CLIA in the Research Context

This Guidance Document provides researchers with a brief overview of CLIA as well as specific guidance as to how CLIA applies to tests performed in the context of research.

What is CLIA?

The Clinical Laboratory Improvement Amendments of 1988, or CLIA, sets personnel requirements and standards for quality control for clinical laboratories to ensure the accuracy, reliability, and timeliness of test results. CLIA applies standards to all laboratories, including those in physician offices.

CLIA defines a "laboratory" as any facility that conducts tests on "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." Laboratory tests are categorized based on complexity into the following three categories, waived testing, moderate-complexity testing and high-complexity testing.

The requirements applicable to a given laboratory depend on the level of complexity of the tests that it conducts.

When does CLIA apply to Research Tests?

Certain laboratories are not subject to CLIA, including "research laboratories that test human subjects but do not report patient specific results for the diagnosis, prevention or treatment of any disease or impairment of, or the assessment of the health of individual patients."

<u>CLIA is applicable to research tests when:</u>

1) Patient-specific results are reported from the laboratory to another entity, **and**;
2) The results are made available for health care purposes, specifically the diagnosis, prevention, or treatment of any disease or impairment, or the assessment of the health of human beings.

- **Does CLIA apply if an IRB has approved the use of test?**
  The IRB does not have the authority to make a determination as to whether CLIA applies to a given test or laboratory.

- **Does CLIA apply if the test is not billed?**
  If patient-specific results will be reported, and the results could be used for health care purposes, then the test must be conducted in a CLIA-certified laboratory. Whether a test is billed to an insurer or patient is irrelevant to CLIA's applicability.

- **Does it matter if a test is reported in a patient's medical record?**
  If a test will be reported in a patient's medical record, then CLIA applies, as that test result could be used for health care purposes. However, just because a test result is not reported in a patient's medical record does not mean that the test can be conducted in a non-CLIA-certified laboratory. For example, if the test result will be reported to the patient directly, the test must be conducted in a CLIA-certified laboratory. If the test will affect the treatment of the individual

under the research protocol in any manner (such as assignment to the treatment arm), then the test must be done in a CLIA-certified laboratory. Note that whether a specific test result must or should be reported in a patient's medical record, while not explicitly directed by CLIA, may warrant further analysis beyond the scope of this Guidance Document.

- **Does it matter if the specimens are coded (i.e., not labeled with identifying information)?**
  From a CLIA perspective, it does not matter if a laboratory received specimens that are fully identifiable or coded. The main concern addressed by CLIA is test quality and accuracy, not privacy. Therefore, if the laboratory will report the test results to another entity that has access to the codes linking the specimens to a specific patient and the results could be used for health care purposes, then the laboratory must be CLIA-certified.

  If a laboratory is only reporting aggregate data, as opposed to patient-specific data, than the laboratory would qualify as a research laboratory that is exempted from CLIA's requirements. An example used by CMS of non-patient-specific results is the following: "10 out of 30 participants were positive for gene X." If only summary results such as this are provided by the laboratory to the investigators, such tests would <u>not be required</u> to be carried out in a CLIA-certified laboratory.

- **What if a laboratory reports patient-specific test results to a study coordinator who uses the results to assign the patient to the treatment arm of the study?**
  These tests must be carried out in a CLIA-certified laboratory. If a given test will affect the treatment of an individual patient in any manner in the conduct of research (such as inclusion/exclusion, assignment to treatment arm, etc.), then the relevant test must be performed in a CLIA-certified laboratory.

In general, if patient-specific results are reported from the laboratory and those results will be <u>*or could be used*</u> to affect the care or treatment received by a patient, then those tests are subject to CLIA.

Does CAP accreditation satisfy CLIA requirements?
All laboratories performing tests on human specimens for health care purposes must be certified under CLIA. Accreditation by the College of American Pathologists, or "CAP," is not a substitute for CLIA certification, however, many laboratories are able to use their CAP accreditation to obtain CLIA certification.

CMS publishes a list of approved accreditation agencies on its website, one of which is CAP. The accreditation means that the lab demonstrates compliance with the CLIA regulations, which is sometimes referred to as "deemed status." That means that CMS has deemed a laboratory to be in compliance with CLIA standards, even though CMS did not directly inspect the laboratory, because it has been accredited by an approved accreditation program, such as CAP. <u>However, it is not sufficient to hold the CAP accreditation alone.</u>

When is FDA Categorization appropriate?
The FDA is responsible for the categorization of commercially available *in vitro diagnostic* (IVD) tests, which allows IVD manufacturers to submit premarket notifications or applications for tests and requests for complexity categorization of these tests under CLIA to one agency.

The FDA's responsibility for CLIA complexity categorization applies to clinical laboratory devices:

- Under premarket review by FDA Center for Devices and Radiological Health (CDRH),
- Under premarket review by other FDA Centers,
- Exempt from premarket notification, and
- That are legally marketed and for which the sponsor is seeking a waiver of categorization.

Clinical Laboratory Devices Under Premarket Review	CLIA categorization of IVD tests is determined by the FDA at the time of review of a premarket submission, a premarket approval application, or a Biologics License Application. FDA database of CLIA categorizations for IVD devices: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCLIA/clia.cfm
Legally Marketed Devices	Manufacturers should submit a request for CLIA categorization when premarket submission is not needed by CLIA categorization is appropriate. The FDA will attempt to notify the sponsor of the categorization within 30 days of the request.
CLIA Waiver Protocols and Applications	CLIA Waivers by Application are not accepted for devices that are under premarket review at the time of submission. A test initially categorized as moderately complex might meet the statutory criteria for CLIA waiver if the device is simple to use and the sponsor demonstrates in studies that the test is accurate and poses an insignificant risk of erroneous results. If a Sponsor of a test categorized as moderate complexity believes their test meets the statutory criteria for CLIA waiver, they may submit a CLIA Waiver by Application to request categorization of the test system as waived.

Resources

Centers for Medicare & Medicaid Services. "Research Testing and Clinical Laboratory Improvement Amendments of 1998 (CLIA) Regulations." Available at https://www.cms.gov/Regulations-and-Guidance/Legislation/CLIA/index.html.

Centers for Medicare & Medicaid Services, Medicare Learning Network. "Clinical Laboratory Improvement Amendments (CLIA) and Medicare Laboratory Services," ICN 006270 (August 2015).

Barnes, Mark *et al*. "The CLIA/HIPAA Conundrum of Returning Test Results to Research Participants," 14 *Medical Research Law & Policy Report* 491 (July 15, 2015).

Todd, Kathy. Division of Laboratory Services, Centers for Medicare & Medicaid Services, unpublished presentation "CLIA and Clinical Trials."

U.S. Food and Drug Administration. "Guidance for Industry and Food and Drug Administration Staff: Administrative Procedures for CLIA Categorization." Available at https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM070889.pdf