# Clinical Trial Documentation


Module 5

# Trial Documentation

- Necessary for conduct of trial- From Scratch to Finish
- Examples:
  - Protocol
  - Investigator's Brochure
  - Informed Consent Document

# Definition of Protocol

"Written mechanism that describes how the study design will be implemented."

**Per ICH-GCP (1.44)**

"A document that describes the objectives, design, methodology, statistical considerations and organization of a trial. It also gives the background and the rationale for the trial."

# Why a protocol?

- Check if objectives can be achieved
- Check feasibility of the study
- Maintain standardization throughout the project
- Prevent failure to collect critical information
- Lay down rules
- Obtain approval from regulators and ethics committee
- Apply for funds
- Easier to write an article

# Elements of a protocol

- TITLE
- NAMES OF INVESTIGATORS
- NAME OF THE INSTITUTION
- INTRODUCTION
- OBJECTIVES
  - Primary (Must evaluate)
  - Secondary (Good to evaluate)
- METHODOLOGY -Study design
- STUDY POPULATION
  - Selection
  - Recruitment process
  - Inclusion and exclusion criteria Withdrawal
  - Number to be screened/recruited (Sample size)

# Elements of a protocol - contd

- Efficacy/ endpoints
- Efficacy analyses
- Safety analyses
- Safety Reporting
- Statistical analysis plan
- Appendices
  - Case report forms (not always mandatory)
  - Informed consent
  - Institutional review board approval (in the final trial master file)
  - Questionnaire (if applicable)
  - Declaration of Helsinki

# Protocol Synopsis Template

| | |
|---|---|
| **Title:** | **Be as specific and descriptive as possible** |
| **Rationale:** | **State justification for the study** |
| **Objective:** | **State either as question(s) to be answered or as hypothesis to be tested** |
| **Setting:** | **State where the study will be done and by whom** |
| **Design:** | **survey or experiment; retrospective, cross-sectional or prospective; parallel-group or crossover; open, single-blind or double-blind; etc.** |
| **Patients:** | **State number and type of patients, with essential inclusion criteria** |
| **Interventions:** | **State what will be done, how, when, how often, how long, etc.** |
| **Outcome measures:** | **State what will be measured for efficacy and for safety** |
| **Data analysis plan:** | **State how the outcome measures will be analyzed and presented** |

# Investigator Brochure

- Basic document required in a clinical trial of a new drug
- Compiles the clinical and non-clinical data relevant to the study of the product in humans
- The pharmaceutical company sponsoring the study provides a copy to each principal investigator prior to the start of a clinical trial

# Contents

- a description of the drug substance and the formulation
- a summary of the pharmacological and toxicological effects,
- a summary of information relating to its safety and effectiveness in humans, and
- a description of possible risks and adverse reactions to be anticipated, and the precautions or special monitoring that the investigator should take

# Contents as per IB

- Title page
- Table of contents
- Summary
- Introduction
- Confidentiality statement
- Physical, Chemical and Pharmaceutical properties and formulation

# Contents as per IB (contd)

- Non-clinical studies
  - Pharmacology
  - Pharmacokinetics
  - Toxicology
- Effect on humans
  - Pharmacokinetics
  - Efficacy
  - Safety
  - Marketing experience

# Informed Consent Form

**Guidance for Information sheets for adults**

- The level of detail should be appropriate to the nature of the study and the population to be studied
- Concern about Information Sheets (IS) are becoming lengthy and complex for recruitment purposes
- So, its recommended that, the IS divided into Part 1 and Part 2

# Part 1:

- What the research is about?
- The condition or treatment under study
- Voluntary nature of involvement
- What will happen to the participant during and after the trial?
- What usual treatment may be withheld?
- Participant's responsibilities
- Potential risks

# Part 2:

- Confidentiality and data protection
- Communication with the GP
- Indemnity and compensation
- Publication, etc.
- Which should be read and understood before the participant can decide whether they want to take part and give informed consent

# Language Used:

- Simple, non-technical terms
- Easily understood
- Short words, sentences and paragraphs with clear subheadings
- Manageable text & font size
- Bullet pointed lists used where instead of unbroken text
- Invitational tone instead of overly persuasive

# General comments on information for children (minors) and young people

- When designing information sheets for children, researchers need to consider their
  - likely attention span
  - potential fear of hospitals/procedures
  - mental capacity if affected by disease
  - disease severity
  - previous experience of illness (some children have greater knowledge as the result of long term illness e.g. cystic fibrosis).
  - It is important to give information about how the study will affect the child at home, school and his/her social activities

# IS for children aged

**13 to 15**

- Study title
- What is research?
- Why is this project being done?
- Invitation to take part. Why have I been asked to take part
- Did anyone else check the study is OK to do?

**6 to 12**

- Study title
- Invitation paragraph
- Why are we doing this research?
- What is the medicine, device or procedure that is being tested?
- Why have I been asked to take part?

# Essential regulatory documents & records

# "Essential" Documentation

**Documentation, Record Keeping, and Retention**

- Permits evaluation of the conduct of a study
- Permits evaluation of data collected
- Demonstrates GCP and compliance with applicable regulatory requirements
- Facilitates study management and oversight
- Allows for monitoring and evaluation of practices

# Essential Documents - Regulatory Binder

- Essential Documents must be organized and retained for the conduct of clinical studies.
- These organized documents are referred to as the REGULATORY BINDER
- The binder must be kept at the Investigator's clinical site

**TIP: Synonyms: Investigator Binder = Regulatory Binder = Investigational Site File (ISF) = Study Binder = Master Trial File (MTF)

# Essential Study Documents Overview

- Study Protocol – signed, dated by all entities (PI, sponsor)
- Study Protocol Amendments
- Informed Consent
- IRB Approval(s)
- Delegate of Authority and Log of Responsibilities
- Curriculum Vitae (CV's) current
- Financial Disclosures – 1571s and 1572s

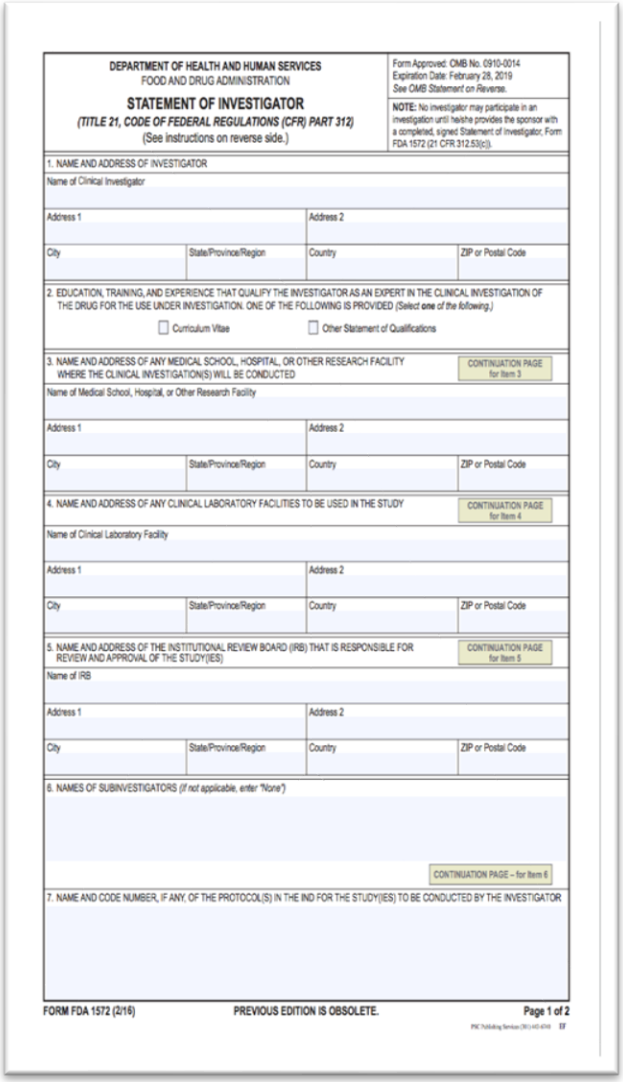
# Essential Study Documents Overview (contd)

- Protocol Training Documentation
- Training Documentation to conduct research, study-related duties or functions
- Adverse Events and/or unanticipated events
- Study Protocol Deviations
- Note to File (NTF)
- Standard Operating Procedures(SOPs); Manual of Procedures (MOPs) and or Appendixes
- All communication s between entities (PI, research team, CRO, sponsors, governing boards)

# Essential Study Documents Overview (contd)

- Clinical investigator's brochure (drug or device)
- Package insert; include labeling for approved medications
- Device information sheet/manual
- Documentation of study-related training
- Documentation of shipping biologics (IATA)
- Procedure training log
- Laboratory reference ranges
- Copy of laboratory certification and accreditations
- Lab Specimen Tracking Log
- Serious adverse event log

# Example: Form FDA 1572:



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

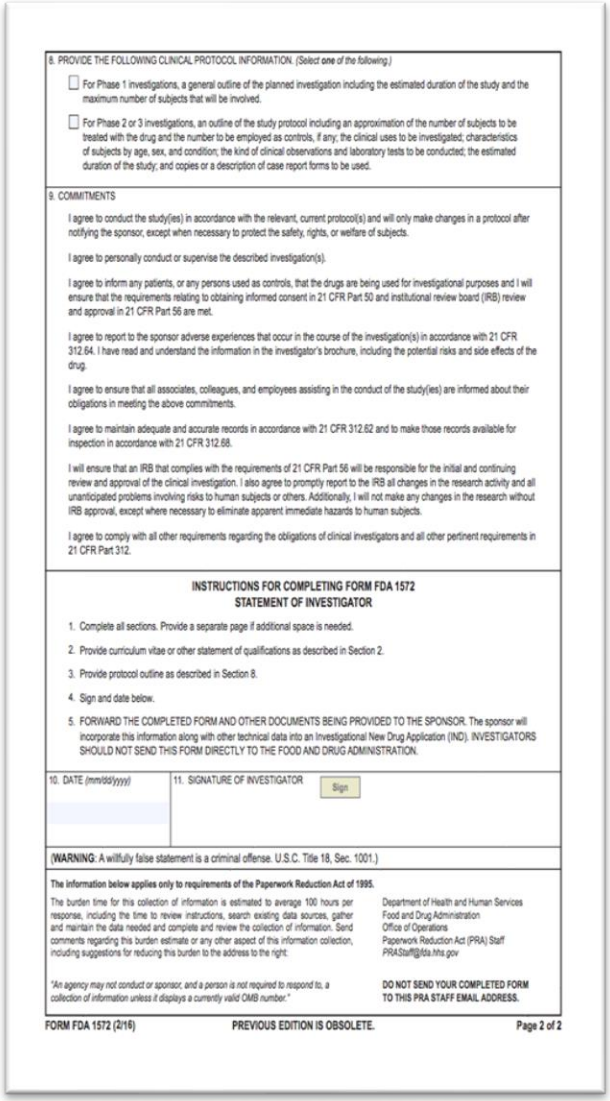
City | State/Province/Region | Country | ZIP or Postal Code

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

# Example: Delegation of Authority (DoR)

**Delegation of Responsibilities Log**

| Investigator Name: | Protocol: | Site Number: |
|---|---|---|
| | | |

List staff to whom the Principal Investigator (PI) has delegated significant study-related duties.

| Name | Responsibilities* | Initials | Signature | Start Date | End Date | PI Initials/Date |
|---|---|---|---|---|---|---|
| | | | | | | |
| | | | | | | |
| | | | | | | |
| | | | | | | |
| | | | | | | |

By initialing above, I, the PI, declare that during the conduct of the above study, I have delegated the following study-related activities:

| *Responsibilities Legend | | |
|---|---|---|
| 1. Administer Consent | 6. Randomize Subjects | 11. Complete Study Forms |
| 2. Screen Subjects | 7. Dispense Study Drug | 12. Provide Discharge Instructions |
| 3. Obtain Medical History | 8. Drug Accountability | 13. Make Follow-up Phone Calls |
| 4. Perform Physical Exam | 9. Assess Adverse Events | 14. Query Management |
| 5. Determine Eligibility | 10. Complete Source Documents | 15. |

Signature of Principal Investigator: _____ Date: _____

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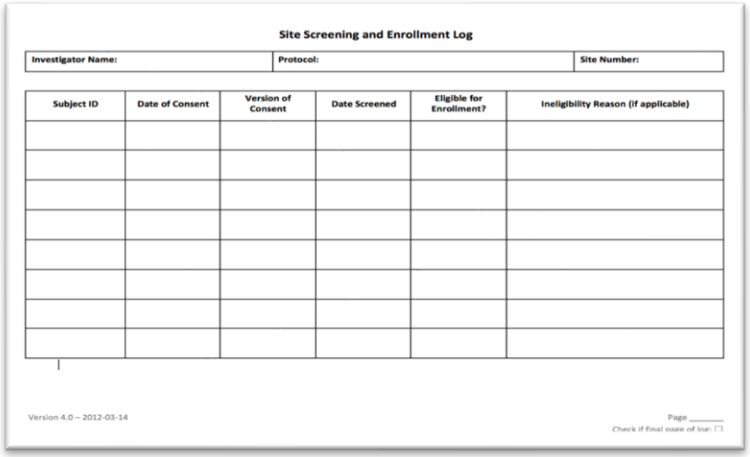
## Screening/Enrollment

- Subjects who were screened; reasons for screen failure
- Enrollment log
- Site screening plan



Site Screening and Enrollment Log

| Investigator Name: | Protocol: | Site Number: |
|---|---|---|

| Subject ID | Date of Consent | Version of Consent | Date Screened | Eligible for Enrollment? | Ineligibility Reason (if applicable) |
|---|---|---|---|---|---|
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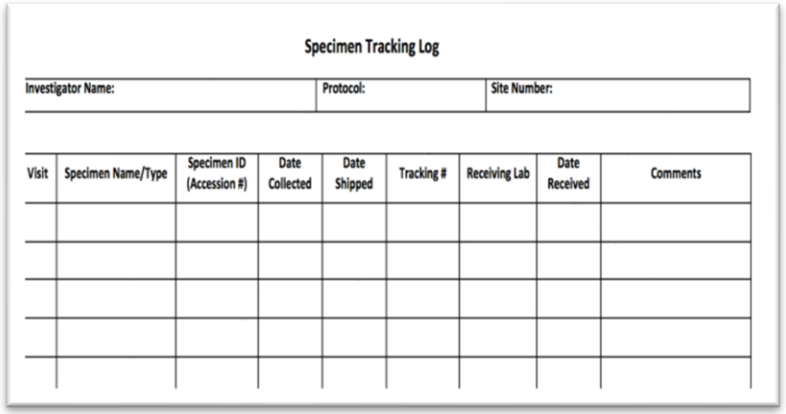
## Signed Consent Documents

- All original signed IRB approved and stamped versions consent documents

## Subject Visit Tracking Log

- Log all enrolled subject visits
- Reasons for Early Termination (ET)
- Tracks/keeps scheduled visits as per protocol



Specimen Tracking Log

| Investigator Name: | Protocol: | Site Number: |
|---|---|---|

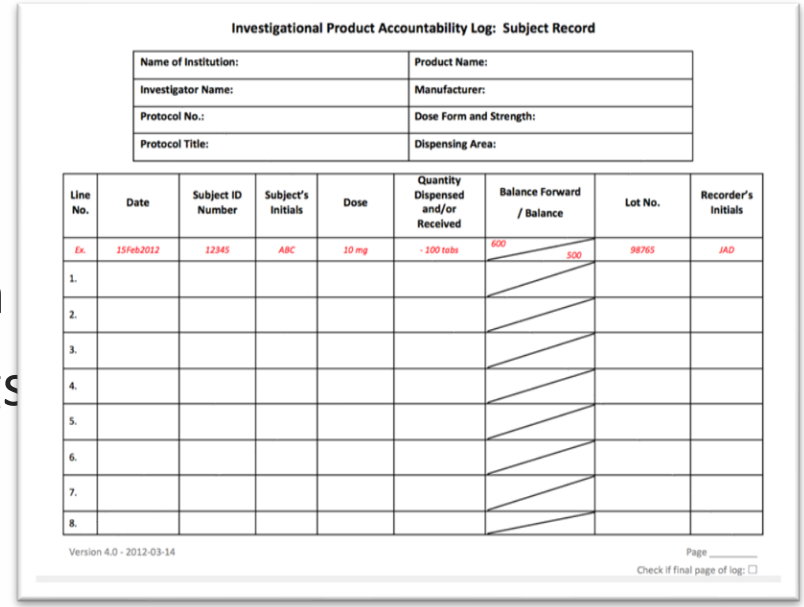
| Visit | Specimen Name/Type | Specimen ID (Accession #) | Date Collected | Date Shipped | Tracking # | Receiving Lab | Date Received | Comments |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | | |
| | | | | | | | | |
| | | | | | | | | |
| | | | | | | | | |
| | | | | | | | | |

## Subject Identification Code List

- Confidential list of subject names
- Link between identity and study code to allow only the
- Investigator to reveal identity of any subject

# Study Product Records

- Documentation of study product disposition
- Investigational Product Accountability Log: Stock Record
- Investigational Product Accountability Log: Subject
- Dispense Record
- Specimen sample log
- Shipping documentation
- Storage temperature logs



**Investigational Product Accountability Log: Subject Record**

| | |
|---|---|
| Name of Institution: | Product Name: |
| Investigator Name: | Manufacturer: |
| Protocol No.: | Dose Form and Strength: |
| Protocol Title: | Dispensing Area: |

| Line No. | Date | Subject ID Number | Subject's Initials | Dose | Quantity Dispensed and/or Received | Balance Forward / Balance | Lot No. | Recorder's Initials |
|---|---|---|---|---|---|---|---|---|
| Ex. | 15Feb2012 | 12345 | ABC | 10 mg | - 100 tabs | 600 / 500 | 98765 | JAD |
| 1. | | | | | | | | |
| 2. | | | | | | | | |
| 3. | | | | | | | | |
| 4. | | | | | | | | |
| 5. | | | | | | | | |
| 6. | | | | | | | | |
| 7. | | | | | | | | |
| 8. | | | | | | | | |

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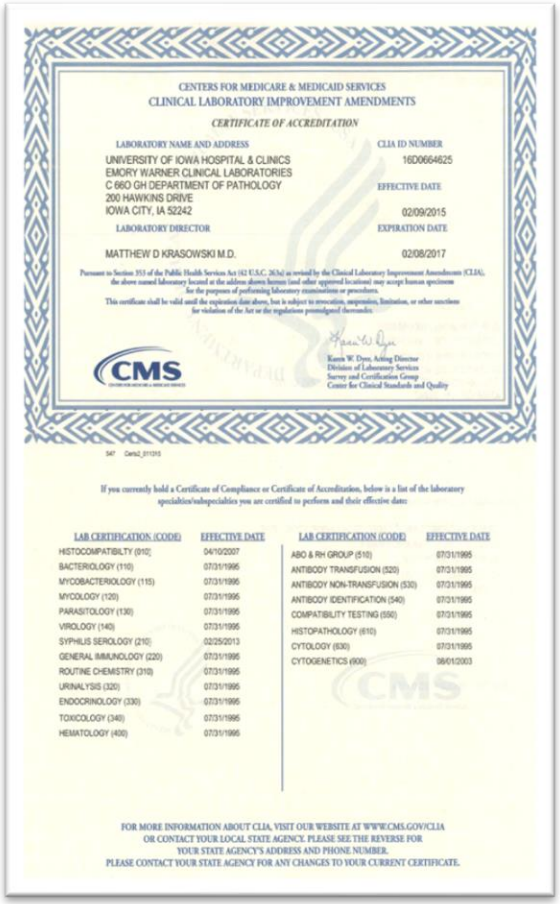
# Local Clinical Lab Certificates



CENTERS FOR MEDICARE & MEDICAID SERVICES
CLINICAL LABORATORY IMPROVEMENT AMENDMENTS
*CERTIFICATE OF ACCREDITATION*

LABORATORY NAME AND ADDRESS
UNIVERSITY OF IOWA HOSPITAL & CLINICS
EMORY WARNER CLINICAL LABORATORIES
C 660 GH DEPARTMENT OF PATHOLOGY
200 HAWKINS DRIVE
IOWA CITY, IA 52242

CLIA ID NUMBER
16D0664625

EFFECTIVE DATE
02/09/2015

EXPIRATION DATE
02/08/2017

LABORATORY DIRECTOR
MATTHEW D KRASOWSKI M.D.

Pursuant to Section 353 of the Public Health Services Act (42 U.S.C. 263a) as revised by the Clinical Laboratory Improvement Amendments (CLIA), the above named laboratory located at the address shown hereon (and other approved locations) may accept human specimens for the purposes of performing laboratory examinations or procedures.
This certificate shall be valid until the expiration date above, but is subject to revocation, suspension, limitation, or other sanctions for violation of the Act or the regulations promulgated thereunder.

CMS

Karen W. Dyer, Acting Director
Division of Laboratory Services
Survey and Certification Group
Center for Clinical Standards and Quality

If you currently hold a Certificate of Compliance or Certificate of Accreditation, below is a list of the laboratory specialties/subspecialties you are certified to perform and their effective date:

| LAB CERTIFICATION (CODE) | EFFECTIVE DATE | LAB CERTIFICATION (CODE) | EFFECTIVE DATE |
|---|---|---|---|
| HISTOCOMPATIBILTY (010) | 04/10/2007 | ABO & RH GROUP (510) | 07/31/1995 |
| BACTERIOLOGY (110) | 07/31/1995 | ANTIBODY TRANSFUSION (520) | 07/31/1995 |
| MYCOBACTERIOLOGY (115) | 07/31/1995 | ANTIBODY NON-TRANSFUSION (530) | 07/31/1995 |
| MYCOLOGY (120) | 07/31/1995 | ANTIBODY IDENTIFICATION (540) | 07/31/1995 |
| PARASITOLOGY (130) | 07/31/1995 | COMPATIBILITY TESTING (550) | 07/31/1995 |
| VIROLOGY (140) | 07/31/1995 | HISTOPATHOLOGY (610) | 07/31/1995 |
| SYPHILIS SEROLOGY (210) | 02/25/2013 | CYTOLOGY (630) | 07/31/1995 |
| GENERAL IMMUNOLOGY (220) | 07/31/1995 | CYTOGENETICS (600) | 08/01/2003 |
| ROUTINE CHEMISTRY (310) | 07/31/1995 | | |
| URINALYSIS (320) | 07/31/1995 | | |
| ENDOCRINOLOGY (330) | 07/31/1995 | | |
| TOXICOLOGY (340) | 07/31/1995 | | |
| HEMATOLOGY (400) | 07/31/1995 | | |

FOR MORE INFORMATION ABOUT CLIA, VISIT OUR WEBSITE AT WWW.CMS.GOV/CLIA
OR CONTACT YOUR LOCAL STATE AGENCY. PLEASE SEE THE REVERSE FOR
YOUR STATE AGENCY'S ADDRESS AND PHONE NUMBER.
PLEASE CONTACT YOUR STATE AGENCY FOR ANY CHANGES TO YOUR CURRENT CERTIFICATE.

COLLEGE of AMERICAN PATHOLOGISTS

CAP ACCREDITED
COLLEGE of AMERICAN PATHOLOGISTS

The College of American Pathologists
certifies that the laboratory named below

**University of Iowa Hospitals & Clinics**
**Emory Warner Clinical Laboratories**
**Iowa City, Iowa**
**Matthew D. Krasowski, MD,PhD**

CAP Number: 1768801
AU-ID: 1183440
CLIA Number: 16D0664625

has met all applicable standards for accreditation and is hereby accredited by the College of American Pathologists' Laboratory Accreditation Program. Reinspection should occur prior to November 20, 2017 to maintain accreditation.

Accreditation does not automatically survive a change in director, ownership, or location and assumes that all interim requirements are met.

Chair, Commission on Laboratory Accreditation

President, College of American Pathologists

https://www.medicine.uiowa.edu/pathology/research/pathology-clinical-trials-support-core

# Clinical Site Monitoring Visits

- Monitoring Visit Signature Log
- Each Visit's correspondence
- Post visit follow up letters

# Confidentiality & Security

- Filing space should be available for the storage of TMF and local ISF during the conduct of the clinical trial. ISFs will normally be stored in an investigator's office or local filing area
- At the end of the trial the files must be transferred to a suitable archiving facility

# Record Keeping

Investigators must ensure that data are recorded and stored correctly and accurately. This not only includes data recorded on Case Report Forms (CRFs) but also all original source data(patient medical notes for example), laboratory test results, radiological images and pharmacy data (drug dispensing records and drug accountability records for example)

# Environmental Conditions

- The minimum requirement is for documentation to be stored in conditions that minimize the risk of damage or loss of information
- The risk of damage from water should be reduced by storing documentation above floor level and away from overhead water pipes
- Documentation should be located in areas with minimal variation in temperature and humidity if stored long periods of time