Interim versus final results of the trial—not the flip side of the same coin!

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Literature abounds in the interim results of the trial before even its final analysis. Are these interim results reliable and reflective in true sense of the final outcome? The answer is a big “No.” I am reminded of early 2000, when drug eluting stents were introduced, and looking at the interim early results of no restenosis with these stents, Dr. Patrick Serruys from Netherlands famously commented, “If I am in a dream, do not wake me up”. It’s only when the follow-up was allowed to go through its full length, that issues such as the Kounis syndrome, the concertina effect, the late stent thrombosis, mal-apposition, and late aneurysm formation were picked up. The same view is now accorded scientific validity and rigour by a recent publication in JAMA [1]—Among trials that had interim findings published, around 21% drew different conclusions between the interim and final publications. This included one study that found the intervention was harmful in the final publication, whereas the interim report indicated, it was beneficial. Four trials switched from “not different” to “beneficial,” three from “not different” to “harmful/possibly harmful,” six from “beneficial” to “not different,” and one from “Inconclusive” to ‘non inferior,’ thus discouraging publications of interim results.

The authors further suggest that even if these results are published, the word “Interim” should always be prefixed and they should “Commit to making the final results accessible by linking interim publications to final reports when ever available” [1]. In fact, more than one

third of these trials, which published interim results, never went on to report the final results. They also issue a caveat that the publications should “be limited to protocol pre-specified analyses performed when enough outcomes occurred for statistical stability and to scenarios, least likely to undermine trial integrity.” Statistical analyses can always be modified, even ethically and scientifically, to suit what the sponsor of the trial desires. In any case, even if the intentions are good, these interim results may not be reflective of the final results. In fact sometimes, the sponsoring corporate authority adds analysis of data outside the pre-specified primary and secondary outcomes and it is in this collateral analysis that most of times errors and misinterpretation, intended or unintended, occur.

I am not at all for a moment suggesting that interim analysis should not be done. To the very contrary, interim analysis is extremely important and desirable part of any research to make mid-course corrections and to keep a watch on safety related issues. This also avoids unnecessary expenditure and saves time, energy and resources involved in retracting from a mis-laden path. However, by the same token, it also has the potential of inadvertently biasing patient selection and conduct of the research, as also its analysis and reporting. In fact, in an another study, Counsell et al. [2] concluded “Published interim trial results were more likely to be associated with larger treatment effect, than those based on final report. Publishing interim results should be discouraged ...”. In fact, they want this embargo to be extended to include conference publications too.

So ladies and gentlemen, we need to hold our horses and not jump the gun by changing our practice based on the interim results of the trials. These results should not inform our practice and we must also learn to read

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in between the lines. Quite often these interim results make sensational and unethical news headlines but are later, during follow-up, proved to be thin in evidence. The analysis may even be manipulatively designed to inform patient or physician decision making for primary interests of the sponsoring authorities. Even meta-analyses, by pooling of data, have the potential of flawed and skewed clinical decision making. Lest I dart askew, this will be a matter for the next issue.

Till then, Ciao!

References

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