

# Adverse Events as End Points: The Need to Account for Both Sides of the Same Coin

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The current issue of *JAHA* features a very welcome article<sup>1</sup> on the need for joint reporting of clinical end points and safety events in clinical trials, especially in large, multisite-multicountry trials. The article refers to a particular trial on acute coronary syndrome,<sup>2</sup> the Apixaban for Prevention of Acute Ischemic Events 2 (APPRAISAL-2) trial but its conclusions can be considered relevant to the widest range of cardiovascular research and, even further, to most areas of interest in clinical research.

The article explores several types of problems that frequently arise when doing multisite and multicountry trials.

(1) Different regulations in the participant countries and different legal requirements for each site might lead to determination of different safety profiles. In some cases, end points that do not meet the criteria of the clinical events classification committee to be adjudicated as a trial event will not be further studied, though they share the same physiological mechanisms of the adjudicated events. This is a very dangerous scenario, as some products could be approved on the grounds of softer regulations than those in the strictest countries.

(2) In this study, less than 20% of the declared adverse events (AE) met criteria of seriousness. In a large trial like this one, it means that some 10 000 AE have to be registered, examined, and reported to authorities and local committees. This results in a large workload, which makes the process of clinical trials cumbersome and prevents independent researchers from promoting trials that should be among the most relevant for patients and clinicians, precisely because of their independence. It has been found elsewhere that

research promoted by independent, noncommercial researchers is closer to patients' expectations than trials promoted by commercial entities.<sup>3</sup>

(3) Geographical variations in the reporting of end points and AE could be explained by at least 4 different mechanisms: (a) Different regulations in different countries. The procedure in this trial, the joint reporting of end points and AE, should have minimized variation. However, more than a quarter of the observed variation in the reporting of events and of serious AE is explained by region. Interestingly, there is no variation when reporting nonserious AE. (b) Another source that could explain geographical variation is different risk profiles in the local populations. Differences may exist in the prevalence of factors, known or unknown, to be associated with the end points of the trial. Differences in prevalence of known risk factors are less likely in large, well-designed trials such as APPRAISE-2. However, differences in unknown factors, related to genetics or to the environment, may occur. This could be the key to new hypotheses and, hence, to new trials. (c) Clinicians do not work under exactly the same circumstances. Trial protocols are usually very strict, but compliance with these protocols may not always be as thorough as demanded. Prior work has found that it can be difficult for clinicians to accept research protocols with military discipline and maintain the desirable "equipoise" when informing eligible patients about a trial and specifically about the randomization process and its consequences.<sup>4</sup> A recent systematic review<sup>5</sup> identified 7 factors related to clinicians' motivation that can contribute to failure to recruit study participants. The 3 most frequent: "prejudice against effectiveness of trial interventions," "new evidence from other studies about effectiveness of trial interventions," and "administrative burden/time constraints." (d) Environmental and cultural circumstances are not the same worldwide, which might account for another potential source of selection bias. The same systematic review referenced above reported up to 8 reasons for which eligible subjects fail to be recruited to a trial, the 2 most frequent being "prejudice against effectiveness of trial interventions" and the "high burden (eg, many visits, invasive procedure, questionnaires, costs)". This potentially biased selection procedure could explain part of the geographical variations encountered.

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The article is timely, as it comes at the very same time when the International Council on Harmonization is about to publish their report modernizing their Guidelines on Good Clinical Practice. The European Society of Cardiology has launched the MoreTrials (<http://moretrials.net>) initiative, after the work of a meeting of the European Society of Cardiology in 2015. Recently, the European Society of Cardiology has also made public their proposal to improve clinical trials through the improvement of the guidelines regulating them. The article, published online in February 2017,<sup>6</sup> recognizes the great progress made by the Council on Harmonization, but also points out the need for a greater involvement of all the stakeholders. It is noteworthy that the European Society of Cardiology, in line with one of the conclusions of the article commented on here, as well as with the most recent US and EU legislation,<sup>7–10</sup> also proposes and promotes initiatives leading to reduce the burden of an “over-interpretation and excessive application of reasonable regulatory requirements.”

Coming back to the issue of the joint reporting of end points and AE, the role of observational studies deserves a few words here. It is known that older patients and other populations are underrepresented in clinical trials.<sup>11</sup> Current improvements in methodology to analyze observational data are also critical to understand the benefits and AEs of the newest, evidence-based advances among populations underrepresented in clinical trials. This is important “real world joint collection and reporting of end points and adverse events.”

In conclusion, the joint reporting of trial end points and of AEs might successfully overcome the secular problem of differing levels of participants’ protection in different countries. It will also reduce the nonsystematic, not justified variability encountered between sites and between countries and even within sites and within countries. Finally, it is necessary to make the process of clinical trials as simple as possible, without excessive application of regulatory requirements.

## Disclosures

None.

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