APPENDIX – Additional details on harms

Relatedness of harms to interventions

While the definition of an adverse event does not require that the event be related to the intervention, attribution of relationship might be useful for determining causality when assessing the types and relative frequencies of specific harms that should expected with interventions.[1–4] Additionally, there are regulatory requirements for reporting harms when causal relationships are suspected with an intervention.[1]

Determining relatedness is subjective and there is little consensus and guidance on how it should be done.[5] Relatedness describes how "likely" the treating physician (or outcome adjudication committee, investigator, study personnel, etc.) believes that a harm was caused by the intervention.[2–4,6] In general, relatedness should be considered based on principles of causality including the temporal relationship to the intervention, other plausible explanation for the harm, and whether the harm was expected given the clinical course, comorbidities, and concomitant medications.[1–5] For newly developed drugs, preclinical research and prior experiences with similar drugs (e.g., in the same class) can inform expectations and the designation of relatedness. Different scales may be used in the classification, but generally, they follow an ordinal relationship from "Unrelated" to "Definitely related" (**Table**).[2,6] Interested readers should explore the various approaches to defining and classifying relatedness to better understand the challenges and nuance therein.

Table. Classification of relatedness of a harm to an intervention according to CTCAE

Relationship	Attribution	Description
Unrelated to intervention	Unrelated	The harm is *clearly **NOT** related* to the intervention
	Unlikely	The harm is ***doubtfully related*** to the intervention
Related to intervention	Possible	The harm ***may be related*** to the intervention
	Probable	The harm ***is likely related*** to the intervention
	Definite	The harm ***is clearly related*** to the intervention

Other dimensions of harms data

Whereas harms are often summarized in studies using counts of occurrence, or by estimating the effect for an intervention group compared with another group (e.g., risk difference, risk ratio),[7–10] ample research suggests that patients want more information than just the likelihood of selected harms.[11–20] For example, patients want information about the timing, recurrence, and duration of harms.[7-22] For a given intervention, some harms appear quickly, after very little exposure. Others take a long time to develop, following a certain dose or duration of exposure. Some harms occur once and then resolve completely, whereas others occur multiple times.

With multiple dimensions and many different types of harms according to affected body systems and severity, the overall magnitude of harm caused by an intervention is difficult to quantify and present. Quantification may be possible through sophisticated approaches involving aggregating harms into compound outcomes and converting experienced harms into utility measures–a task being explored somewhat by the Global Burden of Diseases project.[23] But these methods are not standardized and current approaches to summarizing and communicating harm may be better served by qualitative and descriptive presentation as opposed to quantitative measures.

Data visualization provides a richer method for presenting an overall summary of harms through multiple dimensions of harms data, as compared with tables which are typically included in clinical trial reports.[24–27] Approaches to visualizing harms include the Dot Plot,[21] Stacked Bar Chart,[28] Volcano Plot,[29] Heatmap,[30] Treemap,[31] and Tendril Plot.[32] Examples of these visualizations, as well as code to reproduce them in R, can be found in a public GitHub repository (github.com/rquresh/HarmsVisualization). Efforts are currently underway to assess the value of visualization approaches for communicating harms from the perspectives of different stakeholder groups.[8,10,33,34]

Collection of harms

Systematic assessment of harms

Benefit outcomes are typically pre-specified in studies. Usually, they are systematically assessed for all participants using the same scales and instruments at planned times. Pre-specification of harms is much more difficult because some harms are unexpected or unknown. When harms can be anticipated (e.g., using preclinical studies or studies of similar interventions), investigators might collect those harms systematically.[35,36] Systematically assessed harms are those that are planned to be recorded for all participants in a study using the same methods, like the methods used to assess potential benefits.[37,38] Like potential benefits, systematically assessed harms can be fully specified using five components of an outcome: (1) domain, (2) measure, (3) method of aggregation, (4) metric, and (5) timepoint **(Box)**.[35,37,39,40] Systematically assessed harms are typically assessed using explicit methods to ascertain the presence of the harm, such as questionnaires or laboratory tests at pre-planned intervals.[35,37,41] For systematically assessed harms that are dichotomous, studies observing no events might report that 0 events occurred. Additionally, systematic collection for harms may include richer data for analysis of outcomes that are not assessed as events. For example, the effect of a drug that might cause weight gain could be assessed continuously as the between-group difference in body mass index (BMI).

Box. Example complete definition for systematically assessed harm

Domain: Nervous system effects
Measure (Name of scale): Vertigo Symptom Scale – Short Form (Likert scale of experience: 0 (never), 1 (a few times), 2 (several times), 3 (quite often [every week]), and 4 (very often [most days]))
Measure (Subscale): “Dizziness”
Metric: Value at the end of the study
Method of aggregation: Categorical – Risk difference (Proportion of participants with Score ≥ 1)
Timepoint: 4 weeks

4.2 Non-systematic assessment of harms

Primary studies address the need to gather information about unanticipated events by assessing harms non-systematically. Unfortunately, non-systematic assessment also leads to major challenges in assessing harms. Non-systematic assessment relies on the spontaneous reporting of harms,[37,38] or collecting harms in response to open-ended questions like "Have you noticed any symptoms since your last visit?". The latter differs from the spontaneous reporting in which data on harms are collected passively if volunteered. Harms assessed non-systematically are more susceptible to information bias compared with efficacy outcomes and systematically assessed harms. Moreover, non-systematic assessment reduces comparability of results because of differences in ascertainment across studies.[35–38,41–43] There may also be a reduction in overall power for harms if harms go unreported in both groups because participants are not asked and events are therefore not detected. In contrast to systematically assessed harms, it might not be appropriate to assume that 0 events occurred in studies with no observed non-systematic harms. Lastly, information about non-systematically assessed harms reported in journal articles might not be as rich or statistically useful as information for systematically assessed harms. Previous work from the Multiple Data Sources in Systematic Reviews (MUDS) Study has shown that hundreds of unique harms may be non-systematically assessed over the course of a trial, and many of these are never reported in subsequent trial publications.[41–43]

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