Bayesian Adaptive Design Scope of Utilizing it for Research in Palliative Care

Sir,

Randomized controlled trials (RCTs) are considered the gold standard to investigate efficacy, safety, and feasibility of a new treatment modality, intervention or test when compared to an established standard of care.[1] For having level one evidence, a well-designed RCTs are very important. RCTs could take time for completion depending on the methodology and type of intervention which is under investigation and also incurs a lot of cost. Choice of clinical trial design is important in palliative care (PC).[2] In PC, the problems of recruitment, attrition, and randomization of patients when conducting RCTs are well-established.[3]

Methodology is utmost important, and researchers are expected to follow it diligently without deviating. This could pose problems in PC where patients are difficult to recruit based on the type of intervention. This most commonly performed randomization is also referred to as frequentist randomization. Here, randomization allows also for the use of probability theory to express the likelihood of chance as a source for the difference of end outcome.[4] Type 1 error, type 2 error, effect size, and *P* values are important in RCTs. Deviation from an established or approved study protocol is not acceptable. However, after a null hypothesis is accepted, the frequentist approach does not tell researcher what to do next. Another potential problem is rapidly changing doses, concentrations and volume of a particular medication for treating a particular condition.

To address this problem, adaptive design for clinical trials has been described and has been successfully used in the oncology research. In this design, data from the initial stage can be used to modify methodology for recruiting subsequent patients [Figure 1].[5] This is known as posterior probability which is the revised or updated probability of an event occurring after taking into consideration new information, i.e., information gathered from an interim analysis.[6] Another concept is that of priori or prior probability which is the probability of an event before new data are collected. In other words, priori once revised becomes posterior probability which then guides the research further. Another advantage of adaptive trials is that if the results of initial assessment are not encouraging or have undesirable adverse events, the study can be terminated considering it futile. This saves time, reduces loss of revenue in research and use of potentially ineffective modality in patients which could be even unethical. Similarly, on interim analysis, the results could also suggest that the new modality/medication/intervention is better or comparable to an established standard of care thus justifying continuation of research.

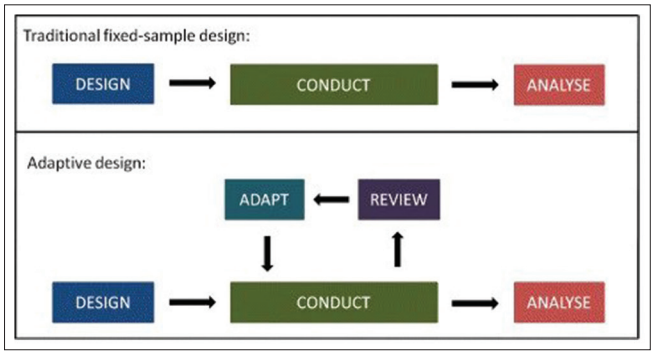

Figure 1: Figure showing characteristics of a randomized controlled design versus an adaptive design[6]

A type of adaptive design that can be used for research in perioperative medicine and regional anesthesia is the Bayesian adaptive design. This uses the Bayes' theorem which describes a mathematical formula to calculate conditional probabilities. Here, the allocation of patients is not 1:1 like in RCTs, but the number of patients allotted in the group which shows encouraging results is more, which could be the standard of care group or the experimental group.[7] Trial is monitored by computerized simulation program. The trial design is analyzed up to 1000 times, i.e., virtual trials to understand sample size required, error rates, strength, and weakness of trial. Variable or preferential randomization wherein patients most likely to benefit is recruited. The unequal number of enrolments could pose a problem on analysis which might affect the power of study. Moreover, the confidence interval and *P* value if calculated in an adaptive designed study using conventional way might give incorrect results.[8] This can be managed by involving a biostatistician right from the beginning and discussing all details such as posterior probabilities and changes made in study design after interim analysis.

Bayesian adaptive design for a clinical trial is more flexible, cost-effective, and can also alert the researcher whether to pursue the ongoing trial or call it off. It allows having a smaller sample size, change in dose or technique, helps in early identification of target population and allows multiple arms in research. The randomization is adaptive or preferential, i.e., patients most likely to benefit are recruited thus prevents potential risk to recruited patients by preventing enrolment in an ineffective arm.

To conclude, with proper planning and design, the Bayesian adaptive design can be used to conduct research in PC. This would facilitate faster research timelines, having multiple

arms, lesser costs, and early application of results in the clinical practice.

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Conflicts of interest

There are no conflicts of interest.

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