Clinical Site Activation

Way forward in speeding up

Site Activation Process

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Abstract

Covid-19 has put huge stress on clinical trials as most of the clinical trials are either paused for 2-6 months or stopped. Sponsors or CROs will need to bring a lot of innovations to speed up the clinical trials or at least clinical trials start-up to gain a part of lost time. So the industry is progressing in a way that in developed markets more adoption of virtual clinical trials is visible as well as exploring new potential clinical trial sites in emerging markets. To speed up Clinical Trial Site activations for new clinical studies they need a much calibrated strategy and local level intelligence. All factors such as Negotiations and Contract finalization with Clinical Trial Sites, Finding and Approving required Investigators, Early Patient Enrolment, Clinical Ancillary Supplies, Regulatory Approvals, Cost fixations with Sites and Investigators, etc. require combined approach. In this article, we will analyze and understand the various requirements for Clinical Trial Site Activation.

Introduction

Clinical Site Activation is a process of initiation of clinical trial study on that particular trial site. This includes a lot of steps such as finding required investigators and fee structure finalization, patients' enrolment, contracts finalization with sites, completion of all documents i.e. technical and non-technical documents, getting clinical supplies, getting approvals from regulatory bodies, etc.

In normal circumstances, the timeline of Clinical Site Activation varies, but roughly it takes anywhere between 2-4 months for First Patient First Visit (FRFV). However, due to the Covid-19 pandemic, most of the clinical trials are either paused or postponed for 2-6 months. Even after this timeline, it is expected that clinical trials will grow slowly due to social distancing norms and fear in the mind of patients. The industry will need to speed up a lot of other processes to reduce the overall delay in clinical trials, Clinical Site Activation being one of such prominent steps.

In the majority of studies Either Sponsors or Contract Research Organizations (CROs) are responsible for Clinical Site Activation. The steps included are mentioned in Figure 1.

Factors Affecting Clinical Sites Activation

Historically, many factors are affecting the speed of clinical trials initiation and these are needed to be addressed urgently to evolve in changing environment. As per our interaction with various investigators, CROs, and other experts from emerging markets in LATAM, Africa, and APAC we have found that issues such as Redundancy of Process and Repetition of data and documents, issues related to site contracts and investigator payments, delay in shipments of clinical ancillary supplies, slow technology adoption, improper patients recruitment, etc. are some of the key factors responsible for delay in Clinical Site Activation process. This further delays the clinical trials resulting in loss of Millions of USDs of valuable investment and resources.

- Site, Investigators, and Patients Identification
- Contract Negotiation and Discussions
- CTA Execution
- Protocol Discussion in Details
- Site Screening and Site Approval
- Investigational Review Board (IRB) Approvals
- Technical and Non-technical Documents are received and Site Requirements are met
- IMPs, Non-IMPs (Comparators), and Clinical Ancillary Supplies are Shipped to Site
- Site Initiation Visits
- Protocol related information sharing with Patients, getting signed Informed Consent Form, & met all criteria
- Patient Begins Treatment

Figure 1: Clinical Trial Site Activation Activities

Based on our interaction with many local experts we have covered key factors which a sponsor or a CRO needs to identify and to prepare proper intelligence before opening a clinical trial site. A detailed discussion of all issues and local experts' suggested solutions is

not possible to include in the current scope of the article. Therefore the factors are compiled in brief in table below:

Important Factors under Clinical Site Activation Process

1. Investigators

Factor	Investigators
Common Issues	Payments Structure, Work Engagement, Contacts with local communities and regulatory, etc.
Description	▪ In LATAM the investigators **work as government employees**. Therefore, the CRO needs to work with the national health network. ▪ In S. Africa the Principal Investigator must be a South African-based scientist **(resident of South Africa)** ▪ Whereas in many other African countries, like in LATAM, the investigators would be government employees ▪ The **payment structure** and currency in which they deal are very important to understand.
Questions one must get answers for:	▪ What is their work model and engagement type w.r.t. clinical sites and regulatory bodies? ▪ What are the preferred and strategic contract models? ▪ What are the various negotiation levers available for payments? ▪ What are various payment models available?

"In Brazil, we have many communities in poor regions that show a trust deficit with pharma companies. There are some ways to get them for clinical trials which include sharing more information with them, finding an investigator whom they trust, and who can explain to them the benefits, etc. So for this to happen, a sponsor needs to have the local presence through CROs. We ourselves remain in contact with many hospitals and maintain a good database of patients." BD Director from Brazil based CRO

2. Clinical Trial Sites

Factor	Clinical Trials Sites
Common Issues	Fee Structures, Past Experience, Supply Chain Connectivity, Success Rate with Patients Retention, Engagement Rules, Storage Facilities, Proximity to Patients Cluster, Repetitive Negotiations, etc.
Description	▪ Many sites have **fixed pharmacy fee or non-refundable start-up fee**. These requirements can be built into Master CTA to reduce the time of renegotiations.

	▪ In China, CROs are more actively working with **academic sites** in efforts to develop them into potential research centers. ▪ In LATAM the sites today need to **share the contract template** with concerned authorities, therefore the hospital and site administrators have greater visibility in such contracts. This leads to extended site negotiations therefore contributing to **lengthy negotiations**. ▪ In many African Countries, the clinical trial sites are generally **government-owned or government-controlled**, and the physicians are government employees. Therefore, the payment structure to both sites and investigators need to be carefully put in place to avoid any legal troubles later.
Questions one must get answers for:	▪ What are their fee structures, fixed and variable components of fee? ▪ Are they able to help in patient enrolment? ▪ Do they provide any advantage w.r.t. regulatory, technology, supply chain, etc. useful for early activation of site? ▪ Are they able to support virtual clinical trials? ▪ Are they able to share demographic data from previous CTs? ▪ What are the KPIs for analysing performance of site(s)?

3. Patient Enrolment

Factor	Patient Enrolment
Common Issues	Past Relationship with Trial Site, if any, Knowledge sharing, Trust in Investigator, Use of Digital platforms, Approach towards clinical trials, Attitude of hospitals for older and female populations, etc.
Description	▪ LATAM has large, diverse, and treatment-naïve population which is very useful for more recruitments. Also, the patients enjoy a strong bond with local physicians. This increases the need for the local investigator's participation in patient recruitment. ▪ In North America and Europe, the use of digital platforms is on the rise for more patient recruitments. This leading to more virtual trials due to Covid-19 ▪ In Africa investigators belonging to Minority Communities are less in number which affects the inclusion of patients from such groups. Secondly, in many cases, the investigators deny referring their patients' contacts for clinical trials due to lack of trust and less knowledge of clinical trials. ▪ Asia is becoming one of the fastest regions for patients recruitment for biotech clinical trials.

Questions one must get answers for:	▪ Are their specific institutes or academies available who can share patient database on local level? ▪ What is patients behaviour towards clinical trials? ▪ Do they prefer self-medication / OTC or do they prefer going to hospital? ▪ What is demographic split for Chronic and Rare Diseases? ▪ Do they prefer other incentives, based on local regulatory approval, other than medication for trial participation? ▪ What is their history towards completing clinical trials? What is drop out rate after trial starts? ▪ Are there specific minority communities available who can participate?

4. Contract Research Organizations (CROs)

Factor	Contract Research Organizations (CROs)
Common Issues	Proper local regulatory know-how, Contacts with investigators, Resources Available, documentation for local and international regulatory, Customs clearance help, etc.
Description	▪ A sponsor may need a local CRO or a global CRO with a local office in LATAM. This is necessary for various aspects such as: – Documents must be submitted in local languages – Local CROs can provide a good regulatory overview of each respective country since in many countries a sponsor needs multiple approvals such as one from the Ethics Committee and other is CA Approval. ▪ It is important to note that in one of the recent surveys it is found that CROs take 20-30% less time to start a clinical study at sites. ▪ Therefore, a local/regional CRO with good understanding & capabilities of all mentioned queries can be very useful for speed up the Clinical Site Activation.
Questions one must get answers for:	▪ Do they have Patients' database for fast enrolment? ▪ Do they have good relationship with various clinical sites? ▪ Do they have good contacts with various investigators? ▪ Can they help in various negotiations with sites and investigators? ▪ Can they help in speed up the local regulatory work and approvals? ▪ How often do they work with same investigator? ▪ Are they able to share demographic data from previous CTs?

5. Process Change

Factor	Process Change
Common issues	Centralized Vs. Decentralized Mix, Hierarchy of Steps to be performed, Work share between responsible parties, Innovations in Patients Recruitment, etc.
Description	▪ PPD unveiled a new patient enrolment model, dubbed as PatientAdvantage, which uses big data to identify eligible patients and then connect them with possible study sites, inverting the traditional steps of clinical trial delivery. ▪ CROs having centralized functional dedicated teams for site-related activities often invest more than twice as much in technology than did those without such a team. According to an industry-wide survey, it was found that more than 80% of respondents who have invested in new technology reported time savings
Questions one must get answers for:	▪ Is early patient enrolment useful to speed up clinical site activation? ▪ How JIT Site Activation can be implemented, and in which all regions? ▪ Which CROs offer centralized management of clinical study management along with proper planning of clinical site activation across various regions?

6. Technology Adoption

Factor	Technology Adoption
Common Issues	Technology Adoption by Large Pharma, streamlined technology flow between all stakeholders, Regulatory Approvals, Adoption rate by local stakeholders, etc.
Description	▪ **Embedded e-Signature** process can shave 15-30 days off the site activation time for a clinical trial in many regions. Companies need to understand the regulatory, technology adoption, and experience of physicians with such technologies for better planning and execution. ▪ Companies have also started leveraging **demographic data** from earlier Clinical Trials experience using a specific database or tools. This can further help in reducing the timeline for patient enrolment process.
Questions one must get answers for:	<u>To find out various stakeholders who can offer the following</u> ▪ Are single source platforms available and useful for given geography? ▪ Is there any platform available (and approved) which can help in reducing data redundancies? ▪ Is there any platform available which can leverage data and documents such as investigator CVs, Contractual documents, demographic information, other non-protocol related information, etc. for new

	clinical trial and can track data, deadlines, and revisions? ▪ Is it possible to use embedded e-signatures in particular regions?

7. Clinical Supplies (IMPs, Comparators, Clinical Ancillary Supplies)

Factor	Clinical Supplies (IMPs, Comparators, Clinical Ancillary Supplies)
Common Issues	Products types identification, Rental Vs. Procurement of Ancillary Supplies, Timeline of shipment, Coordination with site investigator, Kit Assembly and Storage planning, Imports from specific countries, Exports of Biosamples from specific countries, Custom Clearance, etc.
Description	▪ North America and Western Europe is moving towards Virtual Trials which comes with specific challenges of clinical supplies as well as data capture ▪ From Russia and China, the sponsors find issues in exporting biosamples to central laboratories. ▪ Whereas in many other emerging markets the import of certain clinical trial supplies from the US is less entertained. ▪ In Argentina many items such as printed documents, electrical devices, etc. require specific permissions for import. Hence, it is mandatory to identify all types of supplies well in advance and act for getting prior permissions from ANMAT. ▪ In Africa, the supply chain is fragmented in many countries which increases the use of specialty logistics and 3PLs who can manage clinical supplies along with local depots and CROs. The local team helps in getting regulatory. ▪ APAC countries are evolving very fast with an overall infrastructure of clinical supplies. Many specialty local companies takes care of the cold chain and specialty shipments, as well as, their good contacts with customs clearance agents help in quick approvals.
Questions one must get answers for:	▪ What are the local import/export requirements? ▪ Total timeline of import clearance from customs warehouse ▪ What is right strategy for Rental Vs. Purchase of Laboratory and Medical equipment? ▪ Which types of service providers are good for services such as International Shipment, Storage, Customs Clearance, Local Shipments, etc. ▪ Documentation requirement for each type of product to be imported and exported.

	▪ How to manage the destruction of wasted products and reverse logistics of expensive equipment? ▪ If it is fine to gift some items to investigator or trial sites? ▪ What are various options available for real time tracking of shipment?

"Clinical Ancillary Supplies is such a big issue that most of the time the sponsors send overages supplies to our trial sites in order to cover all contingencies. Sometimes the overages are to the tune of 100-150% of original shipment requirements. When a clinical trial is over they are left with huge stock of un-used supplies which is either destroyed or sometimes gifted to trial sites. Better planning can help them save some part of this investment." An Investigator from S. Africa

As per our inputs from our local contacts in various emerging markets the factors such as related to Patient Enrolment, Site Selection, Investigator Payments and Contracts, Clinical Supplies (As well as Clinical Ancillary Supplies), etc. are very major issues. Even a small deviation from the actual process leads to unexpected timeline delays for the Clinical Site Activation process.

Conclusion

Industry requires strategies at two levels such as:

Global Level

- New Innovations in terms of technology adoption, supply chain planning and mapping, relative standardized frameworks for quick contract signing with trial sites, proper hierarchy of processes to avoid wastage in investment, etc.

Local Level

- Local-level intelligence of CROs, Clinical Supply Chain, Investigator Payments and Working, Trust building with patients, Coordination with academics and institutions for getting access to patients data, etc.

Many global companies such as Astra Zeneca, GSK, Sanofi, PPD, Parexel, Icon, etc. are involved in more innovative practices such as Virtual Trials, Wearable Technologies for Data Capture, Process Change such as finding Patients first and linked them to clinical trial sites, collaborating with institutions for patients data access, etc. At the same time local CROs such as those in Brazil, Chile, Egypt, Turkey, S. Africa, etc. are working on local databases of patients as well as they have good coordination with local government institutes. Such

initiatives are welcome steps towards making the Clinical Site Activation process more streamlined.
But the missing key is the lack of local level extensive intelligence with global sponsors and CROs. This needs to be addressed quickly.

As mentioned above a lot of factors get involved in the Clinical Trial Site Activation. All these factors need thorough investigation and inputs at the local and regional levels. We have covered each of the above-mentioned factors from the mind of local stakeholders as

well as on a holistic global level. We are in the process of sharing separate articles on each of the factors in the near future.

For more inputs, please reach out to us at bd@essentialmarketinsights.com

Appendix:

1. Primary Interactions with Investigators in various regions
2. Primary Interactions with CROs in various regions
3. Primary Interactions with Clinical Depots in various regions
4. Secondary Interactions from:
    a. *AppliedClinicalTrials*
    b. *CenterWatch*
    c. *Clinicaltrialsareana.com*
    d. *Outsourcing-pharma.com*