To Participate or Not Participate: Why Do Investigators Reject a Clinical Research?

Clinical research is a complex, expensive, time- and resource-intensive process. Feasibility assessments play a crucial part in this clinical research planning process as it enables the sponsors and contract research organisations (CROs) to evaluate the possibility of conducting clinical research in a particular region or country with the objective of optimising the project completion in terms of timelines, patient enrolment and cost. Investigators are the key individuals in conducting clinical research and their level of engagement has a significant impact on the success or failure of the study. Understanding the reasons of feasibility rejection among the investigators may provide insights into the internal and external factors that affect the uptake of clinical trials, while at the same time being particularly important when developing policies and interventions to promote clinical research in the country.

Background

Clinical research is the backbone of evidence-based medicine and trial outcomes are crucial for comparing and improving the use of drugs, vaccines, medical devices, and diagnostics. The process of conducting clinical research is complex, expensive, time- and resource-intensive. Thus, clinical research feasibility assessment comes into play whereby the sponsor or contract research organisation (CRO) will be evaluating the possibility of conducting clinical research in a particular region or country with the objective of optimising project completion in terms of timelines, patient enrolment and cost.

Clinical Research Malaysia (CRM) is a site management organisation for the Ministry of Health Malaysia. It is a one-stop contact point for sponsors and CROs who plan to conduct clinical research in the country[1]. CRM has established an extensive database of Malaysian investigators in clinical research, as well as trial site facilities/infrastructure in the public and private healthcare sectors. This enables the company to match the clinical research with the right investigators and sites.

There are usually two types of feasibilities provided by CRM. **Pre-feasibility** assessment is information collected for preliminary, macro-level assessment to assist sponsors and CROs to decide which country is suitable to place the study. This assessment includes details on the standard of care, the clinical research registration process, epidemiology, and patient pool[2]. **A full feasibility** assessment is a complete documentation narrowed down to individual site, which necessitates confidential disclosure agreement, protocol synopsis and site assessment questionnaire[2]. It includes but is not limited to patient recruitment rate based on the study protocol, site and investigator's facilities, resources, experiences, and ethics approval.

Feasibility assessment can determine the most suitable trial sites and investigators to conduct specific clinical research. This study aims to evaluate the investigator's engagement rate in feasibility response and identify the reasons for refusal to participate in clinical research.

Methodology

Data extraction from the CRM feasibility assessment database was carried out from 1st January 2019 to 31st December 2019. A total of 348 feasibility assessments were conducted, with 212 and 136 being pre-feasibility and full feasibility assessments, respectively.

Results

The top three therapeutic areas from full feasibility assessment conducted by CRM in 2019 were oncology (n=35, 25.55%); followed by gastroenterology (n=18, 13.14%) and haematology (n=16, 11.68%). These full feasibility assessments were sent out to 466 investigators in 72 hospitals throughout Malaysia. CRM's database received 1059 responses from the investigators for the 136 full feasibility assessments. The majority of the investigators, 55.34% (n=586) agreed to participate in the respective clinical research; while 40.04% (n=424) declined to take part and 4.63% (n=49) did not respond.

Figure 1 shows the reasons for refusal to participate in clinical research among Malaysian investigators. The most common reason given by investigators is insufficient or lack of patient pool at the study site (n=120, 28.30%). This is followed by approached investigators referring the feasibility assessment to their colleagues (n=60, 14.15%), insufficient time to conduct clinical research due to routine clinical work (n=49, 11.56%) and investigators conducting competing clinical research (n=49, 11.56%).

Besides, about 9.43% (n=40) of investigators rejected the feasibility assessment due to study protocol which required strict inclusion and exclusion criteria. In addition, 7.78% (n=33) were not interested in the study and 6.37% (n=27) turned down the study because of the lack of resources in conducting the clinical research. Insufficient time due to other trials is also one of the reasons investigators reject the feasibility assessment (n=20, 4.72%). Other reasons, which made up 4.25% (n=18) of the total responses, are disease-/treatment-related (n=8), patient-related (n=7) and investigator-related (n=3). The remaining 1.89% (n=8) of the responses did not specify the reason for refusal.

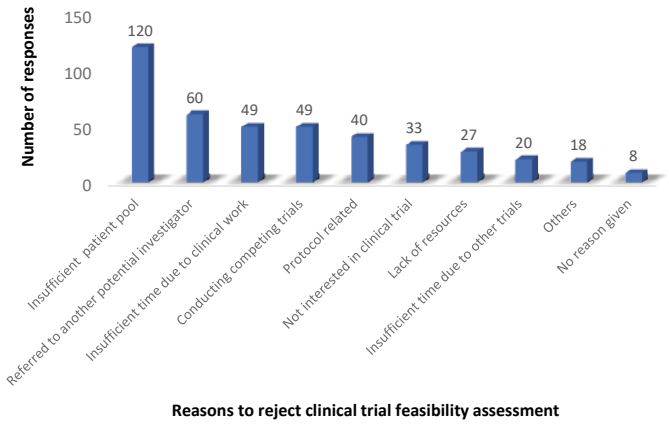

Figure 1: Reasons for feasibility assessment rejection among Malaysian investigators in 2019

Discussion

More than half of the investigators responded positively to feasibility assessment because of the accurate mapping of

potential investigators by CRM feasibility specialists, coupled with investigators being well informed on the importance of clinical research, thus reflecting their interest to contribute to the new science of medicines. Investigators will be up to date on the latest treatment and will be able to treat patients based on scientific evidence[3], thereby improving their clinical acumen.

An insufficient patient pool was the main reason for rejection. Investigators tend to reject low incidence and rare diseases studies, such as autoimmune pulmonary alveolar proteinosis, acromegaly, and low-grade glioma. Furthermore, these diseases are not commonly found among Malaysians and investigators may encounter difficulty in identifying the right patient pool to enrol in clinical research.

Next, investigators also reject feasibility assessment due to the study protocol. This includes complicated protocol, a study involving the multidisciplinary specialist team, close and long duration of follow-up, as well as strict inclusion and exclusion criteria. Oncology studies, for example, have exclusions such as prior chemotherapy, advanced stage of disease or not being newly diagnosed cancer patients. This will lead to a narrow inclusion criterion which may increase the recruitment timeline. As a result, investigators were unable to recruit enough patients for the study within the expected timeline and the sponsor may eventually need to amend the study protocol to recruit additional patients[4].

A few public hospitals practise hierarchical organisational structure, whereby all the feasibility studies to those sites will have to go through the Head of Department for first-round evaluation before responding to the feasibility assessment either as a team or referring the study to other investigators. This led to the reason of referral to other potential investigators as one of the common reasons for investigators' rejection. Besides, referral of feasibility assessment to other investigators may also be an effort for experience investigators to nurture and develop new investigators in conducting clinical research.

Insufficient time due to clinical duty and conducting competing trials are among the common reasons investigators reject clinical research. In the public health sector, clinical service remains the investigator's main priority and with the high volume of patients at these hospitals, the challenge of conducting clinical research is real. Clinical research with extensive follow-up as well as those that require long discussions with patients (patient consent, protocol etc) may increase the tendency of investigators to reject the trial[5]. On the other hand, it is common practice in Malaysia that one investigator is dealing with multiple sites or hospitals, thus they may not have protected time to conduct clinical research.

Other reasons for feasibility rejection include patient-, disease-/treatment-, and investigator-related reasons. Patient-related reasons include ethical issues such as the targeted patient needs

to be hospitalised, is very ill, or there is a high mortality risk for patients. Investigators may not wish to subject these high-risk group of patients to the trial and thus would reject the study. Disease- or treatment-related reasons include investigational product (IP) containing pain-reducing capabilities but not disease-modifying action; IP has various drug-drug interactions and investigators are not confident with the IP mechanism of action in patients. Investigator-related refusal reasons include the transfer to a new hospital and away from work during the time when feasibility studies were conducted; these are reasons for them not being available to answer the feasibility assessments during that point in time, although they may be interested. In addition, insufficient time to answer the feasibility questionnaire within the timeline given (usually five working days) may also be a reason they refuse to participate in the feasibility assessment.

Conclusion

The results of this study showed that more than half of Malaysian investigators that were approached by CRM are interested in participating in clinical research. Similarly, this study also presented several key refusal reasons for investigators to participate in clinical research and the reasoning behind them. The interest of investigators is influenced by numerous factors, some of which are not intrinsic to the study protocol, yet invariably play a direct role in determining the uptake of the clinical trial. The reasons for refusal in feasibility assessments are important key points to consider when engaging with them in future feasibility studies, when implementing motivational interventions to encourage more investigators to participate in clinical research, and when developing frameworks and policies to support investigators' involvement in clinical research in the country.

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