Eligibility criteria: too big, too small or just right?

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In this issue of *Haematologica*, Hantel and colleagues[1] review an important topic that is not commonly discussed: how do eligibility criteria affect the patient population enrolled and, in turn, affect the outcomes and interpretation of studies? On the one hand, eligibility criteria can be too restrictive, thereby reducing the number of eligible patients and decreasing the applicability of the findings to the general population or 'real world'. On the other hand, eligibility criteria can be too liberal, thereby placing patients at an unnecessary risk. Finding the right balance is always a hard task. When writing a protocol, considerable thought and time should be given to the eligibility criteria. Despite that, we do not always get it right. In this study, the researchers reviewed the eligibility criteria in front-line phase II/III leukemia trials listed on clinicaltrials.gov from 2010 to 2019 and analyzed how often do we get it right. They sought to identify two concepts. The first is the consistency (concordance) between the trial eligibility criteria and known drug safety at the time of study initiation, and the second is the difference between the eligibility criteria and the drug safety-based limits.

Overall, the concordance between known toxicity and eligibility criteria was approximately 50%. So we got it right (No safety signal/No limit and Safety signal/Limit) in only half the studies. Surprisingly, approximately 30% of the studies had eligibility criteria that were too liberal (Safety signal/No limit) and approximately 10% were too restrictive (No safety signal/Limit).

Looking then at the difference between eligibility criteria and drug safety limits, we did not do any better. From 50% to 75% of studies had criteria that were more restrictive than the known drug safety limits.

Take bilirubin, for example. In 250 studies, 1.2%, 66.8%, 1.6%, and 30% of studies had no safety signal/no limit, safety signal/limit, no safety signal/limit and safety signal/no limit included in the eligibility criteria, respectively. Of the studies that had a safety signal with limit, that limit was too restrictive in 75% of the studies.

So, in summary, eligibility criteria that were supposed to be included were missed 30% of the time. When they were appropriately included, they were more restrictive 50-75% of the time. This inaccuracy can lead to biases both ways: putting patients on studies and exposing them to unnecessary risk because we as researchers want to enroll more patients on studies, or excluding others that have missed the eligibility criteria by an unjustified 0.1 criteria limit. In addition, this affects the generalizability of findings to the general population, and may affect the efficacy and outcomes of these studies.

The authors of the study acknowledge several weaknesses, mainly that the limits or known safety may not have been fully known at the time of protocol writing. Also, we do not know how many more patients may have been enrolled on those studies had the criteria been 'just right'. Nevertheless, this study highlights the need for careful review of eligibility criteria and the criteria limits included in each study. This can be done by minimizing the use of eligibility criteria 'templates', careful review of the literature, and including only those eligibility criteria that will impact patient safety. The proper use of eligibility criteria has led several groups, including the Food and Drug Administration, to issue specific guidance for including organ dysfunction or infectious disease criteria in studies.[2,3] I acknowledge that, after reading this paper, I for one will pay even more attention to the eligibility criteria of my studies and will continue to aim to get them 'just right'.

Disclosures

No conflicts of interest to disclose.

References

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