

## Solving clinical trial delays: innovative solutions

Our objective was to provide broad perspective on causes and consequences of clinical trial delays and suggest process-oriented and technology-enabled pragmatic solutions to minimize trial delays, in particular context of doing trials in India. The main challenges for successful completion of clinical trials stem from regulatory and ethics review, investigator selection, site initiations, participant recruitment and retention, monitoring and data management issues. Careful planning, sorting out ownership issues in the initial steps and a partnership based on shared issues among all the stakeholders will help reduce the trial delays. Such a shared vision will enable adherence to regulatory requirements, enhance the quality of trial conduct and ultimately enable improved access to new treatments and its benefits to the Indian population.

**Keywords:** clinical trial delays • ethics and regulatory issues • participant recruitment and retention • technological solutions

Clinical trials are an essential component of the drug discovery and development process [1]. On average, a drug spends over 10 years going through different phases of clinical trials and regulatory processes to get a marketing authorization (license) [2]. The success of clinical trials is contingent upon timely completion of several sequential processes: ethics and regulatory review, investigator site selection, site initiations, participant recruitment and follow-up, monitoring and data management, to name a few [3]. Poor management of any of these tasks can affect the performance and outcome of the trial and cause delays, a common problem resulting in increased cost and sometimes premature termination of research [4,5]. Trial delays impose economic and ethical implications: by increasing trial costs for the sponsor, which may translate into increased cost of drug when approved, and delayed access to better treatments for the society [5–7]. While there is no single remedy for the complex issue of trial delays, in this review we outline the most common causes of trial delays, the

consequences and suggest pragmatic solutions to alleviate trial delays, in particular context of doing clinical trials in India.

### Causes, consequences & potential solutions of trial delays

#### Ethics & regulatory review

Ethics and regulatory review, while serving an important function to safeguard trial participants, and ensuring scientific credibility of research study, is generally regarded as a cumbersome and time-consuming process. The ethical and regulatory review in India is still paper based and the whole process takes about a year for multicenter trials. In the recent past, concerns raised by the NGOs regarding unethical practices in clinical trials in India prompted the Supreme Court to intervene and call for an overhaul of the regulatory environment [8,9]. As a consequence, drug trial regulations were amended and new processes to review clinical trial applications and to monitor trial conduct were put in place [10]. The objective was to establish a robust sys-

Kavita Singh\*, M Abdul Salam<sup>1</sup>, Raji Devarajan<sup>2</sup> & Dorairaj Prabhakaran<sup>2</sup>

<sup>1</sup>The George Institute for Global Health, Unit No. 301, Second Floor, ANR Center, Road No.1, Banjara Hills, Hyderabad - 500 034 Telangana, India

<sup>2</sup>Centre for Chronic Condition & Injuries, Public Health Foundation of India, 4th Floor, Plot No. 47, Sector 44, Institutional Area, Gurgaon - 122 002, Haryana

<sup>3</sup>Department of Endocrinology & Metabolism, All India Institute of Medical Sciences, Ansari Nagar, New Delhi - 110029, India

\*Author for correspondence:

Tel.: +91 9899 69 11 50

kavita@ccdcindia.org

tem to ensure scientific and ethical conduct of clinical trials in India. These amendments to regulations were about registration of ethics committees with the regulatory agency, audio–video consenting of trial participants and compensation to trial participants in case of serious adverse events. While all these are considered as steps toward improving research, it adds to the complexity and concerns of doing trials in India. It gets complicated further for academic studies, funded by foreign agencies such as the NIH, USA, with the need for regulatory approval by the Health Ministry Screening Committee (HMSC) in India. The HMSC appraises the flow of foreign funds to academic institutions in India and also oversees the scientific relevance of research studies within national interest. The HMSC approval in turn requires local ethics committee approvals from all participating trial sites and the Drugs Controller General of India clearance letter. Additionally, the NIH sponsored trials require registration of local site Institutional Ethics Committees (IEC) with the Office of Human Research Protection, USA and obtaining Federal Wide Assurance (FWA) for protection of human subjects. It also involves periodic renewal of IEC registration with FWA, and annual renewal of ethics approval for ongoing research studies, which is discordant with the standard practices followed by most local site IECs, resulting in delays [11,12]. Multicenter trials seeking ethics approval of a common study protocol from a multitude of sites poses a major impediment. Because each site's IEC follows different formats (summary sheet) for submission of research proposals, it leads to further delays and increased cost (including ethics review fees). Often, in such cases, obtaining the ethical and regulatory approvals to initiate trial takes an additional 6 months to 1 year, primarily due to shortage of trained manpower, lack of adequate information on review process and lack of coordination, time and commitment from the participating site teams and local IECs [13].

#### Solutions to minimize ethics & regulatory delays

We recommend following potential strategies based on personal/firsthand experiences to streamline and expedite the ethics and regulatory review: submission of trial documents for review by IECs and regulatory authorities using a secured electronic portal (as being currently practiced in many developed countries), which will make the submission easier and faster compared with submission of hard copies. Electronic portal submissions will be useful for tracking the application status online. Queries in relation to the submission can be posted online with a direct email notification being sent to the principal applicant requesting for clari-

fications. This will be opportune for the sponsors to submit prompt responses and will save time generally spent on physical shipments of documents. In addition, use of an online review system will allow us to identify key indicators to map the process measures, with an ultimate aim to improve efficiency of the system. The key process indicators of an online review system could be for example: number of applications received, number of days spent on review, number and type of queries raised, number of days used to provide final decision, number of cases that experienced any delays and reasons for this can be investigated to minimize future delays. Developing an electronic filling and tracking system is believed to bring more transparency, efficiency and expediency. Further, a combined technical review panel can be formed to merge the functions delivered by the HMSC and Drugs Controller General of India. This could reduce the time spent on review by at least 6 months. Also, similar to US FDA and UK MHRA review processes, investigators/sponsors in India could start conversation with the regulatory officials at the beginning of developing a new protocol with a concept note including available preclinical data on the candidate product. Based on the early feedback received from the regulatory authorities, investigators can make changes in the protocol, and go on to develop and submit the full protocol. Engaging patient representatives and/or community gatekeepers/leaders and addressing their issues upfront at protocol development stage would help avoid future queries raised by the ethics committee or regulatory authorities. At a higher level, the Indian Council of Medical Research or an equivalent body in India can take initiative to establish a national ethics review board consisting of representatives from various states to review proposals received from across the country (or at least set-up regional ethics review board to facilitate swift review of study proposals). Having a centralized ethics review board in place will save time, money, manpower and efforts put in by very many ethics committees in reviewing a single proposal, which is to be followed by all trial sites in multicenter studies. In addition, the national ethics review board can collaborate with Office of Human Research Protection to harmonize the peculiarities of FWA registration and annual renewal of ethics approval requirements in NIH-funded trials. To improve uptake of regulatory amendments, drug authorities can organize dissemination workshops and interactive sessions with the research practitioners and should incorporate suggestions arising in those meetings. Regular training of IEC members and regulatory officials by experts (consisting of regulators, clinicians, research scientists, drug manufacturer, legal advisor, insurance provider, social activist and representatives

from patient-group) on technicalities of review process, development of a checklist to be considered in review process and on providing feedback along with the regulatory decisions to the applicants (investigators), will strengthen the review competence and speed-up the review process.

### Investigator & site selection

The investigator and site selection is the foremost step when planning to conduct a clinical trial. Recent amendments in the Indian regulatory guidelines mandate hospitals with minimum 100 beds and site principal investigator handling not more than three drug trials under his/her supervision are eligible to participate in drug trials. Typically, investigator site selection is guided by the prior experience of sponsors working with the investigators [14]. However, for selecting new sites advice is sought from friends in the industry, and investigators that are currently involved in studies run by the sponsors/CROs. Investigator site selection is usually based on following criteria: educational qualification and experience of the investigator in conducting trials, access to large patient pool, resources available at the site (trained research staff, clinical research infrastructure etc.), affiliation of the site with an IEC, frequency of IEC review meeting and investigator site eligibility as per regulations to avoid future hurdles. Failure to select a suitable investigator site may jeopardize the overall performance of the clinical trial. As per industry rule of thumb, one-third of investigator sites recruit no participants, one-third recruit 20% and one-third are 'super sites' that recruit 70–80% of the participants [6]. Therefore, an overarching aim is to select 'supersites' to accomplish recruitment target on time. However, there is no central open-access repository of clinicians interested to take part in clinical trials, which leads to selection of limited number of sites (often overburdened) from existing databases maintained by the sponsors. Selection of limited number of sites results in failure to meet the recruitment target. In such instances, adding new investigator sites contingent upon regulatory and ethical approvals at later stage cause further delays [15]. In circumstances where the investigator leaves the site, important procedural changes are required such as amendment in the clinical trial agreement, investigator undertaking, sending notifications to regulatory body and IECs etc, and this can significantly impact site staff motivation, recruitment and follow-up.

### Solutions to minimize delays associated with investigator site selection

Investigator site selection is an ongoing process and failure to select good sites is a missed opportunity for reducing drug development costs, time and data errors. There are no standard criteria available to eval-

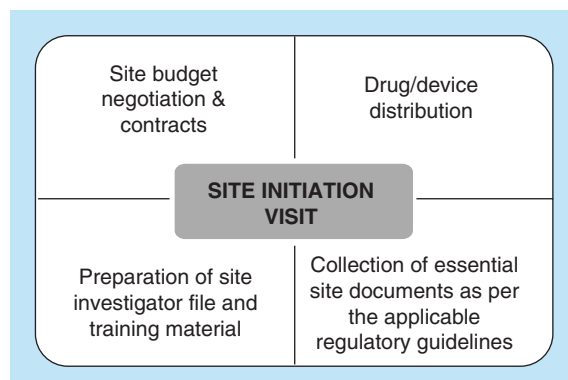
uate or improve the investigator site selection process or to systematically identify, recruit and motivate investigators to generate high-quality data. However, a strategic information-based and systematic approach drawn from individual site performance measures (i.e., quality, cost and responsiveness) can be analyzed to modify the mix of investigator sites selected to conduct a clinical trial. Site feasibility assessment generally helps to further optimize the site selection process. To improve accessibility of potential investigators, hospitals can provide details of experienced and interested doctors by therapeutic area on their website. Alternately, investigators can register themselves with the drug firms or CROs and upload their CV to form a database of experienced investigators classified by treatment area or clinical conditions. Regulatory authorities can also publish a list of all investigator sites who have participated in clinical trials on their website. In addition, to enhance the selection of good performing sites, the list of investigators can be rated by sponsors or CROs in an anonymous fashion based on key indicators: patient recruitment, data quality and completeness, responsiveness and support of trained research staff and clinical research infrastructure. Anecdotal instances suggest that early involvement of investigators at the trial design stage is likely to result in strong investigator commitment and success of the trial when compared with selecting investigator sites at later stages when the protocol is finalized. Engaging co-investigators is always fruitful and ensures that the trial is not adversely affected in case of the loss of site principal investigator.

### Site initiation

Site initiation delays have a direct and substantial impact on patient enrollment deadlines. Achieving enrollment-ready status for a site is a challenge because behind each step (see [Figure 1](#)), a variety of stakeholders are involved: the sponsor, investigator site, vendor organizations, ethics committee, legal or regulatory bodies. Most experts agree that poorly chosen sites and inadequate project management are the prime reasons leading to slow initiations [16]. Since many of the site initiation activities do not follow a chronological path and are indeed interdependent, they are to be coordinated simultaneously to be completed on time, adding yet another level of difficulty to the process.

### Solutions to minimize site initiation delays

The key to successfully initiating all sites to enrollment-ready status starts with choosing optimal sites and establishing rigorous project management methods designed to take into account the variability inherent in the clinical trial process. We propose following



**Figure 1. Site initiation visit: concurrent processes by numerous stakeholders.**

measures to ably handle the multitude of activities that are undertaken prior to site initiations: prepare a legal and ethics submission plan for each participating site concerning site contracts, budgets, insurance, translations of study documents (if relevant) and understanding the ethics submission requirements helps in rolling out the processes timely and prepares the site for initiation. Interacting with the site manager or hospital administrator at initial stages can help clarify or resolve any issues with the contracts and budgetary terms and conditions. In multinational trials, employing a global insurer to set up coverage within each country to include participating institutions satisfies local site IEC requirements. To facilitate the investigational drug/device distribution to the investigator sites, the drug manufacturer, project manager and site manager can work in tandem and identify any barriers to successful delivery and storage of the investigational product. Building a cordial relationship between the site manager and drug manufacturer improves responsiveness as well as turnaround time of collecting essential documents needed for site initiations. In our experience, small and dedicated research teams focused on a few research studies at site level work more efficiently than a large team assigned to numerous clinical trials. Nevertheless, the overall approach should acknowledge the inherent variability in site initiations allowing for midtrial changes or corrections.

#### Participant recruitment & retention

Participant recruitment is crucial to the clinical trial process – without adequate numbers of participants the trial cannot succeed. Typically, the site investigator is in charge of participant recruitment, who normally adopts a recruitment strategy based on participant's concerns about taking new investigational drug or placebo, experiencing adverse events, cultural beliefs about the medicine and the degree to which participants are able to commit time and effort to comply

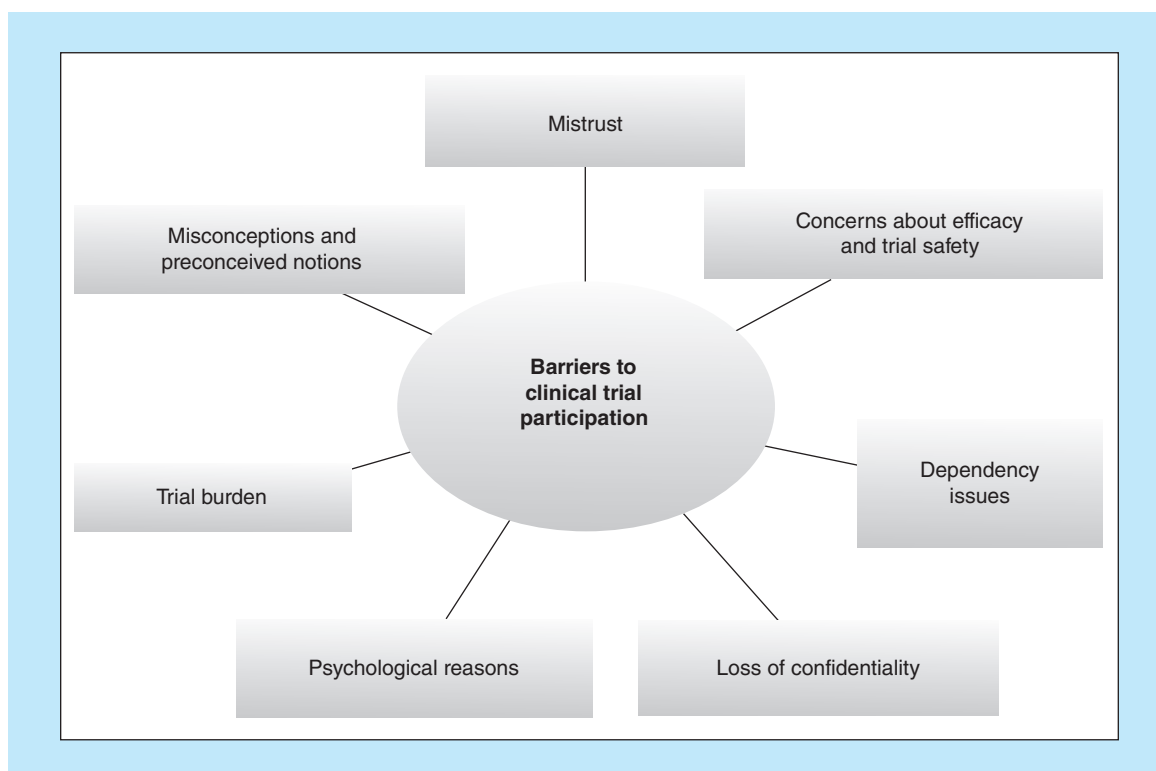
with the trial requirements [17]. Other participant factors: disease severity and distress, lower socioeconomic status and education, lack of social support and minority status also play a crucial role [18]. Previous research has revealed that high study demands (e.g., frequent appointments, long follow-up duration and extra or inconvenient procedures) and greater travel costs deter participants from continuing in research [19–21]. Understanding the barriers and incentives for patients to participate in clinical trials could alleviate recruitment and retention problems (Figures 2 and 3) [22].

Further, the recent regulatory amendment in India requires investigators to obtain audio–video consent of research participants in drug trials. However, it has been debated and argued that no clear guidance is provided to the investigators on the system requirements, execution and archiving of audio–video consents of research participants. Further, most participants feel shy and hesitant to agree for audio–video consenting as a matter of breach of personal privacy, leading to more refusals.

Poor participant recruitment and retention affects different stakeholders uniquely. For sponsors, it may lead to inconclusive results, loss of position and/or revenue for product, decline of confidence in investigators. But for trial sites, it can potentially result in lost revenue for missing recruitment targets, and risk to future trial participation with sponsor. Failure to recruit and retain sufficient number of participants threatens the internal and external validity of randomized controlled trials. High rates of attrition during follow-up can produce bias, and the study results may not be due to the actual treatment effects but rather due to a disproportionate loss of participants who may be more or less symptomatic or unresponsive to the study medication than other participants; hence, limiting the generalizability of study findings [23,24].

#### Solutions to minimize recruitment & retention delays

Prior to beginning with the research study, the investigator/sponsor should understand the study population and address as to why a trial site would be motivated to enroll, and what are the barriers to participation from trial participant's perspective, for example, travel distances, number of clinic visits, etc. At protocol design stage, the sponsor should carefully consider primary study endpoints, and can review other published trials to base the sampling strategy and simplify the study screening procedures as much as possible. Recruitment projections and continuous monitoring of recruitment is important to provide rapid assessment of the recruitment strategies currently being employed and identify areas for improvement [25,26]. Lately, objective



**Figure 2. Barriers to clinical trial participation.**

measures such as recruitment index has been proposed for planning the duration of recruitment period for a new study, or projecting the number of participating sites required to enrol the target number of analyzable patients within a certain period [27]. Electronic decision support tools can be utilized to help with participant eligibility assessment as its use has been justified in multicenter cancer clinical trials [28]. Drug trial regulations should also reconsider the inclusion of audio–video consenting process, given the privacy issues raised by the study participants.

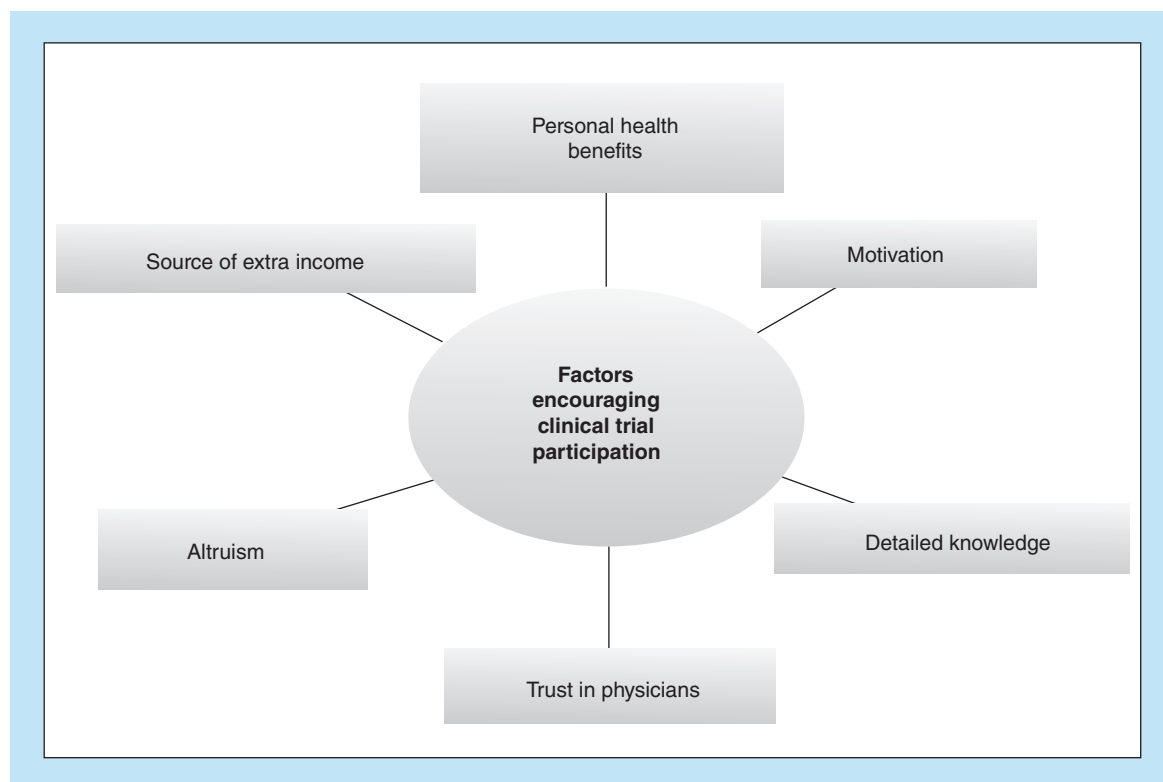
To address patient retention issues, at the first sign of possible study withdrawal or lack of interest expressed from the trial participant(s), the site staff can proactively initiate dialog assistance and intensify communication to prevent possible drop-out. Sending timely visit reminders to trial participants is known to improve compliance. Simple and effective short tutorials or easy to follow educational support pamphlets could be provided to the research participants, especially in trials involving complex procedures. It is well known that informed and satisfied participants can be retained through the study, therefore strategies such as providing special time window for seeing clinical trial patients, transport assistance to avoid cancellation of appointment and building a rapport with the study participants, quick feedback, and swift payments for any travel reimbursements can enhance retention.

Other strategies such as self-monitoring tools, for example, providing patient diary or sending electronic messages to track progress and activity completion is also found to be useful in improving compliance in previous studies. Informing the research participants of the trial results improves confidence and future participation in clinical trials.

#### Site monitoring visits

Frequent on-site monitoring visits by the research coordinating center or CRO during the recruitment and follow-up period creates a significant delay in study related activities by overburdening the trial site staff. It can also result in overworked or unenthusiastic staff [29,30]. On the other hand, central statistical monitoring (CSM) reduces the need for regular on-site monitoring visits [31,32]. CSM could be done at prespecified, fixed intervals at the research coordinating center with a small team and has been found to be an efficient and cost-effective option for tracing data errors which could be completely unintentional resulting from carelessness, fabricated data or falsified data to obtain a desired objective [33,34]. The US FDA and EMA also encourage greater reliance on CSM. Per the recent guidelines by the Indian regulatory authorities, expert committees are encouraged to visit clinical trial sites annually to check the sites compliance with the Indian guidelines namely Schedule Y, India Good Clinical





**Figure 3. Factors encouraging clinical trial participation.**

Practice and other applicable regulatory requirements. This should reduce the burden of on-site visits conducted by the CROs. Limiting the involvement of site staff to a couple of trials may encourage them in taking up new responsibilities of resolving data queries and in delivering the trial more efficiently.

#### Data management (documentation)

CDM greatly influences the quality of data generated and outcomes of the clinical trial. Several processes in CDM such as Case Report Form (CRF) designing, CRF annotation, database designing, data-entry, data validation, discrepancy management, medical coding, data extraction and database locking affects the delivery of the trial [35]. The traditional method of data collection is to employ paper CRFs, which are filled up by the site coordinator according to the CRF completion guidelines and then entered/translated in the database. In the e-CRF-based CDM, the investigator or a designee is able to directly enter the data, in which chances of errors are less, and the resolution of discrepancies happens faster. To meet with the regulatory expectations and to fast track the drug development process, we foresee a gradual shift from the paper-based to the electronic systems of data capture and management. Electronic data capture further offers the unique opportunity to the CDM team

to track the retrieved CRFs for missing pages and to ensure that data are not lost. In such cases, a prompt clarification is obtained from the investigator, and the issue is resolved and an audit trail is maintained. However, the biggest challenge from the regulatory perspective in the use of CDM is the standardization of data management process across organizations, and development of regulations to define the procedures to be followed and the data standards. From the industry perspective, the biggest hurdle is in the planning and implementation of data management systems in a changing operational environment where the rapid pace of technology development outdates the existing infrastructure. In our experience, developing, testing and validating new clinical data management software is a tedious and constantly evolving process and may take up to 1 year. Technology, time and cost constraints further influence the software development. This can be overcome by adapting to existing trial data management software, rather than developing a new electronic database. Freezing the CRFs early and minimizing any modifications done in CRFs later on, also prevents testing and validation time spent in the database once active/developed.

Recently, for document exchange and improved communication, use of a trial-specific website/database is being increasingly used, which has different

levels of user access for sponsors, site investigator, site coordinator, trial monitor, project manager and data management team. Having a centralized online portal to access study documents, and to find study updates, saves great amount of time spent by site staff searching for study documents in their latest versions. This time can be utilized on other important tasks such as recruitment and patient follow-up. However, transfer and storage of information from trial website to electronic Trial Master File should be translated carefully.

### Future perspective

As with any other field, the field of clinical trials is evolving. On one hand, increasingly, as required by the regulatory agencies, pharmaceutical companies are faced with the challenge of enrolling large number of research participants in Phase 3 clinical trials, while on the other hand the benefits of getting a new drug registered ahead of competitors offers lucrative benefits. Multicenter and multicountry trials provide sponsors with the opportunity of enrolling large number of participants in less time. However, weak clinical trial environment in developing countries offset the benefit of doing multicountry studies. Developed nations had a head start of couple of decades, and currently have tried and tested processes in place. Much of these processes are being adopted in developing countries, gradually. There is palpable effort from the policy makers in India to streamline regulatory and ethics review processes, and to bring about systems to ensure ethical conduct of clinical trials in India. With world class healthcare infrastructure, qualified investigators and enormous patient pool of diverse medical conditions, India is surely a potential hub for clinical trial industry. However, of the clinical trials conducted over the past decade, few have been completed on time [35]. The recent overhaul of regulatory environment in India is seen as a much needed course

correction, however, consistent efforts are needed to create environment that enables active engagement of various stakeholders to facilitate rigorous and swift conduct of clinical trials and to shorten the drug development phase. Indeed, it is challenging to perceive and implement system reforms to reduce trial delays and so we often opt to maintain the *status quo*. Despite this, the rewards for incremental changes to avoid delays can be immense since we know that two-thirds of overall drug development cost is spent in clinical trials. We conclude that the trial delays can be addressed using a combination of incremental process-oriented and technology-enabled improvements (integrating trial processes from various stakeholders' perspectives), however, without compromising trial participants safety measures.

### Disclaimer

The contents of this publication is solely the responsibility of the author/s and does not necessarily represent the official views of the National Institutes of Health or the ASCEND Research Network.

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### Executive summary

- Of majority clinical trials being conducted in the last decade only a few have been completed on time and results published or disseminated for wider use.
- Challenges for successful completion of trials range from obtaining ethics and regulatory review, investigator site selection, participant recruitment and retention, to data monitoring and data management.
- Careful planning in advance and use of a checklist for regulatory and ethics submissions steered by an expert regulatory analyst avoids bumpy road ahead.
- Creating online portals to deliver information to the site investigators, and to manage ethics and regulatory submissions, should streamline clinical data collection and clinical trial processes.
- Central statistical monitoring has been found to be an efficient and cost-effective option, when compared with on-site monitoring, for tracking data errors and resolution.
- Care should be taken to ensure that in preventing trial delays and shortening the recruitment cycle, participant safety measures are not compromised in the clinical trial process.

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