Abstract

The central laboratory concept was first implemented in the mid 1980’s in the United States, driven by the need for a more rigorous way to collect, combine and report trial data from different clinical sites. In the mid-1990s, creation of a European Union simplified cross-border transportation in Western Europe and triggered setup of central laboratories in Europe. The main goal among central labs was consolidation of the test results and data originating from different clinical sites. One of the primary goals of the central laboratory is to achieve a 48-hour or less turnaround on the shipment of laboratory specimens from investigator sites to the central lab location for optimization of sample stability.

Problem Statement

- Central laboratory services for clinical trials are complex especially due to the logistics challenges of samples associated with multinational trials that focus on the timely arrival of a patient specimen. Replacing a single patient due to an out of stability or compromised sample can cost sponsors up to USD 25,000. As clinical trials are increasingly focusing on highly specific targets e.g., personalized medicine, rare/orphan indications etc., replacing patients can also be challenging due to smaller / sicker patient populations where each enrolled patient is critical for study completion.
- A sample received outside of stability for any reason is rejected and produces no data toward the clinical trial objective. Most samples must be maintained within an inflexible temperature range to preserve stability. In addition, if patients need to be redrawn, dissatisfaction can potentially cause them to drop out of the trial.

Considering the technical requirements involved in shipping clinical trial samples, the central lab logistics performance is crucial; therefore this whitepaper will focus on the importance of logistics functions in the overall central lab space.

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Opportunities & Challenges in Central Lab Logistics for Clinical Trial Success

Central Laboratory Services

1. Brief Introduction

**Purpose of a Central Laboratory**

Previously, most testing was processed by local or regional laboratories and coordinated by each investigator. Clinical trial sponsors found that gathering data from multiple local laboratories that used different testing methodologies, reference ranges and standard operating procedures (SOPs) increased the possibility for data errors, method, reagent and reference range changes, leading to lengthened timelines along with increased testing costs. Globalization of clinical trials with an increase in pharmacological study complexity triggered the setup of central laboratories in Europe and North America in the mid 80's and 90's. Soon thereafter, expanding central lab operations emerged in Asia–pacific countries like China -- whose regulatory environment makes export of lab specimens extremely challenging, often impossible. Thus, the industry has evolved to require a truly global network of central laboratory capabilities.

Increased regulatory scrutiny has been a stimulus for the development of more effective and consistent quality management systems. Regulators want assurance that the quality of clinical testing work meets appropriate standards, regardless of where or by whom the testing is conducted, and they are holding sponsors and CROs accountable. Globally, the International Organization for Standardization’s accreditation for medical laboratories, ISO 15189:2012, is considered the standard of excellence for central labs and referral (or “external”) labs. Many central labs have attained or are pursuing this accreditation, but very few are willing or able to validate work done by referral labs. A central lab with a validated External Labs Management Services (ELMS) model can mitigate this regulatory risk for sponsors. In 2006, the last pharmaceutical company to maintain an internal central laboratory facility decided to close that operation making the central laboratory industry a 100% outsourced market.

**Types of Central Lab**

**Global Labs:** Central labs have established uniform SOPs (standard operating procedures), IT platforms and QA standards in all of their global lab facilities and hence are able to provide data in a single file format using global reference ranges and units as required by the sponsor. The core value of a quality global central lab is consistency -- generating data from the same analytical method platform, SOPs, equipment, reagents and standards eliminates variables that affect test results. E.g. standardization of a specimen collection kit enhances ease of use for the investigator and staff who do the actual collection of samples.
Regional Laboratory: This is a diagnostic laboratory that provides more specialised testing that cannot be done at a smaller local laboratory. These laboratories cover several cities or a few countries. The total sample volume from clinical trials often represents less than 3% of the volume of these laboratories and may provide advantages for some specific testing.

Local Lab: The lab within a country or a geo-cultural region may offer test methodologies providing low logistical expenditures, rapid result turnaround time, and limited loss of sample integrity due to time and temperature exposure. These entities are often focused on individual physician practices and hospitals, offering convenience and personalized service but not equipped to take part in clinical trial testing.

<table>
<thead>
<tr>
<th>Key Parameters</th>
<th>Global Lab</th>
<th>Regional Lab</th>
<th>Local Lab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shipping Cost</td>
<td>Varies by the location, it can be moderate to high but is dependent of multiple factors and trade-offs</td>
<td>Generally low to moderate</td>
<td>Generally low, although unable to negotiate volume pricing</td>
</tr>
<tr>
<td>Local site support</td>
<td>Varies sometimes limited, due to language barriers and time zones, but truly global providers maintain local presence in dozens of countries</td>
<td>Expected to be good, based on proximity but it may not have insight into clinical trial protocol</td>
<td>Expected to be good proximally (local language and no time difference); support may not extend to clinical trial protocol or context</td>
</tr>
<tr>
<td>Uniform IT platform (DM, reporting and EDT)</td>
<td>Yes</td>
<td>Varies</td>
<td>No</td>
</tr>
<tr>
<td>Global QA</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Single study DB</td>
<td>Yes</td>
<td>Unlikely</td>
<td>No</td>
</tr>
<tr>
<td>Specialty tests</td>
<td>Yes, although there are differences in spectrum across providers</td>
<td>Varies</td>
<td>Yes, in niche labs (narrow range); No in typical local lab</td>
</tr>
</tbody>
</table>

1. Global labs may use external labs to perform tests that are highly specialized, proprietary or relatively low in volume. Depending on the study, the use of an external lab to augment testing performed within a central lab can result in faster turnaround times (TATs) and lower costs. Global central labs are more likely to meet enrolment goals and deadlines, minimizing redraws and maximizing data delivered.

2. The regional labs, local or niche labs may lack the context of the entire global clinical trial, which could create blind spots in standardization and combinability. Specialty or niche labs often feature a relatively narrow but sophisticated technical focus and may be utilized to fill gaps in other labs capabilities or esoteric testing menus.

3. Regional Laboratories do not provide solutions for global clinical trials, have limited scalability and still adjust to the diagnostic laboratory needs of the parent lab where decisions are driven by cost effectiveness of diagnostic testing, not maintaining the consistency needed for pharmaceutical grade testing.

The key difference between a global lab and a high volume diagnostic lab is that the global lab delivers globally combinable, statistically meaningful data providing consistency over time, while diagnostic labs provide individual snapshots of lab results.
2. Managing Global Logistics within a Central Lab Environment

**A. The Importance of a solid and high performing Logistics**

Most samples must be maintained within an inflexible temperature range to preserve stability, and even then, there is a non-negotiable expiration. If the sample is received outside of stability for any reason, it is rejected and produces no data toward the clinical trial objectives. In addition, patients need to be redrawn which can lead to dissatisfaction and potentially cause them to drop out of the trial.

**B. Challenges in Central Lab Logistics**

*Testing Sample Frequency:* The frequency of running a specific assay in the laboratory depends directly on the number of samples received. A small laboratory processing 50 or 100 samples a day may only receive 5 to 10 samples for a specific immunology method. Consequently, it would hardly be able to run this specialized method due to the high cost of instrumentation.

*Logistics Bottlenecks:* The majority of events minimally affecting transportation in a normal environment can easily become major bottlenecks when it comes to moving patient samples around the world. Strikes, extreme weather, natural disasters, political unrest can easily affect the ability of a laboratory to receive samples in a timely manner and test and report specimens within stability.

*Small Shipment Volume:* In a globalized world where all sorts of goods travel the world on a daily basis, very often clinical trial shipments are a tiny fraction of the volumes going through major air hubs such as New York JFK, Frankfurt or Hong Kong etc. The physical size of these packages is also tiny when compared to large pallets or containers and its sometimes specific handling or regulatory requirements make them even more special.

*Sample Courier Provider:* There is significant risk in putting clinical packages into a global network without previously ensuring that the network in question is reliable and offers not only appropriate handling but also alternatives. This vetting process is a critical component to the success of international clinical trials run through the central laboratory.

*Technical Expertise:* The central laboratory must have extensive knowledge of worldwide Logistics networks and regulatory requirements and understand how these components can potentially affect the outcome of laboratory testing.

*Sample Timeliness:* Samples intended to ensure patient safety are time critical and failing to re-route them in a proactive manner due to inclement weather at a transit point, can have dramatic consequences to the patient. Delayed supplies can lead to delayed or lower percentage recruitment rates than initially forecasted in a highly competitive environment and failure to supply or resupply investigator sites in a timely manner will ultimately have financial consequences.

*Lack of Investigator and Support Staff training:* The team at the central laboratory must understand the logistical requirements of a multicenter study (particularly a multinational clinical trial), as it will determine their ability to deliver excellent service. It is important to highlight that Investigators’ attention first goes to patients.

*Packing and Shipping:* The materials must be user friendly and be easy to understand, so investigators and nurses spend little time preparing shipments and dealing with courier companies. Pre-labelled shipping boxes and pre-printed shipping documentation facilitate the shipping preparation and minimize the risk of errors. This also makes Investigators and study nurses training easier and clearer.

*Temperature Excursions:* Temperature management while in transit is one of the major challenges that the logistics industry encounters in moving materials for clinical research or diagnostics within defined standard temperature ranges for ambient, frozen and refrigerated samples.

*Sample Handling:* The Central Laboratory has to manage its transportation vendors throughout the handling procedures at pick-up, while inflight or in transit and at delivery: Samples should always travel in temperature regulated trucks, never be stored in freezers while in transit and should be systematically segregated from other products producing extreme temperatures while in flight and re-iced at any given time if necessary.

*Regulations:* The regulatory requirements can be sometimes challenging, especially in countries like Russia, China, or Brazil. Selecting these countries to participate and to enroll large numbers of patients can represent a challenge and a risk from an operational and financial standpoint. Shipping charges and service offerings amongst the couriers differ greatly across the globe. The choice of these locations can result in higher shipping costs, as those locations tend to be more complex and expensive to ship to/from. The choice of a Central Laboratory that conducts large trials for multiple pharmaceutical companies in these countries and has experience dealing with its regulatory requirements is the best approach to decrease the risk of delays and limit the financial exposure.

*Developing Markets:* There is also an increasing demand for drugs treating non-communicable diseases like Cardiovascular, Respiratory disorders, Cancer and Diabetes. Large pharma can diversify their business and product portfolio and find the path to market in Africa by conducting local R&D studies and more local clinical trials.
C. Current state of Central Lab dedicated Logistics networks

Clinical trial sponsors tend to be interested in three aspects of logistics in terms of measures: Received in Stability (RIS), cost-per-shipment, and the total cost of logistics for their trials. RIS measures a central lab’s ability to get specimens into the lab within testing stability and create the data that is critical to the success of the trial. Achieving a high RIS rate at a very competitive cost-per-shipment and total cost is a strong indicator that a company’s approach to logistics has been successful. It obviates the need for sponsors to directly manage couriers and courier performance data. A dedicated global team of logistics professionals within the central lab is charged with ensuring the highest possible standards with courier partners.

The aggregate volume that a leading central lab handles can yield substantial cost savings, as its clients benefit from scale and buying power. Ultimately, superior logistics systems and performance can be a source of competitive advantage for a global central laboratory. The internal systems, external relationships and financial investment required to be excellent in this domain are a barrier to entry for other labs desiring to enter the space.

D. Ideal state: What should the Central Lab Develop?

I. Central labs needed to achieve proper handling and monitoring of specimens by offering visit-specific specimen collection kits and customized shipping boxes for ensuring stable and convenient shipping to the designated laboratory.

II. They should have dedicated and specialized Central Labs Logistics teams, who understand sponsors’ specimen shipment needs, and build, develop and maintain strong relationships with dedicated couriers who provide the utmost priority and care when transporting those specimens.

III. They should have expertise for customized tracking systems and software that provide visibility of specimens while in transit and detailed logistics reports to ensure heightened tracking and follow-through when working with referral laboratories.

IV. Expertise in handling global transport volatility due to unavoidable interruptions leading to clinical trial delays and added cost. These include dealing with geopolitical unrest, local labor strikes or issues driven by extreme weather.

V. Proper contingency planning and strong courier relationships ensure the safety and stability of sponsors’ most important assets: patient specimens.

VI. Appropriate packaging materials that will offer optimal thermal protection for samples potentially going through extreme temperatures (in the lows and highs). The optimal thermal protection should not have extremely expensive and sophisticated systems.

A central lab must always be vigilant and resourceful in proactively identifying issues that could create a delay and proactively implement an effective solution to ensure that specimens continue movement to their final destination and still in good condition.
E. Solutions in Central Lab Logistics

**Dedicated Logistics Team:** Dedicated staff at the central laboratory is important to a successful study as the logistics team provides study specific instructions and materials to each investigator. Dedicated internal logistics experts who track the status and location of every single package from the moment it leaves the investigator site to the instant it reaches the lab is a critical component of successful day to day operation. Most errors and failures of sample delivery are related to logistical problems that can be avoided by investing the necessary time during the setup phase of the study. Understanding the global transportation networks, regulatory requirements, having key partnerships with courier providers as well having the ability to translate protocol data delivery requirements into operational objectives are key components of a successful international clinical trial. The choice of a Central Laboratory is very obviously driven by its testing and Project Management capabilities and its scientific expertise in most cases. However, if specimens do not make it to their destination on time and within stability, all other attributes are rendered moot. Effective logistics enables the data that drives clinical trial outcomes.

**Regulatory Expertise:** Regulatory requirements differ from country-to-country and change on a frequent basis. The Central Laboratory must not only know and understand the regulatory environment in which clinical trials are executed but also share that information proactively with sponsors so the appropriate set up is completed upfront and accurately. A central database combining regulatory requirements, service availability, contingency options, empirical experience and generic plus special pricing is a minimum requirement to ensure smooth supplies and sample movement across the globe.

**Technological Innovations:** Technology currently plays a limited role when moving supplies or samples for the purpose of Clinical Research. The main interest is probably geo-tracking: the possibility to see the status of a package at any time without having to wait for someone to scan a bar-code. However, the price of current devices is still too expensive and the ease of use by inexperienced investigators still not optimal. The Clinical Research industry will certainly benefit from technology that would collect sample information at source and make it instantly available to the Central Lab and its Logistical partners. There are intriguing tracking applications in Point of Care Testing and other emerging fields. The adoption of these new technologies will be balanced with their reliability and clinical comprehensiveness. It's difficult to predict how quickly these might gain traction, but it's likely to influence how central labs manage specimen analysis and data exchange.

**Logistical Database:** Testing and collection timing information being available upfront would allow the Central Lab to automatically select the most appropriate transportation service, on a sample by sample basis, at the right price; today, however, that decision is based on a country basis or shipment type (ambient vs. frozen).

**Partnering:** Central labs that have fully combinable platforms facilitate easier comparisons of the analytical data within a study and across programs of work in clinical research.

**In-house Testing:** In countries that have stringent sample export regulations, such as China and Russia, some Central labs offer local facilities and testing to comply with specific in-country demands while preserving protocol execution and site support.

**Site Conformance:** Errors lead to delays and extra expenses. The Central Laboratory must have site conformance monitoring capabilities to identify, correct and improve investigator performance when it comes to sample collection and shipping procedures.

### Central Lab Logistics Operational Flow

![Central Lab Logistics Operational Flow Diagram](diagram.png)
Conclusion

Volatility in global transport is unavoidable, and on the rise. When world events occur that can cause interruptions, clinical trial delays and added cost, central lab contingency planning along with strong courier relationships ensure the safety and stability of sponsors’ most important assets – patient specimens. Whether the issue is geopolitical unrest, local labour strikes or driven by extreme weather, a central lab must always be vigilant and resourceful in identifying issues that could create a delay, and proactively implement an effective solution to ensure that specimens continue movement to their final destination and still in good condition.

How a central laboratory handles its transportation system can have a profound effect on how effectively it can serve its customers:

- Following the events of September 11, 2001 the US closed its entire air space. Based on a pre-existing contingency plan, a global central lab was able to use ground couriers in North America and re-route specimens from Latin America to its central lab in Geneva. In total, the company contacted more than 22,000 investigators, every single client contact in less than 3 hours.
- In 2007, Russia cancelled all existing export licenses, blocking all clinical trials. A global central lab deployed internal staff at a regional laboratory in Moscow in less than 24 hours and resumed safety testing locally 36 hours following the Russian MOH decision.

Some providers offer a hybrid model central lab and one or more specialized regional labs in an effort to combine the method standardization and quality benefits of a central laboratory with the proximity and competitive turnaround times of a local laboratory. Regional laboratories involved clinical trials may be CAP/CLIA accredited, and operate in compliance with Good Clinical Practice (GCP) guidelines. To mitigate the risk of data variability and the burden of managing a large, fragmented network of suppliers, pharmaceutical companies may seek a CRO or central lab to consolidate and harmonize the output of all labs. This is best accomplished via the ELMS (External Labs Management Services) approach previously described, such that potentially disparate data can be validated and combined.

Appendix: (1)

Covance Case Study – Sample Management During Hurricane ‘Sandy’
Opposite Opportunities & Challenges in Central Lab Logistics for Clinical Trial Success

Appendix: (2)

<table>
<thead>
<tr>
<th>Key Performance Metric</th>
<th>Definition</th>
<th>Overall Impact (High/Med/Low)</th>
<th>Logistics Impact (High/Med/Low)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Project manager turnover</td>
<td>The number of project managers who voluntarily or involuntarily left the project manager’s role divided by the total number of project managers.</td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td>Logistics turnaround time for samples</td>
<td>The percentage of projects that have the first samples to be shipped on-time, based on the defined expectations between sponsor and central laboratory.</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>Queries resolution</td>
<td>The average time required for resolution from the central laboratory to the site, based on the requisitions received by a central laboratory and vice-versa.</td>
<td>Med</td>
<td>Low</td>
</tr>
<tr>
<td>Data access to investigator site</td>
<td>Percent of data transfers sent to the sponsor within the agreed upon time frame.</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>Contingency measures</td>
<td>Percent of alerts and panics that had the first attempt made within 24 hours, and percent of alerts and panics that were successfully communicated within 24hrs.</td>
<td>Med</td>
<td>High</td>
</tr>
<tr>
<td>Received in Stability (RIS)</td>
<td>Percent of specimens received within stability compared to the total number of specimens received.</td>
<td>High</td>
<td>High</td>
</tr>
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</table>

In October 2012 hurricane “Sandy” affected the US east coast much sooner and more seriously than had been forecasted, resulting in profound difficulties for sample transportation and testing.

Samples in transit from a Covance’s Central Lab to referral labs would require special management, while those already at their destination would need to be kept stable if the referral labs were to close.

Covance closely monitored all shipments and diverted the shipments to their Indianapolis facility where they were safely stored and maintained with dry ice until both courier and laboratory operations returned to normal.

Covance was able to deliver 99.2% of collected specimen within stability for inbound samples for the regions affected by hurricane “Sandy” on the east coast.
Opportunities & Challenges in Central Lab Logistics for Clinical Trial Success

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María has more than 15 years experience managing global operations and has led teams in building industry leading practices and providing Covance customers with peace of mind by protecting their clinical samples and drug development data.

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