

Mini Review

Challenges in Oncology Studies: Review from a Global Perspective

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ABSTRACT

Cancer is among the most important disease groups inflicting mankind in present era. Successful research in oncology necessarily consists of immaculate planning, programming, coordination and application of guidance documents. Conducting Oncology clinical studies are a significant investment in terms of costs, resource and time. Understanding of the challenges especially at various stages is vital to success of the study. This article provides a summary of these challenges and proposes few recommendations in designing, conducting and reporting oncology studies.

Keywords: Cancer, Oncology studies, Study design, Study reporting.

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INTRODUCTION

Conducting Oncology clinical studies are a significant investment in terms of costs, resource and time. Understanding of the challenges especially at various stages is vital to success of the study/programme. This article provides a summary of these challenges and proposes few recommendations in designing, conducting and reporting oncology studies. In the developed world, approximately 1 in 4 people die from a cancer or cancer-related disease, making it the second most likely cause of death (after cardiac-related diseases) worldwide. Globally, it has a share of 13 percent in total deaths (or 8.7 million deaths) [1]. The estimates from Global Burden of Disease (GBD) show that about 2/3rd of all cancer deaths are now happening in among low- and middle-income countries [2]. There is a major focus on developing new treatments to improve the survival of patients with cancer. With so many studies on-going, it is important to ensure that the myriad complexities associated with oncology studies are considered.

STUDY DESIGN

There are several study designs in the early development phase specifically tailored for oncology studies. These include dose escalation designs based on safety and efficacy considerations and incorporation of overlapping dose groups. Phase I studies are almost always based on patients due to the anticipated toxicities. It is rare even in Phase I to be able to include placebo as a comparator due to ethical considerations, although some Phase I Cohort designs can incorporate random placebo insertion. The challenge for all phases is to keep the length of recruitment to a minimum – particularly challenging for rare cancers. This is compounded in the later phases, where larger numbers of patients

are required and there is a need to balance both the recruitment and the length of follow-up with large numbers of sites and countries. Discussions with investigators to identify realistic recruitment rates (adjusting for competing studies where appropriate) will help in these planning aspects. Gold standard for oncology studies from the regulatory perspective [3] would be the endpoint of overall survival (OS) in a randomised double-blind study or studies demonstrating the required clinical superiority compared to the current standard therapy in the chosen indication. Overall survival can take years to collect and surrogate or alternative endpoints such as progression-free survival (PFS) or Quality of Life (QOL) data may be accepted as interim approval endpoints. Double-blind studies are difficult to achieve: treatment regimens differ in length, delivery and complexity making single-blind studies more common. Use of double-dummy is rare, so if it is the only means to blind the patient from the treatment allocation, then open label studies may be the only option. Open-label studies can be subject to intense scrutiny by the regulatory bodies since it is difficult to achieve unbiased assessments. The sponsor is responsible for the provision and blinding of any comparators used, along with funding the standard of care treatment at each of the sites. To allow for effective usage of study and comparator medication, an Interactive Voice (or Web) Randomisation System (IVRS/IWRS) is strongly recommended. Whilst these systems are efficient in managing the Investigational Product, it is important to allocate additional time to the setup phase to establish the system. Consideration of follow-up for overall survival should be built into all studies as part of the Informed Consent (IC) to enable easy access to patient records for 1, 2 or more year's follow-up for the restricted information pertinent to the key endpoints of interest. This requires considerable forethought in the planning processes and will generate more complete follow up at the later stages of the programme, compared to post-hoc data collection

that can be both costly and only partially successful.

PATIENT RECRUITMENT AND RETENTION

Treatment-naïve patients are rare. Competition for patients in most areas is intense and many patients (although suitable for inclusion in the trial) are often exhausted from previous chemotherapy or radiotherapy and are subsequently unwilling to consent. Study related tests that are additional to their current care may also deter participation. Eligibility for the study will be impacted based on previously failing treatment with the selected comparator, thus reducing the recruitment pool further. Recruitment of 1-2 patients per year is not uncommon and this will have a significant effect not only on the quality of the data, the duration of recruitment but also on treatment by centre analyses.

STUDY SETUP AND CONDUCT

Oncology studies are resource-intensive both at site and for the Sponsor with all the setup and monitoring aspects that such studies entail. Some of the major challenges are listed below and these range from site setup, protocol approval with the appropriate authorities, data collection (verification of source data, samples, follow-up, serious adverse events) and independent committees. Ethics committees (ECs) often rightly raise issues regarding patient recruitment, comparator usage and the privacy and legal requirements for anonymisation of scans and samples. This may drive long EC approval timelines (impacting study start up timelines) and may lead to subtle protocol differences across countries. It is recommended to assume at least another 2 EC review cycles per site (for a 10 site study) and 4 EC review cycles (for a 100 site study) in the planning phase before 100% of sites are recruiting. Source Data Verification (SDV) is more difficult than for some indications as the patient notes are complex and voluminous, hence requiring longer to conduct. Monitors shall be familiar with the RECIST criteria [4] as part of the assessment of evaluability of the patient. A high proportion of patients are likely to experience a serious adverse event (SAE) and these cases are often complex. The assessment of causality and distinguishing from underlying disease and concomitant therapies can be especially challenging and emphasizes the need for high quality and complete SAE reports. Many oncology trials will be conducted in high morbidity and high mortality diseases and may have efficacy endpoints that could also be reportable adverse reactions. The systematic breaking of the blind for such cases (as required for expedited reporting to EU competent authorities) could compromise the integrity of the clinical trial: Under such circumstances it may therefore be appropriate to reach agreement with competent authorities in advance concerning SAEs that would be considered disease related and not subject to systematic unblinding and expedited reporting. Differences between regulatory authorities currently exist on this particular aspect but the most comprehensive reporting requirements need to be considered. For blinded trials with agreement not to undertake systematic unblinding and expedited reporting, the appointment of an independent Data Monitoring Committee to review safety data on a regular basis is also recommended. Robust procedures for SAE collection, assessment, follow-up and on-going evaluation is imperative. The volume of SAEs, follow up, regulatory requirements and tracking will be time consuming and requires significant pharmacovigilance and medical expertise.

There will be potentially a large amount of data/samples to

collect/track for the study. These can include (but not be limited to): biopsy samples, images/scans, blood samples (including biomarkers). Collection and shipping may require multiple approvals from multiple countries, potentially creating delays and degradation of samples rendering them unusable, so this aspect needs to be considered as part of the site assessment. Some of these samples/scans may be required for central (blinded) reading leading to dummy patient numbering to protect the identity of both patients and sites. All these data will be eventually required to be analysed so storage in a central place is helpful for the end of study reporting. Given the potential toxicity of such treatment(s) under investigation, it is likely that the study will have a Data Safety Monitoring Board (DSMB) overseeing the overall patient safety. This will necessarily require continuous monitoring and data collection to ensure all appropriate data available at the required time points for the DSMB. Reflective of the disease complexity with multiple treatment regimens and endpoints, the Case Record Forms (CRFs) need to be clear, concise and unambiguous to enable accurate completion. With electronic capture becoming more prevalent, this is enabling on-line validation as data are entered allowing immediate corrections (as needed) to be completed by site personnel. This is increasing the accuracy of entry and enabling queries to be restricted to more complex cross-page checks. This is especially helpful for interim database locks (e.g. for a DSMB) to reduce the time required for answering any outstanding queries. SDV can be recorded on the e-CRF by the monitors, providing an easy way of tracking the SDV required/performed. Tumour assessment pages continue to be the CRF section that generates the most queries. This is not that surprising since tumour shrinkage is likely to be a key secondary endpoint and it is important to track the right lesions and ensure they are consistently assessed and recorded and collected at the appropriate time intervals. The volume of adverse events and concomitant therapies require a significant amount of review to ensure data accuracy and co-correspondence with the safety (SAE) database and ability to report in a consistent format. The number of therapies on-going will be high and indicative of the seriousness of the patient's condition. Structuring the (electronic) CRF for ease of entry at site will support the study nurse and investigator in the entry of data and help the monitor with the monitoring aspects. However, it is important to consider the data management and analysis requirements to ensure that the study can be reported as planned. Consideration should also be given for all the external sources of data upfront and how they will be incorporated both into the database and the analysis. In particular, survival follow up that may continue for many years following study reporting needs to be linked to the original study for ease of reporting.

STUDY ANALYSIS CONSIDERATIONS

Several of the key endpoints in oncology use survival methodology, such as overall survival or progression-free survival which can account for patients that do not achieve the endpoint and can be censored at the point of no further information available. These can be illustrated using Kaplan-Meier plots over time and analysed using the Log Rank test, with summary statistics for median survival and associated 95% confidence intervals. Adjustment for covariates of interest can be applied in proportional hazards modelling or accelerated failure time modelling depending on the underlying model distributions with appropriate treatment comparisons described using hazard ratios.

More complex models to adjust for interval censoring, competing risks and multiple states are available for use as sensitivity models or the main analysis. Even for the more simple analyses, the data collection and understanding of the data available are important in the interpretations drawn from the data. Considerable care needs to be taken for patients censored prior to time point of interest – the reason for lack of information needs to be scrutinised to ensure that the patient does not represent a patient with ‘informative censoring’. The censoring would be considered informative with the potential to bias the results of the analysis. By understanding the importance of how the data are collected and minimising the bias as much as possible with appropriate data collection in place, the data can be appropriately analysed and the analysis plan appropriately setup to take these aspects into account.

CONCLUSION

As an investigator or sponsor conducting oncology trials, a fine balance is required between the requirement for accurate, appropriate and timely information versus the complexity, cost and quality of such trials. It is important to allocate enough time in the setup phase to ensure the scientific expertise is built into the study, with all the design considerations thoroughly scrutinised to maximise the likelihood of a successful study with appropriate sites, endpoints, analyses and reporting. Like many

other indications, the relationship between sponsor and clinical partner(s) will be critical in successful recruitment and retention of patients. Follow-up of patients is critical and success is governed by early identification of requirements and building in survival follow-up at the earliest stages of clinical development. Understanding of the best ways to collect and ultimately report the data will be critical in any successful submission and ability to register new treatments.

REFERENCES

1. World Health Organization. World Statistics Report. Geneva; 2015.
2. Wang H, Naghavi M, Allen C, Barber RM, Bhutta ZA, Carter A, et al. GBD 2015 Mortality and causes of death collaborators. Global, regional, and national life expectancy, all-cause mortality, and cause-specific mortality for 249 causes of death, 1980-2015: A systematic analysis for the Global Burden of Disease Study 2015. *Lancet*. 2016; 388(10053): 1459-1544.
3. FDA Guidance Document: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics, 2018.
4. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). *Eur J Cancer*. 2009; 45(2): 228-247.