JOURNAL OF CLINICAL RESEARCH BEST PRACTICES

Vol. 14, No. 7, July 2018 "Happy Trials to You"

In Vitro Diagnostic Test Development

By Lyssa Friedman

While drugs and devices are designed to treat patients, diagnostic tests are designed to generate information about a patient's (or healthy person's) physical condition. A good diagnostic test quickly, consistently, reproducibly and economically delivers precise, accurate and actionable results with minimal false positives or false negatives. *In vitro* ("in glass") tests operate on samples drawn from the patient. The testing process might involve laboratory technicians, secondary extraction and processing of the sample, measurement equipment, and software algorithms.

An *in vitro* diagnostic (IVD) test might be used in laboratories, healthcare settings, or by consumers at home.[1] A laboratory developed test (LDT) is an IVD that is created and used within a single laboratory or in multiple laboratories under common ownership.[2]

The Centers for Medicare & Medicaid Services (CMS) regulate clinical (non-research) laboratory testing performed on humans in the U.S. under the Clinical Laboratory Improvement Amendments (CLIA) to the Public Health Services Act.[3]

The FDA's Center for Devices and Radiological ealth (CDRH) also has regulatory authority over IVDs, including LDTs, just as the FDA's Center for Drug Evaluation and Research (CDER) has regulatory authority over pharmaceutical products. Although the regulatory environment may be changing, at present CDRH seldom exercises its authority over LDTs, so most LDTs may be used with only CMS/CLIA surveillance.[4]

Study Phases

Development of an *in vitro* diagnostic test needs large numbers of high-quality blood, urine, tissue or other samples to characterize and refine the test. Depending on the test, these samples can be ordered from a catalogue, obtained from a freezer, or collected from live patients.

An IVD study's purpose depends on the stage of a product's development lifecycle. Broadly speaking, there are three study stages:

IVD Study Stages

Phase	Objectives	Characteristics
Feasibility	Proof of concept Biomarker discovery Identification of technical approach Initial assay and algorithm development	Retrospective cohorts may be sufficient Small sample size, rapid accrual Sample collection, often single-visit, with clinical data offering a snapshot of relevant findings at the time of sample collection Samples may not entirely represent the end clinical sample if sufficient results can be generated with a surrogate (e.g., tissue in lieu of a small needle biopsy)

Development	Assay development, training and testing Analytic validation: accuracy and reliability of measuring the analyte Clinical validation: accuracy of diagnosis, prediction or measurement of clinical condition	Subjects and samples match those intended for test use Driven by specific test profile; may include: • Single-visit collection • Longitudinal collection • Short- or long-term follow-up for clinical data
Clinical Utility	Measurement of test's effect on: • Patient outcome • Patient management • Physician decision-making • Cost of care	Prospective, randomized and controlled

Use of an LDT requires only an analytic validation study, although clinical validation from some source is also probably needed. An IVD intended for broader use requires FDA approval based on data from a full development study. Reimbursement by governmental and private payers generally requires a clinical utility study, but manufacturers generally conduct those studies after an IVD is on the market. However, some manufacturers obtain preliminary reimbursement, provided it agrees to complete a clinical utility study within a specified period of time.

Sample Collection Studies

If an IVD study requires collection of samples from live patients, there are three priorities:

- Collect the samples from the right patients, with documentation of demographic information and the presence or absence of the targeted disease or medical condition.
- Collect the right samples in the right way, i.e., in a scientifically correct manner that is safe for both the patient and the healthcare professional.
- Handle and process the samples in the right way.

In addition to collecting samples, IVD collection studies require observation of the study participants. Observation might occur during a single visit or over time, to see whether the test results are consistent with the presence or course of the disease.

In most cases, IVD sample collection studies are dramatically simpler, cheaper and faster than therapeutic drug studies. From concept to marketing, it might take as little as one to three years (plus one to two years for FDA approval) to create a new IVD. Because LDTs do not require FDA submission, their timelines are even shorter.

Sample collection studies must follow Good Clinical Practice (GCP) and HIPAA rules. However, informed consent is abbreviated, and most sample collection techniques, including venipuncture, can take advantage of expedited IRB approval. An FDA 1572 form, financial disclosure form, Sunshine Act report, and clinicaltrials.gov listing are not required. Unless the sampling method is outside standard sample clinical care (for example, an invasive biopsy in a setting where a biopsy would not be required), AEs and SAEs are not anticipated and safety reporting is not required.

For studies with simple sample collection techniques, site qualification and training can be performed remotely. Monitoring is usually risk-based and limited. Drug or device accountability is not required because they don't exist.

Although clinical utility studies measuring patient outcomes need traditional event-based sample size calculations, that is not the case for sample collection studies for feasibility or development. As samples accrue and undergo lab processing, there is iterative learning about the characteristics of the IVD (sample collection, point-of-collection handling and stabilization, shipping conditions, etc.), disease prevalence, and other relevant considerations. As a result, the process of collecting, handling, shipping and processing samples might change during a study. Additionally, some samples might be diverted to side studies, e.g., to test sample stability under different shipping conditions. As a result, sample size calculations are often just estimates, and adjustments should be expected.

Conclusion

Sample collection studies can be simple, fast and cheap, with minimal data management and regulatory oversight, no adverse events or safety reporting, minimal site monitoring, and modest administrative burdens. On the other hand, product lifecycles can be short and modifications during development are common. Study teams might find themselves scrambling to adjust to new information and to rapidly change how they instruct sites to handle samples. For a clinical research professional accustomed to the lengthy time to market for drugs, it is exciting to bring products to market in such fast-paced product lifecycles. IVD studies are different than those of drugs or medical devices and require clinical research professionals to adjust to such a fast-moving environment.

Author

Lyssa Friedman is the owner of Lyssa Friedman Consulting, LLC. Contact her at 1.415.250.8356 or lyssa@lyssafriedman.com.

References

1. https://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/default.htm
2. https://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/LaboratoryDevelopedTests/default.htm
3. https://www.cms.gov/Regulations-and-Guidance/Legislation/CLIA/index.html?redirect=/CLIA
4. https://www.fda.gov/downloads/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/LaboratoryDevelopedTests/UCM536965.pdf