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# Clinical Study Start-Up: Overview of the Process and Expected Challenges

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## Keywords

Clinical trials; Clinical research organization; IWRS

## Introduction

Start-up phase is the base of any project at any type of businesses, and CROs are not an exception. Initially, the emphasis was concentrated on conducting the study, with little attention paid to study start-ups (SSUs), but as stakeholders become more and more aware that the effectiveness of SSU processes is directly related to shorter clinical periods, interest in this opportunity is growing. SSU covers a lot of activities starting from sites identification and completing the enrollment of the first patient - in between this includes site selection and pre-study visits, trial documents submission to competent authorities, contract and budget execution, vendors approval and setup, site activation, site initiation visits and, at last, enrolling the first patient. Each step has multiple components and requires utmost care and attention to minimize the likelihood of study delivery delays from the beginning.

The clinical trials industry is continuing steadily to grow; as of January, 2020, it was found that about 52,300 of recruiting studies posted on ClinicalTrials.gov. Despite the impressive size of the clinical trial market, the site activation process faces several challenges. Failures and incorrect actions during study start-up can impact on the overall success. One of the examples is too fast diving into start-up, which may occur as response to pressures due to several factors - to get to market quickly, sponsor or senior management demands, actual patient needs or competitive products or trials coming to market. Even though speed and efficiency are keys, it is equally important to ensure that the project team managing the study has enough time to confirm that basic start-up factors are ready (for example, no issues with import/export, assurance that the study will be conducted in accordance with the law and


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there are no local restrictions for vendors setup and functioning, the electronic systems work correctly and uninterruptedly). As clinical development becomes more complex, an issue and consequent re-work in even one aspect of site activation can delay an entire study.

## Selecting Countries and Sites

As most part of clinical trials is global and the site selection is become multi-factorial, thus the process of site identification and forming the final site list can take a lengthy 2-3 months, on average.

When talking about the site selection, this means the procedure of assessment and selection of potential investigators for a clinical study. The assessment may include an on-site evaluation of the facility and assessing whether the investigator and site staff are able to conduct the study in accordance with the protocol and applicable regulations.

Of course, CROs and sponsors are looking to get the most eligible and right sites and investigators, and this creates competition between them.

The essential factors in getting the right sites for the study:

1. Estimation of the capabilities of the site for recruiting patients (possible diseases, accessible populations, previous experience in recruitment, the ability to involve the patients from external sources);
2. Qualified site staff and sufficient personnel to fulfill the study needs, including sub-Investigators, study coordinators, data managers;
3. Ability of the site to provide study rooms/equipment/required study procedures, including proper and regular equipment calibration and maintenance;
4. Estimation of the possibility of efficient use of the electronic systems available at the center (for example, electronic source documentation, electronic patient registration system, electronic patient database);

Therefore, the therapeutic area, eligibility criteria, treatment requirements, site structure, and staff capabilities are among the basic characteristics that sponsors and CRO must consider when evaluating sites. Meeting this goal – getting the right sites - involves conducting more efficient and effective site feasibility to identify the best sites according to the sponsor and study requirements (the site staff is adequately qualified and has experience in clinical trials and It is sufficient to conduct the study, the recruitment expectations will be met, all the facilities are present at the site and calibrated etc.). Fortunately, this approach is now possible with the recent launch of purpose-built technologies designed to combine data from multiple sources that point sponsors and CROs toward the right sites, increasing the chances for better start-up execution.

When making country, site and enrollment planning decisions, a common mistake is to rely on too little data or subjective information. This may include selecting countries and sites


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based on personal or corporate preferences, selecting countries because of short start-up timelines without considering overall impact to study performance, or predicting enrollment based on investigator enrollment estimates alone [1-3].

More challenges expected on the way of site selection:

- Issues with the staff involved in the project - work overload, not responsive staff, lack of resources, lack of motivation;
- The possible protocol features – for example, if the patient may need any specific procedure or additional medications during the screening or further (medications for onco- disease, vaccination etc.) they should be available/approved for the country.

**Organization of regulatory submission**

After the selection process of right and appropriate sites is completed, you need to focus on the process of submission the clinical trial documents to regulatory authorities and obtaining approval for the study. In Europe, this is a rather complicated process and should be done strictly in accordance with the local regulatory requirements. Successful submission in many countries requires an extensive package of documents, which may include not only the essential documents, but also specific ones, sometimes certified and provided directly by the pharmaceutical company (depending on the country, this may be a list of equipment, additional documents for the investigational product, original letters to regulatory authorities, etc.). For most of countries Informed consent form (all the applicable for the study) should be adopted according country local requirements and submitted in local language (usually, more than one). The review process lasts 1-4 months and the timelines also depends on the remarks from RA which can be provided during Questions & Answers cycle and require immediate clarification from sponsor in established timelines. As soon as response provided, the decision for the clinical trial to be issued. In the past, for some countries (Poland), an adapted contract agreement template was required for submission purposes and it was also time consuming, but this requirement was canceled last year [4,5].

## Site Activation

Once you have selected and approved the appropriate sites for your study, the next step is moving the selected sites through the process to become activated sites; thus, they can immediately begin to enroll patients. One of the key factors here is to reduce the possible re-work of sites and the study team; means, the sites must perform several specific activities related to documents, submissions, contracts across multiple studies with multiple sponsors. These documents include site feasibility survey forms/ SIFs, protocols, investigator brochures, site contracts, budget worksheets, patient recruitment plans, informed consent forms, and patient recruitment and advertising materials etc. Ensuring the use of the most recent versions of these documents can be challenging if there are several versions and amendments issued before activating the site. Severe paper processes add to the burden of starting a study. On the other hand, the process should be visual, so any necessary


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adjustments can be quickly identified and corrected. The key milestone for site activation is indicating the site is ready to enroll subjects. Pre-requisites for Site Activation include: Investigator site's Essential Document Pack (EDP) is approved, Investigator site has been approved for investigational product release, site staff is fully trained to follow protocol procedures, the site initiation visit has occurred, and the site is fully ready to enroll the patients. Effective planning of the activation process can significantly reduce timelines and speed-up the process - collection of documents, handling of import/export, contracts/budget negotiation and vendors setup may be performed in parallel. An important factor is the use of complex electronical systems that centralize the data that are needful to study groups and enable teams to work with the data,helping to avoid the "human factors" (for example, completion of electronical SIFs/feasibility surveys directly on the portal). This allows the study team to more accurately manage the study activation process and have all its paths functioning quickly and qualitative.

## Improving Start-up

When making decisions about the participation of a country, sites for the study conduct or strategies for recruitment, a common mistake is to rely on too little data or subjective information. This may include the selection of countries and sites based on personal preferences, the choice of countries due to short RA approval timelines without considering the overall impact on the effectiveness of the study or incorrect planning of recruitment strategies. This approach may lead to the necessity to add countries or sites during the patient recruitment phase, to replace countries or sites that are failing to meet expectations, or to extend recruitment timelines due to slower-than anticipated enrollment. Any of these can have a negative impact on efficiency, study budget, and timelines. Feedback from investigators is a critical part of the study planning process; their insights into the feasibility of the study design, treatment pathway, patient population, and recruitment and retention planning allow for solid protocols and operational strategies to be developed.

Technology has become standard practice in the form of electronic data capture (EDC), the clinical trial management system (CTMS), the interactive web response system (IWRS), systems for reporting – the usage of sophisticated systems allows to eliminate the number of errors, and downtime along a continuous run and provide critical performance of the startup team. Standardizing processes, templates, tools and forms is another way to reduce cycle times. For example, the availability of the informed consent form or Investigator contract template, which includes all the specific requirements for the country, may retain significant time at the front end. It is worth noting that more thorough and earlier risk planning discussion - with better focus on site activation & enrolment reduces likelihood of gap between site initiation visit and 'first patient in' due to vendor issues, training not done by site etc.


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## Conclusion

Successful study start-up is an essential first step and relies on overcoming a range of factors. These include country and site selection, regulatory submissions, site activation, proactive planning and patient recruitment strategy - all of which can influence decisions and have a dramatic and positive impact on the conduct of the entire study. A key feature is real-time escalations and proactive foreseeing of potential issues, which help decision makers to take action immediately or before a major setback has occurred, instead of after the fact.

Study start-up is complex, with multiple critical interdependencies and areas where elements can go off track. Aligning processes early in study planning to minimize decision-making and time delays can be particularly important and have a significant impact on timelines and productivity. Reducing the number of decision points for items such as site contracts, as an example, can have a positive influence on the start-up process as well as the overall relationship between the site, clinical research organization (CRO) and sponsor. Effective work and communication with sites, their direct understanding of the promptness of actions (quick signing of a confidentiality agreement, objective and complete filling of questionnaires/site information forms with clarification and highlighting of controversial issues - best of all in 24 hours) will result in excellent collaboration - this will allow the site to receive more trials in the future. Of course, there is always an unpredictable threat of the study start-up not being completed on time, the original protocol is suspect and need to be updated, unavailability of necessary documents or a regulatory agency has stepped not to approve the trial based on unexpected results. When considering an appropriate start-up plan it is important to account for both real-world experience and performance data and regulatory dependencies as part of the standard process.

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