DMID-CROMS ERDG INFORMATION SHEET

Laboratory Essential Regulatory Documents

This information sheet summarizes the basis for and requirements of DMID-CROMS essential document file documentation and record-keeping related to:

- DMID Clinical Central Laboratory
- Clinical Laboratories
- Research Laboratories
- Point of Care Testing, Certificates of Waiver
- Laboratory Confirmatory Testing
- Safety Labs (including lab work, blood work, eligibility testing, screening, baseline testing, post-exposure testing)

In accordance with ICH GCP 8.2.11 and 8.2.12 and DMID guidelines, study essential document files must include documentation that identify all laboratories used during the course of a study, the laboratory normal values or ranges for all laboratory tests done, and documentation of CAP, CLIA, or State laboratory certification. Studies under an IND also require completion and maintenance of an FDA Form 1572 including clinical laboratories and locations where subjects will be seen, study procedures will be performed, and clinical data will be generated or collected.

It is the responsibility of the Investigator to ensure compliance with GCP, IRB, and applicable regulatory requirements.

This information sheet for laboratory essential regulatory documents **is not** protocol or vendor-specific and **does not** include information related to actual laboratory procedures. For information related to specimen collection, processing, labeling, shipping information, lab test value reporting, or data discrepancy resolution, refer to the protocol-specific manual of operational procedures.

Acronyms

CAP	College of American Pathologists – Laboratory Accrediting Organization
CLIA	Clinical Laboratory Improvement Amendments of 1988
CMS	Centers for Medicare and Medicaid Services
COR	Contracting Officer's Representative
CPM	DMID Clinical Project Manager
CRMS	DMID Clinical Research Management System
CROMS	DMID Clinical Research Operations and Management Support contract
CW	Certificate of Waiver
ERDG	Essential Regulatory Documents Group
FDA	Food and Drug Administration
GCP	Good Clinical Practice
ICH	International Conference on Harmonisation (of Technical Requirements for Registration of Pharmaceuticals for Human Use)
IRB	Institutional Review Board
LNR	Laboratory Normal Ranges
OCRR	DMID Office of Clinical Research Resources
POC	Point of Care
SERD	DMID CRMS Site Essential Regulatory Document module
TJC	The Joint Commission
VTEU	DMID Vaccine and Treatment Evaluation Unit

Clinical Laboratory Improvement Amendments of 1988 (CLIA)

The accreditation/certification of a laboratory documents its competence to perform protocol-required tests with human samples and supports the reliability of test results. The CLIA law sets standards for lab testing of human samples to ensure that the test results are accurate, timely, and reliable.

CLIA requires all facilities that perform tests on, "materials derived from the human body for [the] purpose of providing information for the diagnosis, prevention, or treatment of any disease…or assessment of health of human beings," to meet certain requirements.

Any facility performing tests for diagnosis, treatment, prevention, or assessment is considered a laboratory under CLIA and must obtain CLIA certification. CLIA Certification of Compliance **OR** CLIA Certification of Accreditation **AND** certificate from a lab accreditation organization (i.e., College of American Pathologists [CAP] or The Joint Commission [TJC]) are required.

Other CLIA certificates may also apply (e.g., Certificate of Waiver for "point of care" testing such as urine pregnancy tests). All **point of care testing** done at a clinical site falls under the surveillance of the respective institution's laboratory department and a CLIA Certificate of Waiver. Although FDA does not enforce CLIA requirements, the Form FDA 1572 should include information about testing used as part of a clinical trial.

The CLIA certification, certificate from a lab accreditation organization (CAP) and the laboratory normal ranges for all study tests are required for all laboratories performing study **Safety labs** for the assessment of subject eligibility, inclusion/exclusion criteria, or post-test article exposure.

The laboratory documentation (i.e., CLIA, CAP, LNR and if applicable the CLIA Certificate of Waiver and appropriate reference ranges or package inserts for any POC tests performed) should be present in the Sponsor and Site essential documents file in accordance with ICH GCP section 8.2.11, Essential Documents, normal value(s)/range(s) for medical/ laboratory/technical procedure(s) and/or test(s) included in the protocol.

CLIA certification is not relevant/applicable for Research Laboratories. Research laboratories test human samples per protocol requirements but the results of such testing are NOT available routinely for the diagnosis, treatment, prevention, or assessment of the health of research subjects. Research laboratory tests CANNOT be ordered as part of routine medical care and are available only in the context of a research protocol.

Roles and Responsibilities

Role	Responsibility
CROMS ERDG	▪ To maintain the Sponsor's essential document files containing current laboratory documents for site clinical laboratories ▪ As applicable, to maintain the essential documents for the DMID Clinical Central Laboratory main or primary contract and all specialized or subcontract Clinical Central Laboratories for DMID VTEU sites, specifically: • To upload current Clinical Central Laboratory main and subcontract/specialty lab documents to the CRMS SERD module for every site-specific essential document file during the pre-study document collection period, over the duration of each protocol and when notified by the Central Laboratory COR that a specific specialty lab will be used • To track document expiration dates and send a request to the Central Lab COR for updates in advance of document expiration ▪ To request the laboratory normal reference ranges or package inserts for any POC tests performed if a Certificate of Waiver is received from a site monitored by CROMS ▪ To inform the CROMS Clinical Site Monitoring team of expired or due-to-expire laboratory certifications for protocols monitored by CROMS ▪ To notify CROMS ERDG if a protocol will require use of a subcontract/specialized Clinical Central Laboratory
DMID CPM	To evaluate current and subsequent updated laboratory normal ranges in the context of their respective protocol clinical laboratory value parameters during protocol development and over the duration of the protocol
DMID Clinical Central Lab COR	▪ To collect documents for the main and subcontract/specialized Clinical Central Laboratories, including CLIA certification, CAP certification, and Laboratory normal ranges (synonyms – reference ranges, normal values) ▪ To send documents to the CROMS ERDG, including Certifications, Normal Ranges, and Memorandum naming all contract and subcontract/specialized Clinical Central Laboratories ▪ To collect and send updated documents to CROMS ERDG, as needed ▪ To notify CROMS ERDG if a protocol will require use of a subcontract/specialized Clinical Central Laboratory ▪ To notify the protocol-specific CPM if the Clinical Central Laboratory normal ranges in place at the initiation and with subsequent protocols are changed over the duration of the protocol

Role	Responsibility
Clinical Site Staff using the DMID Clinical Central Laboratory	▪ To download Clinical Central Laboratory documents from the CRMS SERD module • To file and maintain Clinical Central Laboratory documents in the site's essential document file • To name all Clinical Central Laboratories (including the main laboratory and any specialty laboratories supporting the protocol) on the FDA 1572 Form or IOR form • To upload 1572 Form or IOR form to the CRMS SERD module for CROMS ERDG review *If study samples will be tested locally on site, the site must:* ▪ File local laboratory documents (CAP, CLIA and LNR) in the site essential document files and upload local laboratory documents to the CRMS SERD module for CROMS ERDG review *If POC tests will be performed by the site staff, the site must:* ▪ File a CLIA Certificate of Waiver and appropriate reference ranges or package inserts in the site essential document files and upload the CLIA Certificate of Waiver and appropriate reference ranges or package inserts to the CRMS SERD module for ERDG review
Clinical Site Staff NOT using the DMID Clinical Central Laboratory	▪ To submit to the CRMS SERD module the following: – Clinical laboratory certification documents (i.e., CLIA, CAP) – Normal reference ranges, and – If applicable, POC testing CLIA Certificates of Waiver and appropriate reference ranges or package inserts for any POC tests performed ▪ To file laboratory documents in the site's essential document file ▪ To name clinical laboratories (i.e., the main and any specialty laboratories supporting the protocol) on the FDA 1572 Form or IOR form ▪ To upload 1572 Form or IOR form to the CRMS SERD module for CROMS ERDG review
CROMS Clinical Site Monitors	▪ To monitor the site's essential document file, laboratory section per established clinical site monitoring procedures ▪ To inform the Site Staff and DMID of laboratory essential document file discrepancies

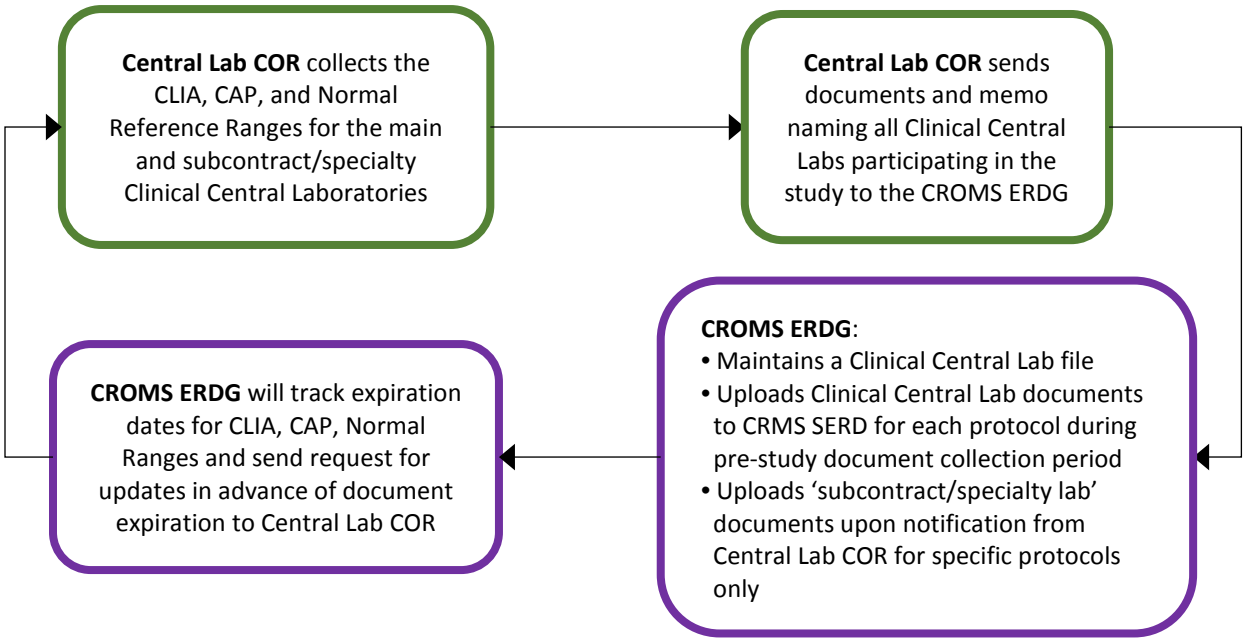
Federal Agency - Roles and Responsibilities

Three federal agencies are responsible for CLIA: the FDA, the CMS and the CDC. Each agency has a unique role in assuring quality laboratory testing.

Agency	Responsibility
FDA	Categorizes tests based on complexity, Reviews requests for Waiver by Application, Develops rules/guidance for CLIA complexity categorization, link: http://www.fda.gov/medicaldevices/deviceregulationandguidance/ivdregulatoryassistance/ucm124105.htm
CMS	Issues laboratory certificates, Collects user fees, Conducts inspections and enforces regulatory compliance, Approves private accreditation organizations for performing inspections, and approves state exemptions, Monitors laboratory performance on Proficiency Testing (PT) and approves PT programs, Publishes CLIA rules and regulations, link: https://www.cms.gov/Regulations-and-Guidance/Legislation/CLIA/index.html?redirect=/clia/

Agency	Responsibility
CDC	Provides analysis, research, and technical assistance, Develops technical standards and laboratory practice guidelines, including standards and guidelines for cytology, Conducts laboratory quality improvement studies, Monitors proficiency testing practices, Develops and distributes professional information and educational resources, link: http://wwwn.cdc.gov/CLIA/Default.aspx

Diagram of DMID Clinical Central Laboratory document flow



Additional Information

Contact the OCRR COR for Clinical Central Laboratory contractor information. For information related to laboratory specimen collection, processing, labeling, shipping information, lab test value reporting, or data discrepancy resolution, refer to the protocol manual of operational procedures.

For CROMS ERDG contact information, guidelines, and forms click here.

Other Questions? Contact your DMID protocol-specific Point of Contact or email the DMID Office of Clinical Research Affairs, OCRA Help.

Attachments

1. CLIA information excerpted from the CMS.gov website, Clinical Laboratory Improvement Amendments (CLIA)
2. CLIA certificate information excerpted from the CMS.gov website, CLIA Brochure
3. Laboratory related documentation excerpted from the FDA.gov website, INSTRUCTIONS FOR FILLING OUT FORM FDA 1572 – STATEMENT OF INVESTIGATOR

ATTACHMENT 1

CLIA information excerpted from the CMS.gov website, Clinical Laboratory Improvement Amendments (CLIA)

Research Testing and Clinical Laboratory Improvement Amendments of 1988 (CLIA) Regulations

The Clinical Laboratory Improvement Amendments of 1988 (CLIA) were established to strengthen federal oversight of clinical laboratories to ensure the accuracy and reliability of patient test results. CLIA applies to **all laboratories** that examine "materials derived from the human body for the purpose of providing information for the diagnosis, prevention, or treatment of any disease or impairment of, or the assessment of the health of, human beings." (42 U.S.C. § 263a(a)).

CLIA regulatory requirements vary according to the kind of test(s) each laboratory conducts. Tests are categorized as waived, moderate complexity or high complexity.

With respect to CLIA applicability, the CLIA regulations do not differentiate between facilities performing provider-ordered testing and those performing non-provider-ordered testing. All facilities that meet the definition of a "laboratory" under the CLIA statute and regulations must obtain an appropriate CLIA certificate prior to conducting patient testing. Whether a test service is billed to Medicare has no bearing on CLIA applicability.

How does CLIA define a "laboratory"?

The CLIA regulations define a laboratory to be "a facility for the biological, microbiological, serological, chemical, immunohematological, hematological, biophysical, cytological, pathological, or other examination of materials derived from the human body for the purposes of providing information for the diagnosis, prevention, or treatment of any disease or impairment of, or the assessment of the health of, human beings. These examinations also include procedures to determine, measure, or otherwise describe the presence or absence of various substances or organisms in the body" (42 C.F.R. § 493.2 (definition of "laboratory").

How does the Centers for Medicare & Medicaid Services (CMS) determine CLIA applicability?

CLIA applicability is determined using the regulatory definition of "laboratory" quoted above. Specifically, CLIA applies when: (1) patient-specific results are reported from the laboratory to another entity; **AND** (2) the results are made available "for the diagnosis, prevention, or treatment of any disease or impairment of, or the assessment of the health of, human beings." As stated above, whether a test service is billed to Medicare has no bearing on CLIA applicability. Therefore, if a facility performs tests for the above-stated purposes, it is considered a laboratory under CLIA and must obtain a certificate from the CLIA program that corresponds to the highest complexity of tests performed.

What facilities need to have a CLIA certificate?

CLIA requires **all** facilities that perform even one test, including waived tests, on "materials derived from the human body for the purposes of providing information for the diagnosis, prevention, or treatment of any disease or impairment of, or the assessment of the health of, human beings" to obtain a CLIA certificate and meet CLIA regulatory requirements. v. 12/10/2014.

What facilities are exempt from needing a CLIA certificate?

Facilities that only perform testing for forensic purposes are excepted from the CLIA regulatory scheme.

Depending on the circumstances, research testing can be either excepted from CLIA or subject to CLIA. Specifically, testing facilities may qualify to be excepted from CLIA certification if they meet the description of "research laboratories" provided by the CLIA regulations at 42 C.F.R. § 493.3(b)(2). In accordance with

that regulation, only those facilities performing research testing on human specimens that **do not report patient-specific results** may qualify to be excepted from CLIA certification. An example of a non-patient-specific result would be "10 out of 30 participants were positive for gene x." The result in this example is a summary of the group data, and is not indicative of an individual's health. An example of a patient-specific result would be "participant A was positive for gene x" in which the result is specific to participant A.

What types of research testing are subject to CLIA?

In most cases, research testing where patient-specific results are reported from the laboratory, and those results will be or could be used "for the diagnosis, prevention, or treatment of any disease or impairment of, or the assessment of the health of, human beings" are presumed to be subject to CLIA absent evidence to the contrary.

In cases where patient-specific test results are maintained by a statistical research center for possible use by investigators in which the results are not reported out as patient-specific and could not be used "for the diagnosis, prevention, or treatment of any disease or impairment of, or the assessment of the health of, human beings," CLIA would not apply.

What if the research testing has Institutional Review Board (IRB) approval?

IRBs do not generally assess whether or not CLIA would apply to a given testing situation, and they do not have authority to determine CLIA applicability on behalf of the CLIA program. The Federal regulations that govern human research subject protection are unrelated to the CLIA requirements, and the IRBs that consider human research subject protection considerations would not be expected to consider the applicability of the CLIA regulations. And, even if they did, IRBs would have no authority to authoritatively opine on the applicability of those CLIA provisions.

What CLIA requirements apply to research testing?

As stated above, CLIA regulatory requirements vary according to the kind of test(s) each laboratory conducts, and whether the results are made available in such a way as to make that testing facility a "laboratory" under the CLIA regulations.

Tests are categorized as waived, moderate complexity or high complexity. If a laboratory test system, assay or examination does not appear on the lists of tests in the Federal Register notices, it is considered to be a test of high complexity until such time as the test system is reviewed and assigned a categorization in accordance with the CLIA regulations (for more information, see http://www.cms.gov/Regulations-and-Guidance/Legislation/CLIA/Categorization_of_Tests.html). Thus, if a research testing system is not categorized, and test results will be reported out, it would be considered a high complexity test system that is subject to the CLIA regulations for laboratories performing high complexity tests.

ATTACHMENT 2

CLIA certificate information excerpted from the CMS.gov website, CLIA Brochure

CLIA Program, Types of Certificates

What Is a Certificate of Waiver (CW)?

The Certificate of Waiver (CW) permits a laboratory to perform only waived tests. Waived tests are so simple and accurate that little risk of error exists when done correctly.

Examples of waived tests include:

- Certain testing methods for glucose and cholesterol;
- Fecal occult blood tests;
- Pregnancy tests; and
- Some urine tests.

Routine on-site surveys are not required for a CW unless there is a complaint. Along with enrolling in the CLIA program and paying the fee, a laboratory must follow the manufacturer's instructions for test performance.

What Is a Certificate of Compliance (COC)?

A laboratory may receive a COC after an on-site survey finds that it complies with all applicable CLIA requirements. Laboratories with a COC that perform moderate and high complexity tests must be surveyed every 2 years.

The surveys:

- Assist laboratories in improving patient care through education and by emphasizing standards that directly impact the laboratory's quality test performance; and
- Determine a laboratory's regulatory compliance.

The surveyor determines whether the laboratory meets CLIA requirements through:

- Interviewing the laboratory's personnel;
- Observing the laboratory's past and current practices; and
- Reviewing the laboratory's relevant records.

What Is a Certificate of Accreditation (COA)?

A laboratory that performs moderate and high complexity tests and meets the standards of a private non-profit accreditation organization approved by CMS may receive a COA. To receive CMS approval, a non-profit accreditation organization's requirements must equal or exceed CLIA program requirements. Periodically, each organization must receive re-approval to ensure it maintains equivalent, or more than equivalent, requirements. Each year, CMS evaluates each organization's performance in enforcing CLIA requirements.

An accreditation organization inspects the laboratory once every 2 years, and CMS may perform a validation survey to evaluate the results of the most recent accreditation organization inspection.

ATTACHMENT 3

Laboratory related documentation excerpted from the FDA.gov website, INSTRUCTIONS FOR FILLING OUT FORM FDA 1572 – STATEMENT OF INVESTIGATOR

INSTRUCTIONS FOR FILLING OUT FORM FDA 1572 – STATEMENT OF INVESTIGATOR

Field 3: NAME AND ADDRESS OF ANY MEDICAL SCHOOL, HOSPITAL, OR OTHER RESEARCH FACILITY WHERE THE CLINCIAL INVESTIGATION(S) WILL BE CONDUCTED

Provide the address(es) of the location(s) where the investigation will be conducted and clinical data will be generated or collected and to where the test articles will be shipped.

Field 3 is intended to identify facilities where study activities will be conducted and clinical data will be generated or collected. This includes facilities where subjects will be seen and study procedures will be performed, e.g., locations such as health care facilities where the test articles will be administered, or where physical exams will be performed. Facilities where other important clinical investigation functions are performed may also be identified. For example, a research laboratory where the test article is prepared, a special storage facility where the test article will be kept, or a location where tissue specimens are collected should be in this section.

If an investigator sees study subjects at more than one site, the name and address of each of the study sites should be identified in Field 3. However, if the protocol specifies that the investigative product can be administered at a subject's home (for example, the protocol allows for daily injections to be administered by a registered nurse in the subject's home), the subjects' home addresses do not have to be listed on the Form FDA 1572. Study records should reflect that the test article was administered at subjects' homes per the protocol.

Use the Continuation Page if additional space is needed.

Field 4: NAME AND ADDRESS OF ANY CLINICAL LABORATORY FACILITIES TO BE USED IN THE STUDY

Identify clinical laboratories or testing facilities directly contributing to or supporting the clinical study (for example, diagnostic labs performing blood work, imaging centers, cardiology labs, etc.). This may include analytical labs that provide pharmacokinetic analysis, and laboratories supplying efficacy data for clinical investigations conducted under an Investigational New Drug Application (IND).

If a laboratory is sending samples to satellite or other contract labs for additional testing, it is only necessary to list the primary laboratory, provided that laboratory can trace the samples to each of the satellite and/or contract labs where the tests were performed.

Use the Continuation Page if additional space is needed.