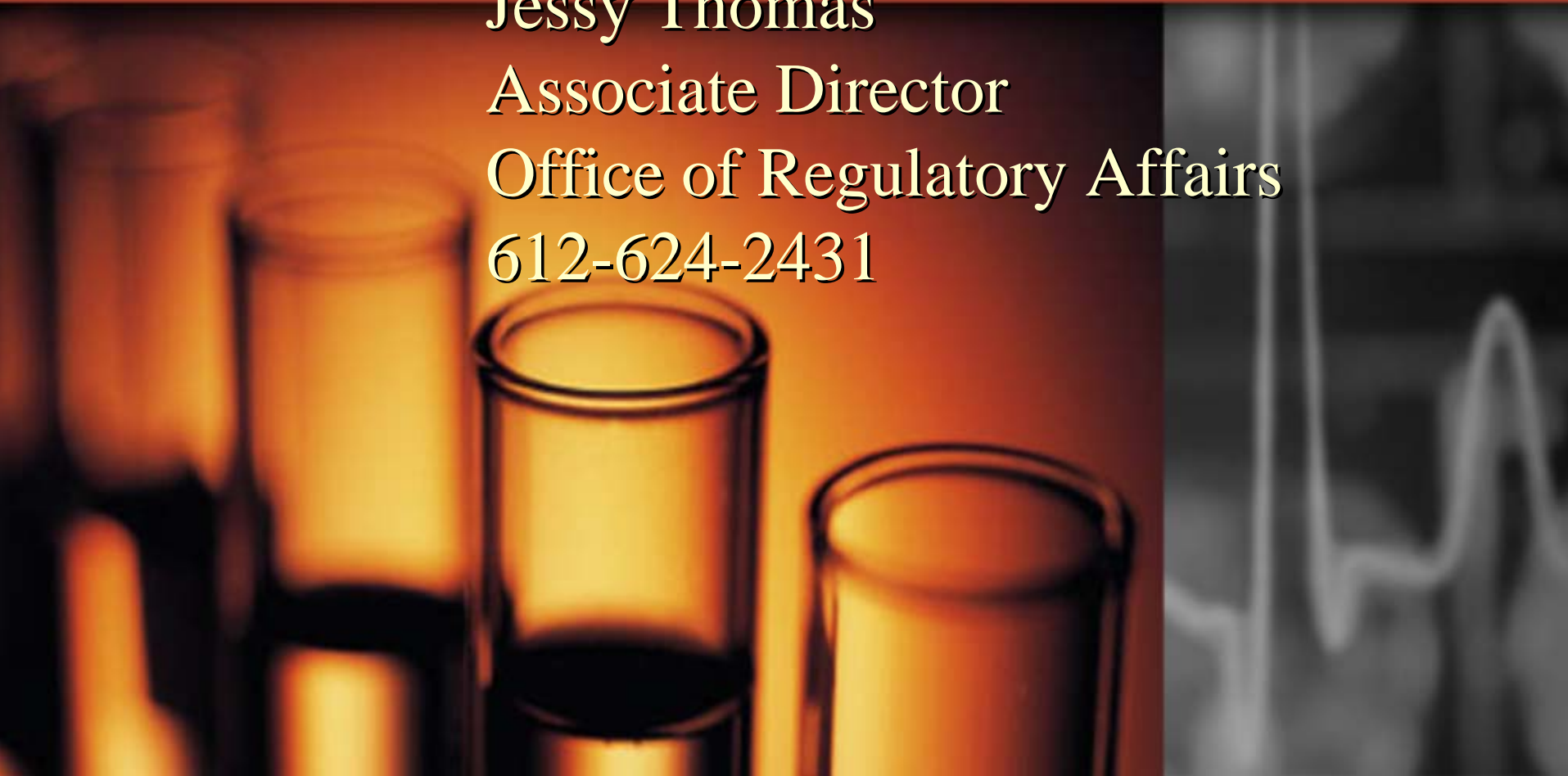
Essential Documents During the Clinical Conduct of the Trial

Jessy Thomas

Associate Director

Office of Regulatory Affairs

612-624-2431



Don't read like the Panda!



Example:

“Your participation in this study is entirely voluntary and you are free to refuse to take part or withdraw at any time, even after you sign below, without jeopardizing your current or future relations with the University of Minnesota. If you choose not to participate, it will not affect your participation in the Study.



“nice lady – Says she wants to drop out – I
talked her in to



Few years later—

“She wished she never signed up for the
study”



Several years later----

“no I don’t want to give you any information.
You have enough.”

Investigator's Brochure updates

To document that investigator is informed in a timely manner of relevant information as it becomes available



All revisions to:

- Protocol/amendments and CRF
- Informed consent form
- Any other written information provided to subjects
- Advertisement for subject recruitment (if used)

To document revisions of these trial-related documents that take effect during trial

Dated, documented approval of IRB/IEC of the following:

- Protocol amendments

- Revisions of:

- Informed consent form

- Any other written information provided to the subjects

- Advertisement for subject recruitment

- Continuing review of trial

To document that the revisions have been approved by the IRB/IEC



Curriculum vitae for new investigators and sub-investigators



Updates of medical/ laboratory/technical procedures/tests

- Certification or
- Accreditation or
- Established quality control and/or external quality assessment or
- Other validation (where required)

To document that tests remain adequate throughout the trial period



Documentation of investigational
products and trial-related materials
shipment

For tracking and accountability



Monitoring visit reports

To document site visits by, and findings of, the monitor

Documentation of relevant communications

- Letters
- Meeting notes
- Notes of telephone calls

To document any agreements or significant discussions regarding trial conduct, adverse event (AE) reporting, protocol violations



Signed informed consent forms

To document that consent is obtained in accordance with GCP and protocol and dated prior to participation of each subject in trial



Signed HIPAA forms



Source documents

To document the existence of the subject and substantiate integrity of trial data collected. To include original documents related to the trial, to medical treatments, and history of subject



Signed, dated and completed case report forms

To document that the investigator or authorized member of the investigator's staff confirms the observations recorded.




Documentation of CRF corrections

To document all changes/ additions or corrections made to CRF after initial data were recorded



Notification by investigator to sponsor of
serious adverse events and related reports



Notification by sponsor and/or investigator,
where applicable to:
regulatory authorities and IRB(s)/IEC(s) of
unexpected serious adverse drug reactions and
of other safety information



Notification by sponsor to investigators of
safety information



Interim or annual reports to IRB/IEC and
authorities



Subject Screening Log

Subject identification code list

To document that investigator/institution keeps a confidential list of names of all subjects.

Allows investigator/institution to reveal identity of any subject



Subject enrollment log

To document chronological enrollment
of subjects by trial number



Investigational products accountability at the site

To document that investigational products have been used according to the protocol



Signature sheet



Record of retained body fluids/tissue samples (if any)

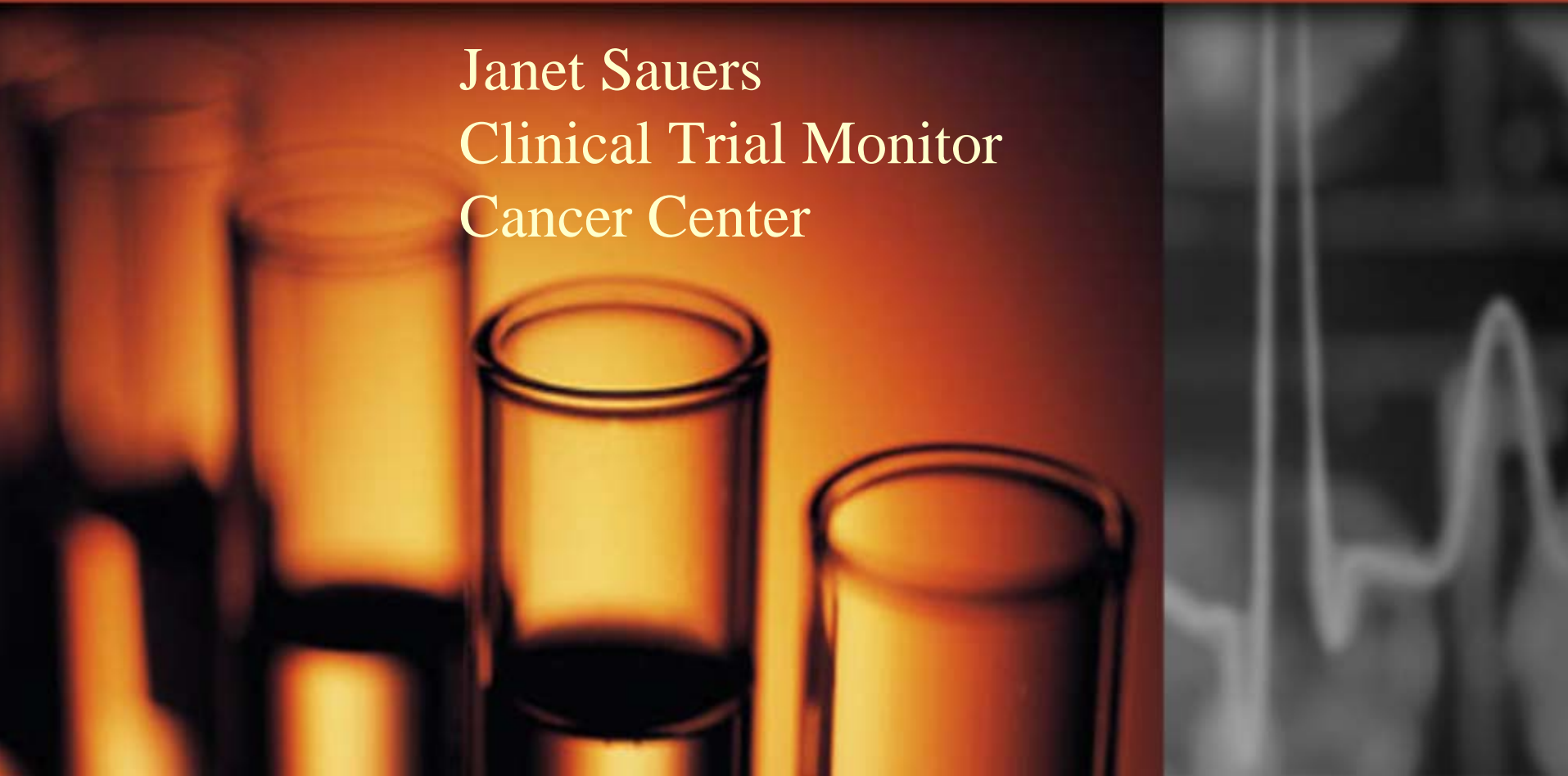
To document location and identification of retained samples if assays need to be repeated

Questions ?



Essential Documents After Completion or Termination of the Trial

Janet Sauers
Clinical Trial Monitor
Cancer Center



Investigational Product(s)

Accountability at Site

To document that the investigational product(s) have been used according to the protocol. To document the final accounting of investigational product(s) received at the site, dispensed to the subjects, returned by the subjects and returned to the sponsor

Located in the investigator/institution and sponsor files

Examples

- final reconciliation of the drug accountability log
- shipping records or receipts
- notes-to-file for any unaccountable vials, blister packs, etc.

Documentation of Investigational Product(s) Destruction

To document destruction of unused investigational product(s) by the sponsor or at the site

Located in the investigator/institution (if destroyed at site) and sponsor files

Examples

- destruction records for any product(s), used or unused, for which the sponsor has given permission for or requested on-site destruction
- may record destruction directly on drug log if allowed by sponsor

Completed Subject Identification Code List

To permit identification of all subjects enrolled in the trial in case follow-up is required. List should be kept in a confidential manner and for agreed upon time

Located in the investigator/institution file

Examples

- electronic or paper database which links subject ID# to name of subject
- can be used if necessary to inform study participants of new toxicities associated with use of the investigational product that are late developing

Audit Certificate (if required)

To document that an audit was performed

Located in the sponsor file

Example

- certificate indicating date(s) of an audit and names of individuals conducting the audit

Final Trial Close-Out Monitoring Report

To document that all activities required for trial close-out are completed, and copies of essential documents are held in the appropriate files

Located in the sponsor file

Includes

- verification that all case report forms were reviewed and collected
- verification that all queries were resolved and collected
- verification that requirements for records retention were discussed
- verification that all SAE reports were closed and collected
- verification that written IRB notification of study closure was done

Includes

- verification that study supplies were returned or destroyed
- verification that the regulatory file was reviewed to ensure that all required essential documents were present
- documentation separate from the trial regulatory file to indicate where the essential document file will be stored and for how long

Treatment Allocation and Decoding Documentation

Returned to sponsor to document any decoding that may have occurred

Located in the sponsor file

Examples

- documentation of any subject decoding done by site rather than by sponsor for blinded studies
- site emergency decoding envelopes for blinded studies



Final Report by Investigator to IRB/IEC Where Required, and Where Applicable , to the Regulatory Authority(ies)

To document completion of the trial

Located in the investigator/institution
file

Example

- written notification to IRB of study closure

Clinical Study Report

To document results and interpretation of the trial

Located in the investigator/institution (if applicable) and sponsor files

Example

- IRB study closure report

University Records Retention Requirements

- Records retention schedule at:

<http://recmgmt.finop.umn.edu/retention.htm>

- Records retention policy (Financial Policy 3.9.1) at:

http://www.fpd.finop.umn.edu/groups/ppd/documents/policy/record_retention.cfm

IRB Records Retention Requirements

- **IRB, IACUC, IBC Records Retention**

- Investigators should maintain a file of all documents concerning their research. The principal investigator's **records** should be the mirror image of the IRB, IACUC, or IBC's: where IRB, IACUC, or IBC holds an original, the principal investigator should hold a copy, and vice versa.
- The documents that researchers should have on file include:
 - a copy of the original application submitted to IRB, IACUC, and/or IBC
 - an original of the committee's response,
 - a copy of responses to the committee's stipulations or requests for additional information,
 - the original notice of final approval,
 - a copy of the Certification of Approval sent by the RSPP office to any funding agencies,
 - copies or originals of all other correspondence with the IRB, IACUC, or IBC
 - copies of completed continuing review forms and attachments,
 - the original notice of renewal of approval and certification, where applicable, and
 - copies of any inspection reports and follow-up action.

The investigator should retain these **records** for at least three years, although every discipline has its own **retention** standards. In some fields, researchers may need to retain their **records** for as long as seven years. These **records** are subject to inspection by federal authorities. Sanctions for incomplete or nonexistent **records** include suspension of funding, fines, exclusion from future funding, and suspension of laboratory access.

GCP Records Retention Requirements

- For studies done to support a drug or device approval by the FDA – at least 2 years after:
 - FDA approval,
 - no more requests for approval are contemplated, or
 - after work on a new drug or device has been discontinued

GCP Records Retention Requirements

- If you are doing an industry sponsored study – check your research agreement for retention requirements
- GCP states that it is the responsibility of the sponsor to inform the investigator/institution when documents no longer need to be retained (see GCP 4.9.5)