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Global Goals

When implementing a clinical trial, many considerations have to be taken into account. With factors ranging from global and cultural regulations to clinical constraints, one must be familiar with key issues when instigating the development process

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The achievement of the first patient enrolled (FPI) into a clinical trial is one of the most highly anticipated events of the drug/device development process. The pressure to realise this milestone – whether to meet a corporate target or outpace the competition as the baton passes from one trial to the next – is intense and may precipitate premature study starts, resultant delays and an overall decrease in potential revenue. The fleeting elation at the start of enrolment is quickly abandoned. Anxiety regarding the next and arguably more important milestone – last patient out – builds rapidly. In the rush to achieve FPI, thoughtful study design and reasoned start-up considerations are often neglected to the detriment of the overall development timeline. Re-prioritising study design, in addition to careful consideration of multifactorial influences associated with international studies, will facilitate study start-up and help ensure the rate-limiting, last patient out occurs within expected timeframes.

Right the First Time

Due to the intense pressure to achieve FPI, the industry does not often get protocol design right the first time, resulting in a negative impact to overall timelines and cost. 86% of clinical trials are estimated to experience delays, and 94% of clinical trials are delayed by over one month (1). The protracted timelines associated with the clinical development process directly correlate with increased costs and decreased revenues. The projected costs to bring a new drug to market are currently between $161 million and $2 billion (2). For each day a clinical trial is delayed, up to $8 million in revenue is lost. The cost to implement a substantial amendment is approximately $500,000-$1 million, comprised of internal administrative and investigator expenses, contract change orders or new contracts with service providers, additional drug supply and regulatory fees (2). Thus, careful protocol planning is key to preventing design-related delays, which impede last patient out milestones and generate unnecessary costs associated with protocol amendments.

In addition to the complexity of protocol design, studies are increasingly being conducted in multiple countries and regions in an effort to achieve the required

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patient numbers to address rare diseases or run large outcome trials, which can create complexities that may not have been anticipated when the protocol was originally conceived. Factoring international considerations into trial design may facilitate a more efficient development process and provide earlier access to medicines for patients (3). To expedite trial start-up, reduce the need for amendments and increase acceptability of the data produced, the protocol should be carefully planned and designed in advance of study start-up. In a 2016 paper, Tufts Center for the Study of Drug Development found that:

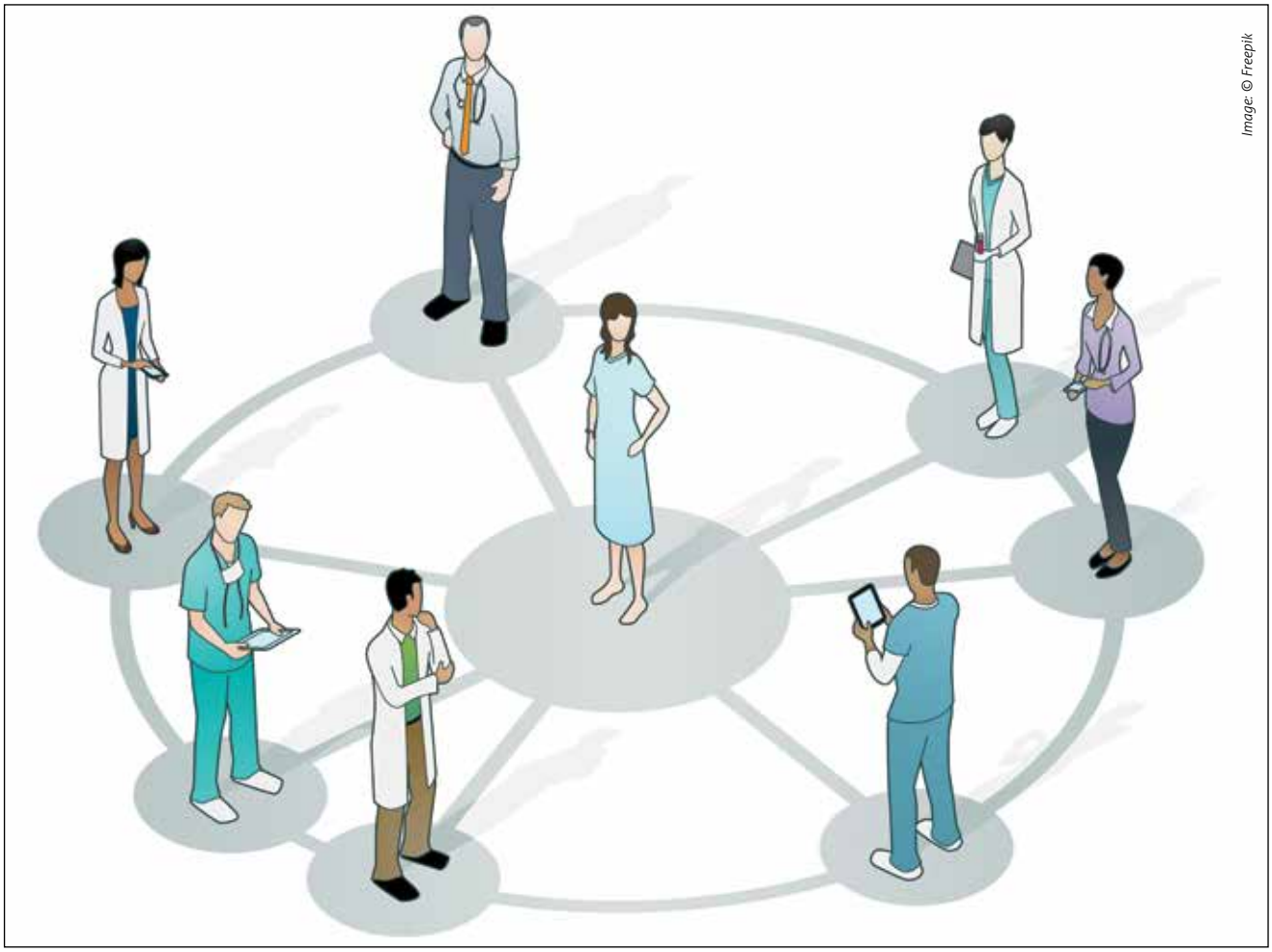
- 57% of protocols had at least one substantial amendment, with nearly half of these considered 'avoidable'
- Approximately 2.3 global amendments were seen across Phase 3 studies
- Protocols with at least one substantial amendment fell below patient recruitment targets compared to those without (4)

Multiple Geographies

To thoughtfully design studies in the context of a development programme, it may be beneficial to conduct exploratory trials in multiple regions. These can provide valuable insight on the impact of extrinsic and intrinsic factors on pharmacokinetics, pharmacodynamics and study execution, as these could inform planning of the larger, more expensive, confirmatory trials. Intrinsic and extrinsic factors should be considered in the following categories: product, start-up, clinical and culture.

For product factors, careful consideration needs to be given to the choice of background therapies, concomitant medications and even the source of the comparator(s). Although, in principle, a background therapy should be the same in all trial countries, the sponsor may find a product is not licensed in a particular country, and obtaining the necessary information and approval to import it can prove difficult and time-consuming. Similarly, the logistics of central sourcing can be problematic if standard-of-care is different among trial countries. If differently sourced comparators are used, justification, such as bioequivalence data, may be required (3).

Start-up factors include dealing with sometimes contradictory regulatory authority requests, such as differing primary and secondary endpoint requirements and divergence in the requirements for the control arm (5). Clear inclusion/exclusion criteria that can be globally applied helps mitigate many issues. Thinking about how endpoints may be viewed across regions, particularly those using scales or questionnaires, and recognising that validated, translated versions should be available for all proposed countries is important.



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“Local legislation can mean a non-interventional trial designed for one country is considered interventional in another, requiring full regulatory authority and ethics committee approvals”

Individual regulatory authorities can impose secondary endpoints, so it is good practice justifying them clearly to reduce the likelihood of country-specific amendments being imposed. Alternatively, consider incorporating them in a sub-trial. Regulations defining when the use of a placebo is appropriate can vary, and, therefore, a placebo-controlled trial may not be approvable in one or more of the expected countries. Differing global regulations can affect paediatric trials in particular. Age ranges related to consent can differ, which means it is critical to word the protocol appropriately and ensure the correct consenting documents and procedures, including the involvement of parents/guardians, are in place.

Some countries require the sponsor to sign agreements to supply patients with a study drug for a (prolonged) period after the trial, which can have a cost and logistical impact on the sponsor. It may not even be possible to run some types of trials globally. For example, expanded access trials are not permitted in many countries and a different type of protocol would be required to gather similar data on a worldwide scale. Local legislation can mean a non-interventional trial designed for one country is considered interventional in another, requiring full regulatory authority and ethics committee approvals. Genetic sampling and bio-banking requirements can vary, and consideration should be given to making the genetic component/consent optional to avoid a negative impact on recruitment of the main study. Additional review bodies can be required in some countries, depending on the product and/or trial procedures. These can add to start-up timelines both in terms of document preparation and review times. For example, consider using standard-of-care imaging where possible to avoid additional reviews by radiation bodies.

Managing the Challenges

An issue that can impact global start-up for smaller companies in particular is the requirement in some countries to have a locally based entity or applicant. If the sponsor has no regional presence, knowledge of this requirement up-front can allow time for contracts with vendors to be agreed, so as not to delay submissions. Likewise, knowledge of the local delegation letter process allows a sponsor to build in time for Apostille and notarisation where required. Even the phasing of country start-up can be important, as an approval for the trial in the sponsor country or by a respected authority (eg UK’s Medicines and Healthcare Products Regulatory Agency) can facilitate approvals in other countries, such as India and China.

Clinical factors can include differences in standard-of-care with variations in medical practice, including disease definitions, as well as differences in healthcare access, criteria for hospitalisation and treatment, diet, smoking, alcohol consumption, placebo responses and adverse event reporting (5). These distinctions need to be considered when planning a global trial to avoid start-up delays and minimise amendments. As ICH E17 proposes (3), small differences almost always exist in medical practices across regions, and these can be acceptable. However, substantial differences

may have a large impact on the study results and/or their interpretation. Ethnic factors, such as genetic polymorphism or receptor sensitivity polymorphism of drug metabolism, may need to be considered when choosing participating countries. Pooling ethnic populations from different sources to reduce start-up costs in individual countries could be considered. Nonetheless, obtaining regulatory authority advice would be advisable to support the acceptability of this approach.

Culturally, some unusual issues can surface. One country may not recognise another's right to exist, and a product manufactured there or distributed via that region cannot be imported. Sponsors may need to consider the impact on country selection of having bovine or porcine excipients/components in their products, the use of which may be contrary to local beliefs. Sensitivity must also be given to justifying procedures based on another authority's regulations or advice. Cultural differences on the use of contraception and routes of administration exist, and patient recruitment and retention materials should be planned with a global trial in mind. Countries can also have different views on what is considered promotional, ethical or coercive. All these factors should be taken into account when designing a global trial.

The Final Hurdle

Once a carefully planned study design is in place, the next steps include generating the equally important resultant regulatory submission (start-up) documents. All the elements of a sound study design lend themselves to generating these accompanying articles. Having clear, cogent final submission documents not only impacts timelines, but also reduces costs. These include, but are not limited to:

- Protocol (and synopsis)
- Investigator's brochure
- Investigational medicinal product dossier, which includes a qualified individual's declaration (transmissible spongiform encephalopathies certification and certificate of analysis, manufacturing authorisation); a summary of the product characteristics; a patient package insert; a list of previous studies with the same investigational medicinal product and a guide to the commercial availability per country
- Investigational product labels templates
- Informed consents/assents (eg main, parental, genetic, short-form, pre-screen, two-part, screening and randomisation, extension etc)
- List of national coordinators (where required)
- List of research sites
- Delegation letters
- Insurance certificates (number of subjects required)
- Clinical trial agreement and budget
- Patient items (eg reported outcomes, diaries, questionnaires)
- Case report forms
- Data safety monitoring review committee charter (as needed)
- Central institutional review board
- Translations (certifications)

It is challenging to keep abreast of current global requirements that may have an extensive impact on study design, particularly for smaller companies. Understanding evolving regulatory start-up requirements is critical. Appreciating the influence of global diversity on clinical practice, availability and acceptability of various products and practices, while slightly more subtle, is every bit as important. Early creation of a thoughtfully designed development plan and the ability to keep a clear global goal in mind at all times facilitates multi-regional development. CROs with a global reach are a great benefit in providing both additional resources to manage global trial activities, as well as in delivering the intelligence to get the design strategy right the first time.

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