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Futility stopping in non-inferiority trials

In a non-inferiority trial, the goal is to demonstrate that the effect of a new treatment is not inferior to the effect of the active control by a specified amount, called the non-inferiority margin. There can be flexibility in selecting the margin depending on the new treatment's potential advantages (e.g. fewer serious adverse effects or less frequent dosing) over the active control. The Food and Drug Administration (FDA) issued a guidance document on non-inferiority trials in 2016, which covers some major aspects of their design and analysis [1].

One aspect of non-inferiority trials that is not specifically discussed in the FDA's guidance document is the potential for futility early stopping following an interim analysis. Having the potential to stop a trial early for futility is an essential feature of sequential clinical trials, which is particularly important for non-inferiority trials as it can substantially reduce the exposure of patients to inferior experimental treatments. Various statistical methodologies exist in the literature for determining the futility boundaries at interim analyses. For example, Pei et al. [2] and Yi et al. [3] reviewed some methods based on conditional power and predictive power for setting the boundaries. Intuitively, a trial may be terminated early for futility if the probability of achieving non-inferiority at the end of the trial is low based on interim results. The likelihood of demonstrating the advantages as hypothesized based on the interim results may also be incorporated into the futility decision.

Despite the importance of interim futility analyses in non-inferiority trials the interim monitoring plans for contemporary non-inferiority trials have been sub-optimal. Tanaka et al. [4] reviewed 72 oncology non-inferiority trials and noted that only 36% of the trials reported a planned interim analysis, and the specified plans for those trials with interim futility monitoring were often sub-optimal for reducing patient exposure to inferior treatments.

Gillison et al. [5] recently reported the results of a randomized non-inferiority trial comparing radiotherapy plus cetuximab to radiotherapy plus cisplatin in patients with papillomavirus-positive oropharyngeal cancer. The main objective of the trial was to determine whether cetuximab would maintain patient survival and reduce acute and late toxicity. The primary endpoint for the trial was overall survival, and there were three interim analyses (after 45, 90 and 135 of 180 deaths) in a group sequential design with the Haybittle-Peto boundary. The non-inferiority margin was 1.45 for the hazard ratio of overall survival. At the third interim analysis the hazard ratio for overall survival was 1.45, which was significantly worse with cetuximab (two-sided 95% CI 1.03–2.05) than with cisplatin. Proportions of acute moderate to severe toxicity and late moderate to severe toxicity were similar between cetuximab and cisplatin groups. The observed 1.45 hazard ratio did not exceed the 1.56 futility boundary for the third interim analysis as specified in the protocol. However, the Data Monitoring Committee (DMC) that oversaw the study recommended the disclosure of the study results. A recent article by Korn and Freidlin [6], which established that non-inferiority trials can be reliably stopped for futility if the observed hazard ratio equals or exceeds the prespecified non-inferiority margin after at least 50% of events, factored into the DMC's decision. Korn and Freidlin [6] also pointed out that non-inferiority trials have frequently used monitoring methods developed for superiority trials, which may offer insufficient protection in the non-inferiority setting when the experimental therapy is inferior to the standard treatment. As an example, they pointed to a trial that assessed the non-inferiority of a shorter duration of radiation therapy for localized prostate cancer with a non-inferiority margin of 1.32 for the hazard ratio [7]. This trial required an observed hazard ratio that exceeds 1.57 to stop for futility at 50% of events, as opposed to their rule that would only require the hazard ratio to exceed 1.32. Futility boundaries based on monitoring methods for superiority trials can be highly conservative and can lead to the continuation of a trial despite the conditional probability of achieving non-inferiority at the end of a trial being exceedingly low.

The clinical trials community needs to pay more attention to futility stopping in non-inferiority trials, which is particularly important when patient enrollment is still ongoing or enrolled patients are still receiving experimental treatments. Trial sponsors should consider the statistical methodologies that exist in the literature for determining the futility boundaries for non-inferiority trials instead of relying on monitoring methods developed for superiority trials. Institutional Review Boards (IRB) should carefully assess the futility stopping criteria during the protocol review process. Data Monitoring Committees should consider making futility recommendations based on the totality of the interim data irrespective of the futility boundaries specified in the trial protocol. In addition, DMCs should consider adding additional futility analyses when the interim results at a pre-specified interim analysis are trending towards futility instead of waiting for the next pre-specified analysis. The tradeoff between the cost of futility interim monitoring, which is a slight loss of study power and minimizing patient exposure to inferior experimental treatments should be carefully considered by the study sponsor, the IRB and the DMC to ensure the successful design and conduct of a non-inferiority trial and sufficient protection of trial participants.

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