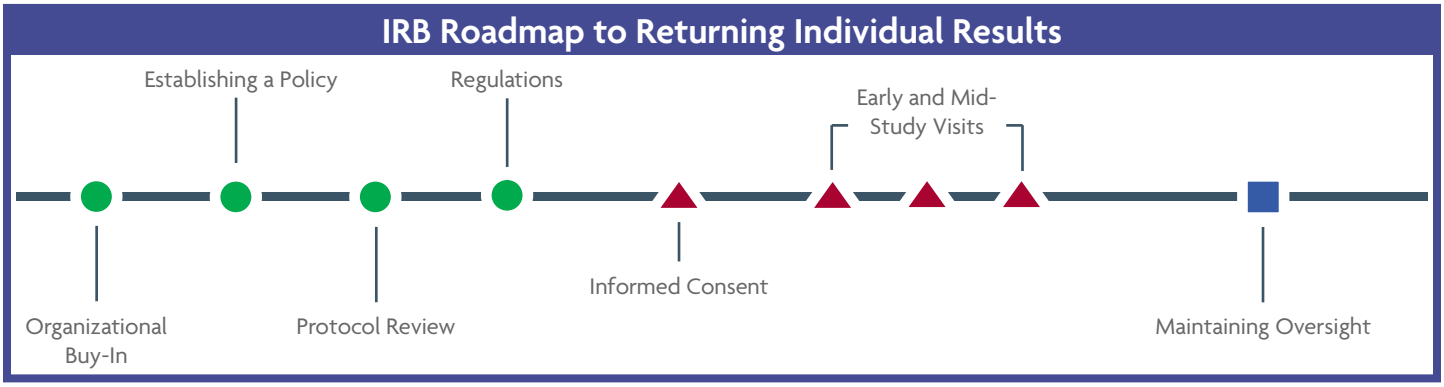
MULTI-REGIONAL CLINICAL TRIALS
THE MRCT CENTER of BRIGHAM AND WOMEN'S HOSPITAL and HARVARD

Returning Non-Validated Test Results

This case study describes how an IRB navigated returning results of a new COVID-19 assay from a non-CLIA-certified lab during a public health emergency.



The roadmap above shows steps for IRBs to consider when a study proposes to return individual results to participants. This case study focuses on the on-study part of the timeline illustrated by the red triangles.

Background

A university was creating a repository for current and future research involving the epidemiology and pathogenesis of emerging viral infections including the coronavirus SARS-CoV-2. A secondary aim was to validate a university-developed assay to test for COVID-19.

Samples were collected from hospital inpatients and outpatients either suspected of exposure to COVID-19 or exhibiting symptoms of infection. Samples were first tested in a non-CLIA-certified laboratory using a university-developed assay. All COVID-19 samples were then re-tested in a CLIA-certified lab to validate the results.

The IRB and researchers considered whether to return unvalidated positive COVID-19 results from the new assay immediately to treating physicians or participants without waiting for CLIA lab confirmation, or to wait for validation.

In the US, 42 CFR 493 sets forth the conditions that all laboratories must meet to be certified to perform testing on human specimens under the Clinical Laboratory Improvement Amendments of 1988 (CLIA). Other countries may have regulations or quality measures to ensure validity of research results.

Approach

The IRB weighed the risks of waiting to get the samples re-tested in a CLIA-certified lab against the violation of the CLIA regulation if they were to return non-CLIA-certified results to participants.

Due to the unique circumstances posed by the COVID-19 pandemic and the contagiousness and significant health risks associated with the virus, **the IRB determined that it was an ethical obligation to alert providers to the following:**

- A "potential unconfirmed finding" of a positive COVID-19 test
- Samples were being re-tested in a CLIA-certified lab for confirmation
- The CLIA-certified results would be returned to the providers directly for any required action including mandatory reporting to health authorities and hospital infection control

The IRB also required that the samples be initially tested within 12 hours of collection and sent to the CLIA-certified laboratory within 24 hours of collection, regardless of whether the participants were outpatients or had been exposed to or previously tested for COVID-19.

The study was being conducted at the beginning of the COVID-19 outbreak and testing was neither readily accessible nor available in all clinics and physician offices. The IRB required that the investigators emphasize to participants that participation in the study did not replace clinical care; participants were encouraged to continue to seek care from their providers.

The decisions regarding how to approach return of results in this study were made based on the following principles:

1. Regulatory Requirements

Based on the review of guidance issued during the COVID-19 public health emergency, it did not appear that any exceptions to CLIA requirements were permissible. However, it was considered permissible to alert providers of potential unconfirmed findings based on non-validated results in order for them to recommend precautionary measures to their patients until CLIA confirmation of the test results.

2. Harm Reduction

The IRB recognized that the report of a false positive finding could result in psychological distress, disruption of work and daily life due to the need to quarantine, and potential economic costs. However, the possibility of the infection worsening and the potential infection of others (including potentially vulnerable persons) warranted alerting poviders, further testing, and precautionary measures. The IRB considered the consequences of inaction for a true infection to outweigh the inconvenience and short-lived psychological distress of a false positive, particularly since the latter results would be corrected by CLIA-certified testing within 24 hours. Any delay in notification and monitoring would contribute to a likely foreseeable, and possibly substantial, harm.

3. Scientific Integrity

The researchers had data that showed strong preliminary evidence that the test results were scientifically reliable even if the test and the university lab were not CLIA-certified. Had there been less confidence in the likely validity of the test, the IRB may have concluded that the risk-benefit ratio did not favor the return of results.

Communicating with Participants and Their Providers

The IRB consulted with researchers regarding language for the informed consent form and for alerting participants' providers of the potential unconfirmed positive COVID-19 test result. Sample language is below.

For participants:	For providers:
The results of the testing that we do as part of the research study will not be available to you, your family, or your personal physician and these results will not be placed in your medical record. There is one exception to this: if research testing on your bodily fluid suggests that you are infected with COVID-19, we will immediately tell your personal physician about the unconfirmed finding. We will also send your sample for re-testing for COVID-19 and tell that lab to return the results directly to your personal physician so that they can follow up with you regarding any necessary medical care.	*We are alerting you to a potential unconfirmed finding of COVID-19 based on a non-CLIA-certified COVID-19 assay that was done as part of a research protocol and for research purposes only. We have sent the sample for testing for COVID-19 to a CLIA-certified lab and instructed the lab to return the results directly to you. Required reporting of the test results from the CLIA-certified lab and follow-up with your patient will be up to you and the lab as required by hospital policy and applicable regulatory and mandatory reporting requirements.*

Outcomes

The contagiousness and health risks of COVID-19 led the IRB and researchers to conclude that there was an ethical duty to alert participants' treatment providers of a "potential unconfirmed finding." They also made provisions for results of secondary testing in a CLIA-certified lab to be returned promptly to the providers so that appropriate treatment decisions could be made.

Successes:

- Research participants were provided with validated test results from a CLIA-certified lab through their treatment provider.
- Alerting the providers of potential unconfirmed findings gave them the opportunity to recommend precautionary measures to patients to prevent the spread of the virus until the confirmed tests were returned.

Challenges:

- Early in the COVID-19 pandemic, there was a major challenge receiving timely test results from CLIA-certified labs due to high demand for testing.
- Identifying ways to balance regulatory requirements with participants' immediate health needs and the risk of infecting others during the COVID-19 pandemic required creative thinking and extensive communication among all stakeholders.

Conclusion:

Emergencies require critical considerations of the impact of regulations on whether and how the usual course of action may need to be modified to protect the health and safety of participants. In this case, the issues raised by the impacts of a global pandemic on this research study warranted a strategy that carefully balanced regulatory requirements and the relevant risks and benefits to participants.

Although not its objective, the study created the unexpected opportunity to identify persons infected with COVID-19. The IRB and researchers worked together to develop a creative response that promoted benefit, reduced risk, and allowed regulatory adherence. The consideration and action by the IRB and investigators resulted in a plan that was consistent with the intent of the regulations – regulations that were not created to address the unique circumstances of a pandemic.

Key Takeaways

Federal and state regulations apply in public health emergencies.
Always seek advice or exemptions from regulatory authorities before approving any changes to protocol that might counter the regulations.

Adhere to the principles of research ethics.
Consider making changes that are clinically or personally meaningful to participants but ensure you adhere to core ethical principles.

In times of public health crisis, expect disruption and delays, and communicate often.
Establish bilateral communication with researchers so they can inform participants of any changes to the protocol and reconsent them in a timely manner if necessary, and so that the researchers, in turn, can tell the sponsor of evolving conditions.