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Evolving trends in clinical trial designs

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In the current competitive era of drug development, establishing the superiority of a new medical intervention compared to a relevant standard with a big effect size is difficult. If a moderate to small effect size is all that can be realistically expected, persuading regulatory bodies, clinical practitioners and patients to use the intervention will require demonstrating other advantages such as improved safety, better quality of life, cost-effectiveness and convenience of administration. From a commercial angle, it is also critically important to shorten the development timeline in order to enjoy longer patent protection time or market dominance before a competitor appears. Thus, pharmaceutical companies and academic researchers are in constant search for innovative clinical trial designs which can accelerate the drug development process, save resources, assess the advantages of the intervention in multiple ways and that are acceptable to regulatory bodies.

One of the recent initiatives for improving clinical trial efficiency is to use adaptive designs. These allow more flexibility in trial

conduct such as re-estimating the sample size as the trial is ongoing, dropping a less efficacious intervention arm after an interim evaluation, combining phase II and phase III trial designs and re-randomization of patients to an alternative intervention after the primary intervention fails. Such designs help to shorten the clinical development timeline, allow testing of multiple intervention strategies in the same trial and reduce exposure of patients to less efficacious interventions.

Research methodologies for analyzing data from several types of adaptive designs are still evolving and under debate. The primary concerns are the chance of erroneous positive conclusions and the difficulty in interpreting the results from a complex trial design. Hence, adaptive designs are mainly employed in the exploratory phase, with as yet limited application in confirmatory clinical trials. A recent helpful development is that regulatory bodies such as the US Food and Drug Administration and the European Medical Agency have issued guidelines declaring which adaptive designs are "well-understood and have valid approaches to implementation" and which are "not well-understood".

In addition to analysis and interpretation, adaptive designs place additional challenges on trial execution; demanding strong project management and effective cross-function coordination. Activities such as patient recruitment, drug supply, remote data capture, site monitoring and data cleaning need to be highly integrated.

There are several instances where the infrastructure and processes developed for conventional clinical trials do not meet the requirements of an adaptive designed trial and adapting the conventional processes can be a challenge. For example, the requirement of short timelines for clean and verified data to support decision-making at the interim stage of the trial may not be feasible with conventional site monitoring and data cleaning frequency practices. The study team will need to be creative to find a solution for this, for example, by prioritizing data verification and cleaning only for the key endpoints required for decision-making at the interim stage. Thus adaptive designs may look attractive, but the challenges involved in planning and conducting the trial may outweigh the benefits. However, in the long run once enough experience is gained with such trial designs, it could be rewarding.

Another prominent trend in clinical trial design is to incorporate assessments of patient-reported outcomes (PRO) such as quality of life (QoL) into intervention effectiveness measurement. Because PROs by definition are important and relevant to patients, significant improvements can be advantageously incorporated in product labeling. In 2009, the US Food and Drug Administration released a guideline on the use of PRO measures to support labeling claims. Recently, in 2014, the European Medical Agency also published a draft guideline on the use of PRO specifically for oncology studies.

Many questionnaires measuring multiple dimensions of QoL (e.g., mobility, pain, depression etc.) have been developed. They are broadly classified into two groups: generic QoL questionnaires and disease-specific QoL questionnaire. A disease-specific QoL questionnaire covers dimensions that can potentially be affected by the disease or its treatment. For example, the EORTC's QoL questionnaire, EORTC QLQ-C30, developed for cancer patients measures QoL using dimensions related to functional activities (physical, role, cognitive, emotional, social) as well as cancer-specific symptoms such as fatigue, pain, nausea/vomiting, appetite loss etc. In contrast, generic QoL questionnaires are not disease-specific and can be used for patients with any medical conditions.

A general belief is that a disease-specific QoL questionnaire can detect a change in the QoL more sensitively than a generic QoL questionnaire. However, in reality, this is not necessarily true. For example, a recent Singapore study of breast cancer patients found that a simple generic questionnaire, the EuroQol-5 dimension (EQ-5D) with only 5 questions, is discriminatively non-inferior to a more complex disease-specific questionnaire, the Functional Assessment of Cancer Therapy-Breast (FACT-B) with 44 questions. On the other hand, generic QoL questionnaires can sometimes be insensitive to particular aspects of QoL in certain conditions. In such cases, it is useful to include a disease-specific QoL questionnaire. In practice, different QoL questionnaires are suitable for different types of research questions, depending on how a particular intervention impacts on QoL. Currently, the EQ-5D questionnaire is the most commonly used QoL questionnaire. It is available in many languages and validated in many medical conditions.

A generic QoL questionnaire, such as EQ-5D or Short Form-6 dimension (SF-6D), is preferred in late-stage clinical trials because it provides utility values (preference for the health states). Currently, very few of disease-specific QoL questionnaires provide utility values. Utility values are required in order to calculate quality-adjusted life years (survival time discounted for QoL) - an important outcome for pharmacoeconomic evaluations. An intervention that requires less money per quality-adjusted life year is considered more cost-effective. Such studies also require collecting healthcare cost data under realistic conditions, which is not an easy task. Due to dramatically rising medical costs, economic evaluation of healthcare interventions has received increased emphasis among various stakeholders. It helps stakeholders judge if resources were well spent on the intervention. In countries where government is the major payer for healthcare such as Canada, UK, Australia and some European countries, medical reimbursement and coverage decisions are increasingly based on cost-effectiveness evaluations.

Investigators and policy makers in the Asia-Pacific region have also started evaluating healthcare interventions from the cost-effectiveness perspective. This has resulted in the increasing use of QoL questionnaires in clinical trials. Many researchers are also focusing on methodological research related to QoL and pharmacoeconomics. For example, initially in 2002, the EQ-5D utility valuation set derived from the Japanese general population was the only available utility valuation set for the EQ-5D health states in the Asia-Pacific region. But in recent years, locally derived EQ-5D utility valuation sets have become available for use in Singapore, Malaysia, Thailand, Taiwan and South Korea. Furthermore, researchers are increasingly publishing "mapping" algorithms to convert a QoL summary score from a disease-specific QoL questionnaire into a utility value of a generic QoL questionnaire whose utility valuation set is available. This would enable researchers to perform an economic evaluation in a clinical trial, which has collected QoL data using a disease-specific QoL questionnaire, but not a generic QoL questionnaire.

Although clinical trials are increasingly used as a vehicle for economic evaluations, there are several potential difficulties with this integration. The key focus of clinical trials is to assess the intervention effect under strictly controlled conditions defined by inclusion/exclusion criteria and adherence to the trial protocol. On the other hand, the economic evaluation expects to collect healthcare cost data under pragmatic conditions without the trial protocol-driven restrictions. There is no straightforward way to overcome these challenges, though some recommendations are available on how to conduct economic evaluation alongside clinical trials. If carefully addressed, conducting an economic evaluation alongside a clinical trial provides an invaluable early opportunity to produce estimates of cost-effectiveness of the medical intervention.