Weighing up the Options

Feasibility studies are an essential component of study set up, analysing the key regulatory considerations and practical implications of conducting clinical research in a particular location.

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A comprehensive feasibility study is one of the key success factors for any clinical study. It is critical for cost optimisation, resource allocation and return on investment – all crucial elements across phases of new product development. Feasibility questionnaires, an important tool in feasibility studies, should aim to examine both the regulatory environment specific to the area and the country, as well as: the clinical environment with respect to epidemiology of the disease; gold standard clinical practices; adherence to relevant guidelines; expected recruitment rates; access to an eligible patient pool; evaluation of study-specific assessments; site logistics related to the study; and last but not least the experience of the investigators in specific and relevant clinical research projects.

Regulatory environment assessment outlines the process and timelines needed to receive approval for a clinical trial. Other related items such as insurance, reimbursement policies, drug import/export licences, and all other special requirements, may also be included in the regulatory environment evaluation.

Feasibility for Regulatory Environment in Europe

The European Clinical Trials Directive 2001/20/EC (EUCTD) was introduced in 2001 to establish standardisation of research activity in clinical trials throughout the EU. In Europe, all EU member states have implemented the EU Directive, facilitating the feasibility process in these countries. However, variations continue to exist such as the different local, regional or national ethics committees in each member state. The financial regulatory bodies that usually handle the site study budget may vary in each country, hence the variation in time it takes to receive approval for each submission.

These variations are usually the reason for delayed study starts and should be considered for the supply of investigational product. These factors should be carefully evaluated before selecting the regions in a clinical study.

The EU is an amalgamation of diverse countries. One of these diversities is language and therefore all essential documents need to be translated before submitting to the regulatory authorities. However, while some document translation requirements are common (such as the patient information leaflet), other translation requirements are country-specific (for example, full protocol in Spain and Greece), which can add considerably to the translation processing time.

Apart from regulatory variations, costs can also vary considerably between member states. This is a result of differences in submission and administration fees, insurance premiums and fair market value compensations for principal investigators. Careful financial planning can minimise surprises along the way.

The EU is the world's biggest trader, accounting for 20 per cent of global imports and exports. Free trade among its members was one of the founding principles of the EU, and accounts for the free import-export of drugs between EU member states. A permit is necessary only when materials and study drugs originate from a non-EU member state. Prior consideration and planning are necessary to ensure a constant supply of investigational product and other study material. A general solution to this problem is to import the study supplies to a central EU location that will act as a depot. The depot, in turn, arranges country and site shipments or alternative shipment options. In any case, early planning is essential in aligning central and local procedures.

Other factors that should be evaluated are:

- Finding an appropriate courier
- Central or local purchase of any competitor drug for the study or lab materials
- Local labelling requirements of member states
- Duration of the project and stability of the investigational medicinal product
- Handling and destruction of used and unused clinical trials material during and at the end of the study

Limitations in the procedure of destruction in particular regions may necessitate destruction of material in another member state where EU requirements are met. However, there are always options of exporting used clinical materials for destruction. For non-EU member states, there are import/export procedures for study drug and materials, further complicating the logistics of a clinical study when non-EU countries are involved. Additional custom costs, which in many cases are considerable, and extended timelines for processing should be taken into account when non-EU countries are considered for a study. Labelling, storage and distribution restrictions may also apply.

Whether planning a global study involving numerous sites in many

countries (both European and non-European) or choosing one or two countries for a smaller clinical study (EU member states only), regulatory questions must be answered in order to ensure optimisation of study plans and timelines during the start-up, implementation and close out of the study phases that apply. The regulatory information should then be evaluated closely against the clinical information available in order to make the optimum decision on countries to be involved in a clinical study.

Feasibility for Clinical Environment in Europe

Clinical environment feasibility is related but not limited to the following factors:

- Epidemiology of the disease
- Gold standard practices
- Adherence to relevant guidelines
- Access to eligible study patient pool
- Expected recruitment rates
- Evaluation of study-specific related assessments
- Site logistics issues in relation to the study
- Disease and clinical trial (ICH-GCP) experience of the investigators

The first step of a feasibility assessment is a thorough investigation of the available literature on the study indication along with the available epidemiology data per country and/or region. In cases where epidemiology data in the literature are not sufficient, questions related to epidemiology of the indication should be included in the feasibility questionnaire to the investigators for collection of such data. In some cases, even when epidemiology data is available from the literature, some questions relating to epidemiology of the indication may still need to be included in the feasibility questionnaire as regional or local variations may apply depending on the indication under investigation.

Similarly, investigation of gold-standard practices and adherence to international, European and/or national guidelines should be evaluated. The results of such an exercise would be compared to the procedures outlined in the study protocol and would therefore help to identify early on any challenges for protocol adherence by potential investigators and sites. In some cases this comparison would also indicate any potential challenges in the study approval by ethics and regulatory authorities.

Access to an eligible study patient pool becomes one of the most important factors, reflecting the expected recruitment rates per site, and the evaluation of the study-specific related assessments. Sponsors consider these key success factors for a go/no-go decision for the study timelines and for the number of countries (and sites) involved.

Delays in study conduct are mostly due to delays in recruitment. Therefore, an objective feasibility assessment is absolutely essential. Site and investigator experience on clinical study execution under ICH GCP is necessary not only for the smooth running of a clinical study, but also to increase the confidence level in the site recruitment rates and timelines.

In most cases, if not all, the feasibility studies are expected to take place either during study planning or during the early start up phase of a clinical project. It is estimated that in order to obtain a 20 to 40 per cent return rate on a feasibility exercise at sites all around the globe, the number of questionnaires that need to be sent out is three to four times the number of responses needed. As a result, the CRO and sponsor often end up spending additional time and effort contacting the sites in order to ensure that they receive the completed questionnaires promptly.

The construction of the feasibility questionnaire is among the most important factors of a feasibility exercise. The feasibility questionnaire should be short and to the point, but also detailed enough to cover all key aspects of a project. The quality of the questionnaire will be reflected in the quality of responses, hence the reliability of the study plans. Key questions that limit the length of the questionnaire will further help the study go in the right direction, preventing delays and refusal of investigators to respond to long and time consuming questionnaires. Therefore it is crucial that experienced and knowledgeable personnel are involved in the development of a feasibility questionnaire for a clinical study.

Optimistic prediction of recruitment potential is a widely observed phenomenon across investigators. This effect can be eliminated by clearly outlining the potential challenges of the clinical study in the feasibility questionnaire. The feasibility exercise is much more accurate when considerable study details are shared with the investigator. Detailed review of the inclusion/exclusion criteria through draft protocol increases accuracy; vague assumptions and limited inclusion/exclusion criteria for the study might lead to poor-quality responses. In this case a re-evaluation of the information received from sites and investigators would be necessary once the study protocol is further developed.

Timeline Considerations

The timeline of the feasibility exercise itself is very important. In efforts to limit the feasibility timelines, sponsors and/or CROs often reduce the time given to investigators to complete the feasibility questionnaires to a minimum, hampering the quality of the responses. This in turn maximises the potential queries raised per questionnaire, increasing time and efforts by the sponsor and/or CRO in addition to the investigators, who will be contacted again for clarifications.

In cases where very tight timeline restrictions apply for a feasibility exercise, careful evaluation of the length of questionnaire along with the specific questions to include should take place to maximise the quality of data received by investigators and sites. The data received following preparation, dispatch and collection of questionnaires to potential investigators and sites should be thoroughly examined and carefully analysed by feasibility experts in sponsor

and CRO teams. Adjustment of data may be necessary based on specific disease, earlier practices at site, previous experiences by sites and sponsor/CRO, historical data of similar studies performed in the industry, competitive studies running in the industry and so on. These factors should always be considered in addition to other study-specific factors, when analysis and adjustment of the feasibility results are done, in order to maximise the possibilities of stating realistic recruitment timelines and recruitment figures for any planned clinical study.

The Importance of a Strong Study

An unsuccessful feasibility study is only a failure if efforts and money were spent in the specific clinical programme, resulting in poor results due to barriers that failed to be identified in advance.

A good feasibility study would review the study strengths and weaknesses, its relevant to the medical world, and study financial implications. It would also include information on the competitive studies in the market, primary sites, and any relevant industry trends. This sort of overview provides sponsors with an objective view of the situation and opportunities. By providing detailed information on study challenges and needs and how best to meet them, a feasibility study can lead to a successful clinical programme.

The second and final part of a good feasibility study should focus on the proposed plan of action and provide a detailed estimate of its costs and benefits. In some cases, a feasibility study may even lead a sponsor to determine a better designed clinical programme or study via optimal cost and efforts. If the proposed study is determined to be both feasible and desirable, the information provided in the feasibility study can prove valuable in implementation. The information should be used to develop a strategic plan for the project, with well structured tasks and goals. A clear breakdown of concrete steps should be outlined in order to ensure successful implementation. Throughout the process, the feasibility study should show the various consequences and impacts associated with the plan of action for the clinical study.

A feasibility exercise should also provide information and guidance for potential 'back up' plans. Careful analysis of the data obtained should not only be used for developing a strategic plan for the study, but should also identify a well-evaluated alternative plan in case the initial proposed study strategy is delayed due to environmental factors that could not be forecasted (such as unpredicted regulatory changes or delays). Validation of site recruitment projections by historical review of recruitment performance against previous forecasts will add credibility and strength to the overall recruitment projections.

To be able to provide a meaningful analysis of the data, the chosen CRO should have expertise in the industry and in the relevant geographical areas where the clinical study is planned to take place. It is also important for sponsors to assign an internal person to help gather and analyse information for the feasibility study. Exchange of past experiences between CRO and sponsor, in addition to careful analysis of the information received during feasibility, will minimise the gaps between planning and implementation of the study. This will maximise the possibilities for success.

Finally, it should be remembered that even a well conducted feasibility study only represents a picture of the project environment at the point at which the study was conducted (the 'feasibility snapshot'). The conclusions of the feasibility study need to be re-evaluated at project initiation, particularly if a significant interval has elapsed.

Conclusion

In all cases, sponsors must perform a feasibility study before study implementation. Feasibility assessments are absolutely necessary during the planning or start-up stage for any clinical study. Evaluation and assessment of the regulatory and clinical stages of the clinical study in each potential country and site are crucial before study start. Careful preparation of the feasibility questionnaire along with sensible distribution and collection timelines are necessary. Detailed analysis and justifiable adjustment of feasibility results and data collected are invaluable, as they will lead to realistic study recruitment figures and study timelines allowing appropriate planning and optimisation of study resources. Furthermore, a strategic plan with well-structured goals and tasks in addition to an alternative plan for unpredicted challenges during study implementation may be prepared based on feasibility information in order to optimise the clinical study implementation.

Further reading

1. Getz KA, Is investigative site feasibility feasible?, *Applied Clinical Trials* 17(7): pp36-47, 2008
2. Arain M, Campbell MJ, Cooper CL and Lancaster GA, What is a pilot or feasibility study? A review of current practice and editorial policy, *BMC Medical Research Methodology* 10(1): p67, 2010
3. Medical Research Council, Complex interventions guidance, available at www.mrc.ac.uk/complexinterventionsguidance

About the author

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