Can You Assess the Net Health Impact of a Drug? Serious Adverse Event Reporting in Clinical Trials

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Background

- A serious adverse event (SAE) is defined as any occurrence of the following:
  - Death
  - Initial or prolonged hospitalization
  - Congenital abnormality
  - Life-threatening condition
  - Persistent or significant disability
  - Any medically important event requiring urgent intervention
- Total SAEs can provide a precise measure of the net health impact of a studied intervention

Objectives

- To characterize reporting of SAE definitions and results in a sample of large randomized controlled trials (RCTs):
  - The proportion reporting a SAE definition
  - The components and location of the SAE definition
  - The proportion reporting SAE results

Methods

Design	Descriptive analysis
Database	PubMed 1990-2015
Inclusion Criteria	• Drug therapy RCTs • ≥ 1000 participants • Published in top medicine journals
Exclusion Criteria	• Substudy publications from a larger RCT
Sample Size	• Assumed 30% will report a definition • 305 RCTs for 95% confidence (+/- 5%) using systematic random sampling
Independent duplicate data extraction	

Table 1: Characteristics of included RCTs

Mean Size	N=5479	
Publication Date	205 RCTs 2003 or later (67%)	
Duration	181 RCTs >1 year in duration (59%)	
Registered	160 RCTs (52%)	
Disease State	Cardiovascular 42%, Cancer 13%, Infectious diseases 12%, Other 33%	
Funding	Industry 60% Mixed 25%	Non-industry 14% Not reported 1%

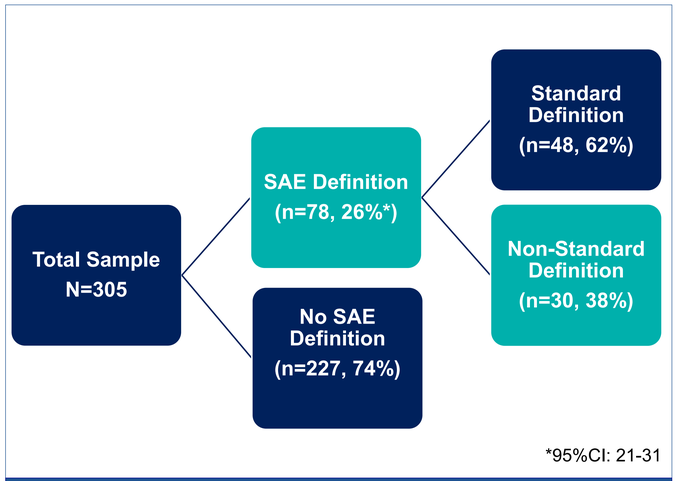

Figure 1: SAE definitions in RCTs

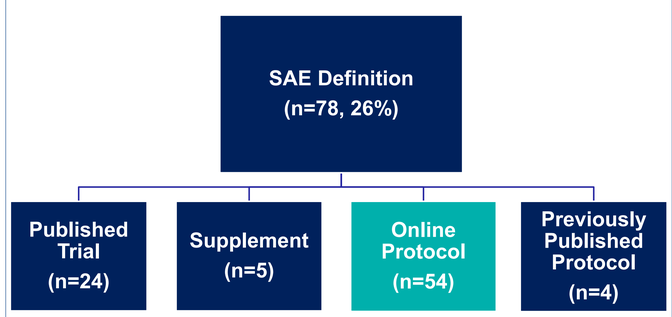

Figure 2: SAE definitions by location

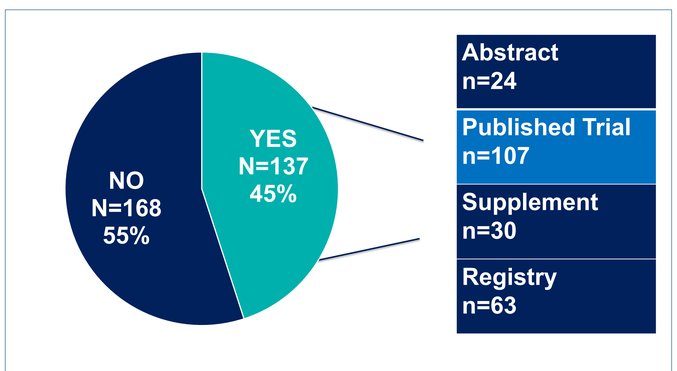

Figure 3: SAE results and locations

Results

- SAE definitions were reported in 26% of RCTs. Of the 38% which reported a non-standard definition, the most common reason was the exclusion of medically important events and congenital abnormalities.
- SAE definitions and results could be found in more than one location, however SAE definitions never differed between locations.
- SAE results were reported in 45% of RCTs. Readers are mostly likely to find this information in the published article or registry.

Table 2: Components of SAE definitions

RCTs with a primary endpoint that was a SAE	**256 (84%)**
SAE definition (n=256):	
Excluded study endpoints	20 (8%)
Included study endpoints	15 (6%)
Information not explicitly reported	221 (86%)

Table 3: Examples of SAE definitions: the good, the bad and the ugly

AMPLIFY: "Suspected DVT or PE that occur at anytime after enrollment should also be reported as a SAE."

MEGA: "The non-fatal clinical primary and secondary efficacy endpoint events, with the exception of strokes, will not be considered SAEs. All strokes will be reported as SAEs."

ROCKET AF: "The following clinical efficacy endpoint events will not be considered SAEs: myocardial infarction, ischemic stroke, and non-CNS systemic embolism."

Discussion and Conclusions

- SAE definitions are underreported in clinical trials and generally not readily accessible to the average reader.
- Often there is not enough information to interpret SAE results accurately.
- There is potential to misinterpret benefits vs harms of studied interventions.
- Journal editors and peer reviewers should require complete and transparent reporting of SAE definitions and results prior to publishing.