Statistical issues associated with terminating a clinical trial due to slow enrollment

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It is not unusual for clinical trials to end before the planned enrollment has been reached. ClinicalTrials.gov defines a trial as ''terminated'' if ''recruiting or enrolling participants has halted prematurely and will not resume''.[1] In a recent examination of the ClinicalTrials.gov database, Williams et al. found that 12% of posted trials were listed as terminated.[2] These authors noted that insufficient recruitment was the most common reason for termination, with an estimated 38.7% of terminated trials being halted due to slow enrollment.

Focusing specifically on cardiovascular trials, Bernardez-Pereira et al.[3] confirmed that slow enrollment is the most common reason for study termination. Their analysis suggests that the rate of termination for cardiovascular trials (10.9%) is similar to the overall rate reported by Williams et al.,[2] but that insufficient recruitment may be a more pressing issue: an estimated 53.6% of terminated cardiovascular trials were terminated due to slow patient accrual. The IAEA-SPECT/CTA study described in the paper by Karthikeyan et al.[4] published in this issue provides an example of a trial that was terminated before reaching the target enrollment.

Carlisle et al. examined the trial characteristics that were associated with termination due to slow recruitment.[5] The fewer number of research sites was found to be a significant predictor of termination due to inadequate enrollment. As noted by Karthikeyan et al., this was indeed a factor in the IAEA-SPECT/CTA study's failure to meet the target enrollment: only six of the planned 13 sites were approved to enroll participants.[4] Studies with stricter inclusion/exclusion criteria were also found to be more likely to be terminated for insufficient recruitment.[5]

A primary concern for termination due to slow accrual is the potential loss of study power. As the power to detect a significant effect is closely tied to the sample size, failure to reach the target enrollment will surely mean less power. While studies are often designed to have approximately 80% power, planning and budgeting for enough participants to achieve a slightly higher level of power (e.g., 85 or 90% power) may mitigate this concern; if the target sample size is not reached, the study is more likely to still have sufficient power. Note that the planned sample size for the IAEA-SPECT/CTA study was 500 subjects, which, assuming a 10% rate of loss to follow-up, would have led to 90% power to detect a significant difference in the primary endpoint, the rate of downstream testing.[4] Even though only 303 patients (60.6% of the target enrollment) were recruited, the study still had 83% power.

When designing a clinical trial, investigators must weigh the possibility of termination and plan accordingly. There are well-developed procedures for terminating a study due to safety or futility (see for example[6]), but the possibility of termination due to insufficient recruitment must also be considered. Investigators can design their trials to make termination less likely. For example, Korn et al.[7] recommend obtaining early estimates of the likely accrual rate by initiating the trial in a few investigational sites. This information will help determine whether the target enrollment is feasible under the planned design and may also be used to justify increasing the number of investigational sites or modifying enrollment procedures and entry criteria. If terminating due to inadequate enrollment is still a concern, powering the study at a higher level may reduce the likelihood that the study will terminate without sufficient power to assess the primary endpoint.

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As demonstrated by Karthikeyan et al.,[4] even terminated trials can still yield meaningful results.

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