Designing and Executing a Robust Feasibility in Rare Disease Clinical Trials

Global Feasibilities
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Introduction
Rare disease studies, especially those conducted in paediatric populations, present considerable challenges at a country, site and patient level due to their complexity and the fact that many stakeholders need to be involved. A thorough and well-planned feasibility will allow sponsors to gain valuable insights enabling important decisions to be made, most importantly if the study is feasible to be conducted at all and if yes, where it will be conducted, under which conditions, how much support and intervention will be required and how long recruitment will take. All these factors will also affect the cost of the study. Only when a robust feasibility is conducted can these important questions be answered and an appropriate study execution strategy be developed. The more accurate the feasibility data the more likely any risks can be mitigated. Clinical trial feasibility is the best means for predicting the speed at which Investigators will enrol patients. The outcome may also be useful for pre-identification of patient pools for future studies, registries or for marketed products. In the industry it is common practice that feasibility is performed quickly and usually are superficial in nature, where the focus is on immediate study start and quick site set-up. Investors for example prefer to see more near-term KPIs which allows them to validate their investment progress as early as possible. Consequently, instead of focusing on when the last patient will enter the study, more attention is paid to when the first patient will be recruited which in the worst case scenario can lead to slipping timelines for drug approval. According to recent studies, identifying sites in rare disease studies is one of the most difficult tasks. A well designed and executed feasibility which builds on validated data is crucial for a successful clinical trial and the design of a solid product development plan. Ideally the feasibility should be impartial and results should solely be data driven. This white paper explores critical factors that should be taken into consideration when conducting feasibility studies.

Data Review, Epidemiology and Patient Identification
A high-level strategy would be to determine where patients with a particular rare disease are located around the world and to find where the highest concentrations of the patients exist, keeping in mind that practicalities like patient's access to join the clinical trial are highly significant. The importance of data searches to pre- identify possible countries and sites is paramount, especially when no established database of Investigators for many of the rare disease indications exists and when information is scattered. In case very few patients are scattered globally, which may be the case in ultra-rare diseases, one strategy can be to first target countries with a high population and density, relying on probability of finding more affected patients. Considering all aspects, it may still be useful to conduct feasibility in many countries and not be too restrictive. In some cases, pockets of a disease are found in certain regions, which may be due to factors such as consanguinity.

There may be countries that are not considered for various reasons, *e.g.* political unrest, but it would be prudent not to eliminate countries for reasons of perceived challenges too quickly. Taking a balanced approach between selecting high risk countries promising higher patient numbers and lower risk countries with lower recruitment potential should be considered especially in ultra-rare diseases. Once a thorough feasibility is performed and all relevant facts are known, an informed decision can be made. Extensive data research needs to be performed to consolidate all information that is already available about the disease under investigation. Availability of data will depend on how "common" a rare disease is, *e.g.* for more common diseases like Cystic Fibrosis a lot of data is available whereas in cases of ultra-rare diseases data is most likely to be scarce. Data for emerging regions such as Asia Pacific, South America and Africa may also be limited. As a starting point and where possible, epidemiology data should be established, however incidence and prevalence rates alone will not provide enough information to include in which countries the feasibility should be conducted. Prevalence in conjunction with the defined target population as per the protocol however will give a much better guidance which countries to choose.

Other information that will support the decision-making process with respect to narrowing the country selection and tailoring the feasibility according to the protocol requirements include:

- Genetic variability from country to country or regional variability
- Start-up timelines and regulatory environment
- Patient pathways and standard of care
- Competing trials
- Patient advocacy, support groups and social media
- Patient participation and travel support
- Availability and reimbursement of supporting concomitant medications or therapies
- Set-up of health system, referral networks and patient access
- Sites with clinical trial experience but lower population vs. clinical trial naive sites with higher patient population

Genetic Variability from Country to Country or Regional Variability
Depending on the degree of variability and the protocol requirements, this factor may not play such an important role. However, data should be collected and taken into consideration. If required, the sending of samples to genetic screening labs should be explored.

Start-up Timelines and Regulatory Environment
Assessing study start-up timelines in each potential country and comparing them to Sponsor projected timelines for study completion

(if available) is of significant interest when determining where to conduct feasibility. Feasibility teams should have knowledge of country specific challenges from experience and be able to provide valuable information such as overall start-up timelines from preparing regulatory submission to SIV, including specific Regulatory, Ethical and site contracting timelines with import and export licences as required. Country-specific nuances need to be taken into consideration too. For example, India does not usually allow Phase I studies, however under special circumstances approval may be granted for rare disease studies where there is no available treatment and the risk of the disease burden outweighs that of receiving treatment.

Patient Pathways and Standard of Care

When planning a clinical trial, it is essential to know the standard of care on a global, country and even site level. Sometimes guidelines on treatment exist which may provide some uniform guidance within a country or region such as the EU. Other countries in more emerging regions will most likely have a site-specific standard of care. It will be necessary to obtain further information for the specific indication by approaching each potential site. The patient pathway is of extreme importance for recruiting in rare diseases. As many rare diseases are affecting many organ systems, these patients are seen by many specialists. It will be important to determine how and by whom the patient is treated. This will enable your feasibility efforts to be directed at the appropriate personnel, where you may need to approach different disciplines for the same trial. Thus, enabling you to identify the most appropriate investigators for the clinical study. Some patients will only be eligible once the disease is active or severe and may first be seen in the emergency department. Knowing the patient flow at site and where these patients are coming from will ensure a maximum of eligible patients are directed towards the clinical trial and patients are not unnecessarily lost.

Competing Trials

Rare disease trials competing for the same or similar patient population can be a key concern, as there is a limited patient pool and limited number of key specialists working in the field. When selecting countries and sites it is prudent to take into consideration the competitive landscape, such as: number, location, phase and size of trials being performed in a country and at each site. The knowledge of existing marketed products or products close to market, in your specific indication in any particular country, may influence the decision on country selection. Information is readily available in databases such asclinicaltrials.gov and in the EU Clinical Trials Register. In addition, there are also country specific databases where all trials being performed in the country must be registered. However, the feasibility team should appreciate that from these databases a complete list may not be available and it will be best to ascertain the current status individually at each site. It may also be possible to get an indication of future planned trials at the site. If after careful consideration it is not possible to avoid placing the trial at a particular site with other ongoing trials in a similar or the same indication, a detailed dialogue needs to take place with the site personnel outlining the recruitment strategy and impact on resources.

Patient Advocacy, Support Groups and Social Media

Each country and disease indication has patient advocacy and support groups that are established at different levels. However, it is less likely that groups are formed in emerging countries where disease specific advocacy is not set-up and patients may connect to umbrella organisations that cover the therapeutic area.

Identifying and connecting with these groups and engaging with them can support the trial in the following ways:

- Financing early development of clinical trials
- Providing early feedback/ input into the protocol design, to determine if the study is acceptable from a patient's perspective
- Helping drive disease awareness
- Enhancing recruitment through connecting patients and running forums

In many developed countries social media is widely used to connect patients and during the feasibility social media channels can be identified that are disease specific and connect the community.

Patient Participation and Travel Support

Whilst conducting the feasibility it should be investigated if country and regional factors will influence patient participation. In some regions such as the Middle East it is part of the culture to involve the larger family and relatives in the decision-making process, before giving consent. The intensity of patient involvement in a trial may affect the consent process. Factors such as the extra burden to the carer, need for hospitalisation, missing school, frequent visits, repeated blood sampling and large travel distances may deter patients. For countries and sites where patient travel and additional support can be provided, a higher recruitment may be seen. Patient travel support can be considered for patients that are referred to a central location within a country where a key specialist is located.

Availability and Reimbursement of Supporting Concomitant Medications or Therapies

Lack of reimbursement or unavailability of concomitant medications / therapies that are required as specified in the protocol may result in the inability of the study to proceed in a particular country. Availability of already marketed products for the indication can also influence recruitment. Set-up of health systems, referral networks and patient access Patient access to specialists will be a requirement to conduct the trial and in four countries where there is access to electronic health records, patients can be more

easily identified. A key component to take into consideration is to validate the recruitment projections at any one site. This activity can be performed by reviewing historical information regarding patient numbers and reviewing anonymized patient data. Referral networks are set up for some indications especially in Europe and the US, however referring a patient to another site may also have its challenges, if patients have to travel long distances or are treated by a different specialist in an unfamiliar environment, where they are less likely to give consent.

Site and Investigator Selection

Selecting the right sites is fundamental to every clinical study, but the impact is greater if the wrong sites are recruited in rare disease trials, where misjudgements in the site selection can potentially lead to complete trial failure. The first step should begin with designing a detailed feasibility questionnaire, tailored to the specific study. Assessing Sites in a systematic way will give an indication of the sites' competency to conduct the trial in terms of experience, resources, medical knowledge and patient access. Site infrastructure the type of site and infrastructure can vary considerably. It should be determined what kind of equipment, calibration and tests are available and required as per the protocol. Alternative sites may also be used to conduct some of the tests and additional equipment may need to be supplied.

Evaluating Investigators

Site specific experience in the disease under investigation is a clear advantage and investigators are more likely to be able to input into protocol development and design and be able to tell if study specific procedures are in line with existing medical practices. However, when finding sites on a global scale it is not always the case that all sites will have worked in the defined indication. Varying levels of experience is to be expected and occasionally it will be possible to transfer experience from a similar study indication. Sites with no experience should not be immediately excluded, especially if they have a good recruitment potential. Instead, it should be determined which kind of training is required, such as indication, protocol, assessments and GCP specific training. In some cases, site support is recommended, especially for sites in emerging countries where both experience and/or site resources are scarce, but the investigator remains motivated and is willing to participate.

Providing a site coordinator can be beneficial and this strategy tends to work well, however most likely extra associated costs will be generated and this has to be weighed up with the number of patients the site will contribute to the overall study.

Patient Recruitment and Retention

Subject enrolment is particularly more complex when conducting rare disease studies, especially in paediatrics and can be considered the most important part of the feasibility. The recruitment potential of each individual site, indicated by subjects per month or over the entire duration of the study when low patient numbers are expected, should be used to track predicted vs actual recruitment. There are many factors that the investigator must take into consideration when providing an estimation of the recruitment. It is not sufficient to only consider the inclusion and exclusion criteria when other factors such as patient motivation and concomitant medications will also drive recruitment and eligibility. Often, patient recruitment is overestimated by the site which is seen in indications where there is diagnostic uncertainty as in complex rare diseases. Equally important is for the investigator to give a good prediction of screening failure, reasons for failure, drop-out rates and possible retention figures. Thus, once a completed feasibility questionnaire is received the information must be discussed in detail with the investigator by senior personnel within the feasibility team. Data should be confirmed and where possible historical and current data should be validated and checked regarding patient recruitment. This may involve checking patient medical records or site databases, whilst adhering to data protection regulations in the specific country.

Data Mining and Undiagnosed Patients

Several data mining companies are now established that have access to patient data covering specific regions of the world. They usually have access to large data and patient records which include data on prescriptions and concomitant medications. These are then used in combination with refined algorithms to find both diagnosed and undiagnosed patients. With some accuracy it can be predicted if an undiagnosed patient is likely to have the disease under consideration. However, these services are usually engaged as a second avenue to find patients when recruitment is not on target.

Conclusion

Site selection as one of the most important steps in any trial can be a daunting task especially with the choice of trial countries expanding in recent years and the absence of an organised global network of trial centres in the rare disease arena. Rare disease clinical trial feasibilities should be approached in a holistic way moving away from a one size fits all approach as only a tailored feasibility will lead to a successful and efficient patient recruitment strategy. Listening to the client needs, their objectives and experiences should be the starting point to facilitate the design of a robust feasibility. It is important to work with the experts within the sponsor organisation to review the important criteria. Feasibilities should not be hurried as when they are performed within short timelines many aspects may be overlooked including the patient's perspective. With appropriate resources and taking into consideration the above points, a comprehensive feasibility can be performed in six to twelve weeks. Aspects that can affect the delivery time can be the size of the feasibility, holidays, need of CDAs to be signed, review and approval of questionnaires etc. which all need to be factored in when setting up timelines.

At the conclusion of the feasibility process and when the data has been scrutinised and confirmed, a customised report should be produced that includes recommended sites to be further explored and identifies potential high enrolling sites. A comprehensive report highlighting challenges when selecting certain countries and sites will be of great value. Analysis of the feasibility data may show that it is necessary to conduct the trial in countries where there are certain underlying risks. Sometimes mitigation strategies can be put in place to address or reduce these risks. The sponsor should be made aware of the challenges as part of the feasibility, so an informed decision can be made when selecting the final sites for the clinical trial. Feasibilities when conducted with diligence and accuracy can lead to the successful trial completion within the planned timelines.