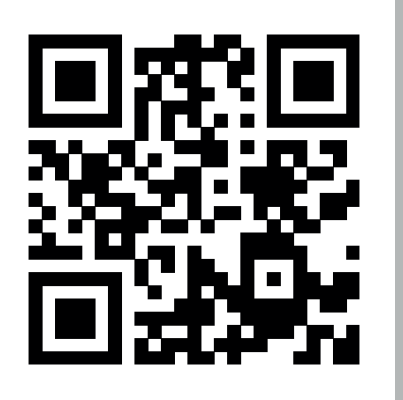


Analysis of MPIP recommendations and adverse event reporting in industry-sponsored primary clinical trials

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Poster number 69



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Background

- Balanced reporting of adverse events (AEs) in scientific publications is vital for healthcare providers to make informed treatment decisions¹
- Guidance from Medical Publishing Insights and Practices (MPIP) was published in 2016 to provide recommendations to improve drug AE reporting in industry-sponsored clinical trial publications (**Table 1**)¹
- Observations from MPIP indicate that clinical trial publications often use general phrases when reporting AEs, such as “safe and well tolerated” or “no clinically significant or unexpected adverse events”. Variations of the phrase “safe and well tolerated” appeared in approximately 6000 published clinical trials from 1990 to 2015¹
- In addition, there is room for further improvement in the reporting of clinically relevant drug AE data as part of a comprehensive safety profile. These data are important to help healthcare practitioners to assess the benefit–risk profile for the drug intervention¹

Table 1. MPIP recommendations for AE reporting¹

Section	MPIP recommendations to improve AE reporting for industry-sponsored clinical trial manuscripts
Methods and results	- Identify and communicate the most clinically relevant^a drug AE data as part of a comprehensive safety profile. We recommend authors develop a “clinical relevance” filter to identify AEs of greatest clinical interest given these considerations, and clearly state the rationale for focusing on these in the publication’s methods section with references to evidence when available - Report timing, frequency, duration, and other potentially relevant descriptors when clinically appropriate. Authors should also report whether AEs were non-elicited (passively collected) or elicited (proactively collected), adding explicit detail about the data collection methodology for both types in the methods section - Use statistical analysis for clinically relevant AEs (where appropriate). Numerators and denominators should be specified. Overall, we propose that formal statistical comparisons when reporting AEs should be selectively used where there is clear justification. We recommend using an approach that determines the appropriateness of statistical analyses via a tiered system that assumes it is important to report information about all events but only some events require formal hypothesis testing
Abstract	Avoid use of overly general text descriptions for AEs, including in abstracts. Abstracts should include a phrase or sentence summarizing the most clinically relevant AE data with frequency percentages consistent with those presented in the main text of the publication
Discussion	Discuss AE findings in the broader context of available evidence and maintain consistency of data across different public reports

^aAEs that are always clinically relevant and should always be reported include deaths; serious AEs as defined by the US Food and Drug Administration – that is, AEs that (in the view of the investigator or trial sponsor) were fatal or life threatening, or resulted in inpatient hospital admission or prolongation of existing hospital admission, persistent or significant incapacity or substantial disruption in the patient’s ability to perform normal life functions, or a congenital anomaly/birth defect; and AEs resulting in discontinuation of trial agent(s) (as specified in the clinical trial protocol)
Table adapted from Lineberry N *et al.* 2016¹
AE, adverse event; MPIP, Medical Publishing Insights and Practices

Objective

- To evaluate adherence of industry-sponsored publications to MPIP AE-reporting recommendations #1 and #4: “Communicate the most clinically relevant drug AE data” and “Avoid use of overly general text descriptions for AEs, including in abstracts”, respectively¹

Methods

- Included articles were identified using the process shown in **Figure 1** then assessed and categorized based on parameters shown in **Figure 2**

Results

- Of the 237 articles identified by the literature search, 124 met the inclusion criteria (**Figure 1**)
- The top three therapeutic areas of the included articles were oncology (31/124 articles, 25.0%), dermatology (18/124, 14.5%), and infectious diseases (16/124, 12.9%) (**Table S1**; available via the QR code)

Figure 1. Identification of articles

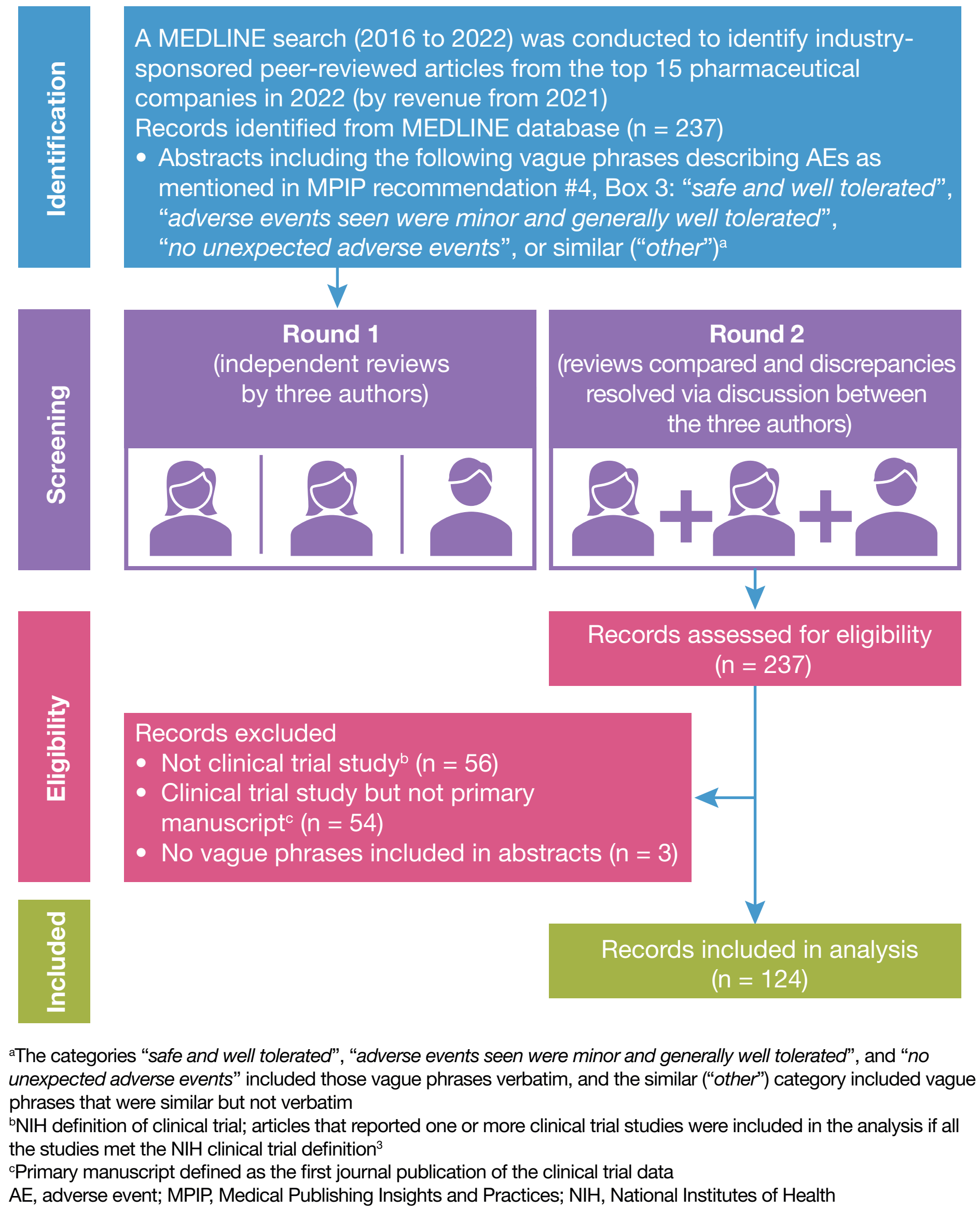


Figure 2. Parameters assessed

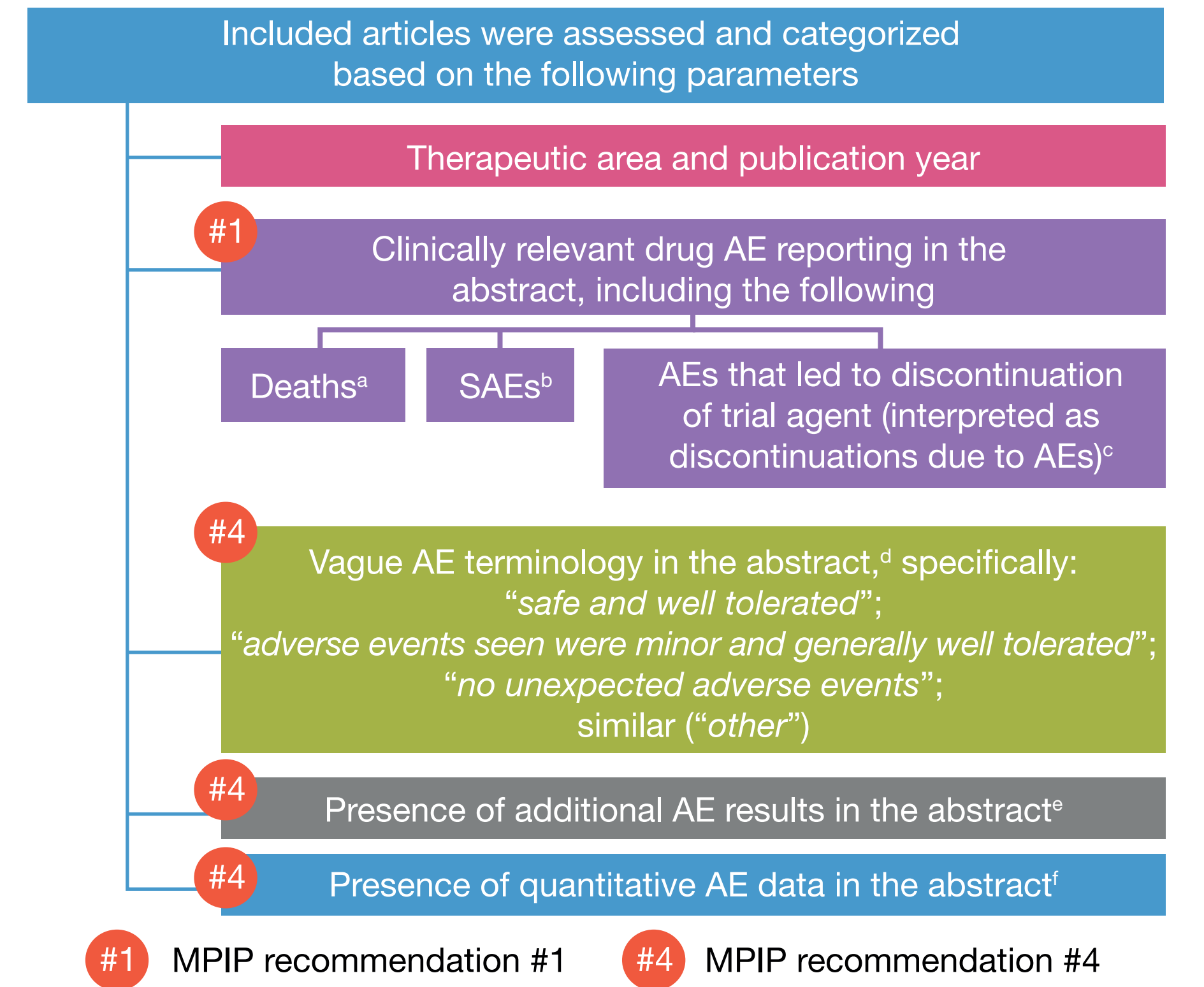


Figure 3. Abstracts reporting on clinically relevant AEs^a

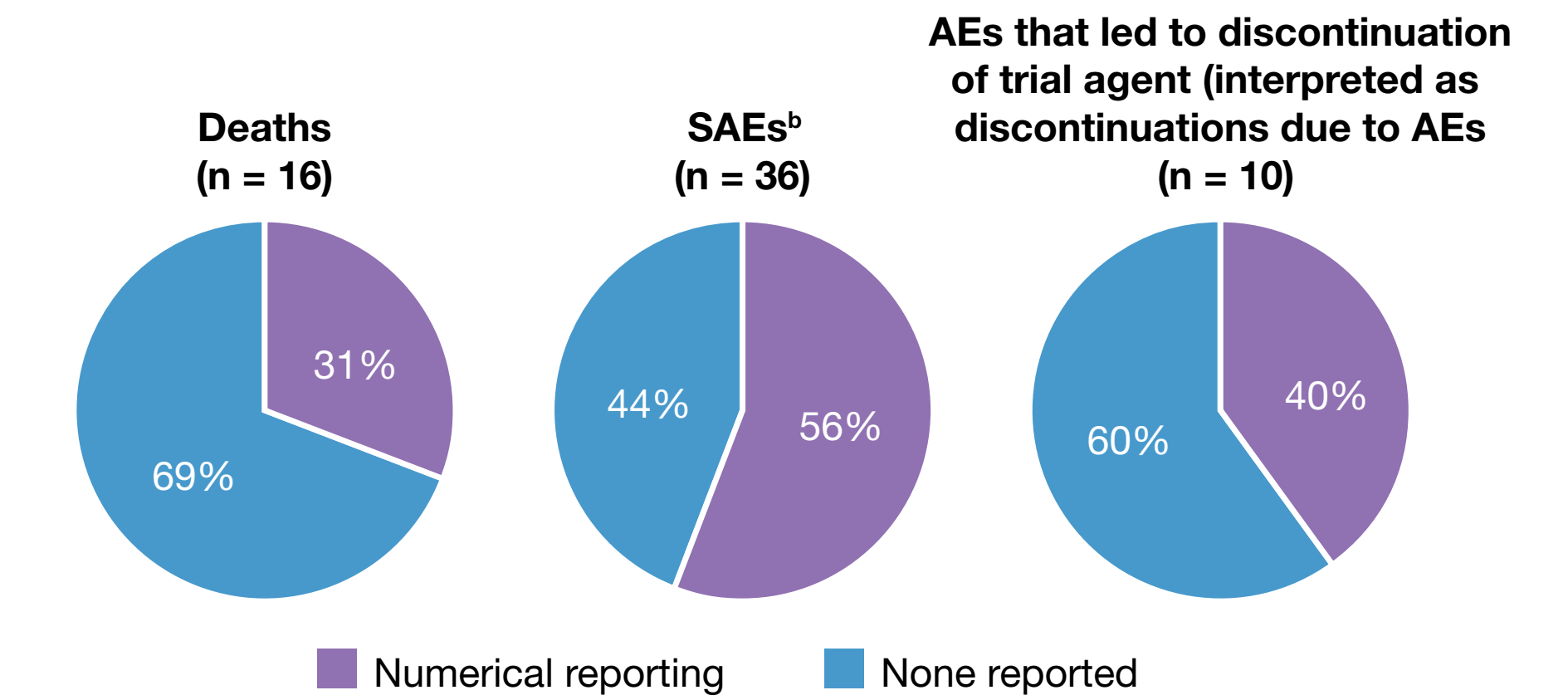
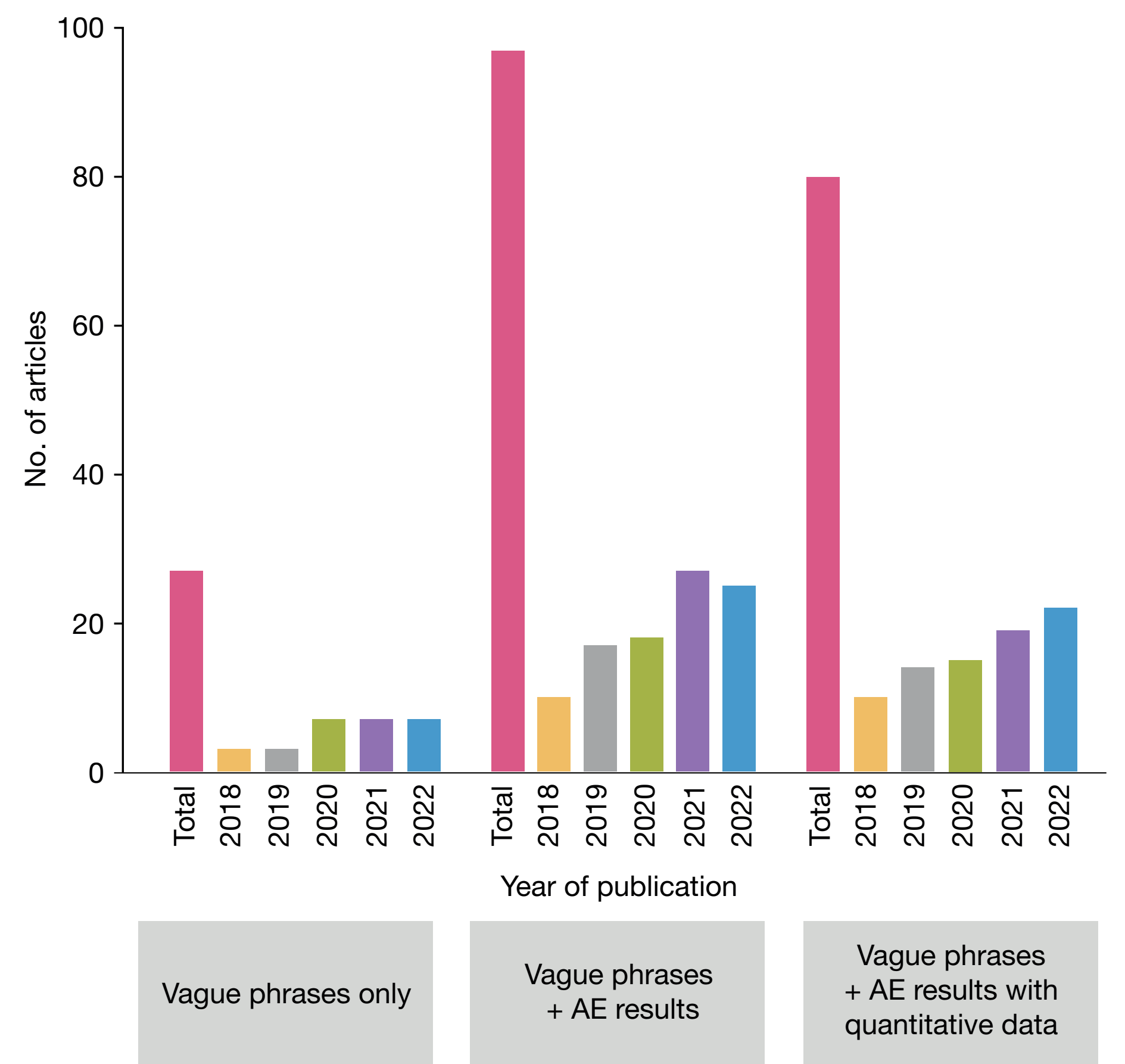


Table 2. The top 8 commonly used variations of the MPIP-defined AE vague phrases in the similar (“other”) category^a

Phrase	No. of articles (n = 124) ^b
well tolerated	61
generally well tolerated	24
safe	6
tolerable	5
acceptable safety profile	4
no [new/significant] safety concerns were identified	4
favorable safety profile	3
no new safety signals	3

^aThe full list of these variations can be found in **Table S2**; available via the QR code
^bArticles could have contained more than one of these variations
AE, adverse event; MPIP, Medical Publishing Insights and Practices

Figure 4. Articles containing vague phrases and/or AE results



MPIP recommendation #1

- Of the included articles, 47/124 (37.9%) reported on one or more clinically relevant drug AEs (deaths, serious adverse events [SAEs], or discontinuations due to AEs); no articles reported on all three of these AEs in their abstracts
- In their abstracts, 16/124 articles (12.9%) reported on deaths, 36/124 (29.0%) reported on SAEs, and 10/124 (8.1%) reported on discontinuations due to AEs (**Figure 3**)

MPIP recommendation #4

- Of the included articles, 112/124 (90.3%) included a modified version of the MPIP-defined vague phrase(s) in their abstracts and 20/124 (16.1%) included “safe and well tolerated” (eight articles contained vague phrases in both the “safe and well tolerated” category and the similar (“other”) category)
- The three most common vague phrases in the similar (“other”) category were “well tolerated” (n = 61), “generally well tolerated” (n = 24), and “safe” (n = 6) (**Table 2**)
- In their abstracts, 97/124 articles (78.2%) contained additional AE results (quantitative or qualitative data) and 80/124 articles (64.5%) provided additional quantitative data when reporting AEs (**Figure 4**)

Limitations

- This study focused on a comprehensive review assessing the application of MPIP recommendations #1 and #4 in clinical trial manuscripts. Other MPIP AE-reporting recommendations will need to be evaluated similarly
- Additionally, given that only the abstracts were assessed in this analysis, there could have been clinically relevant drug AEs that were reported in the main manuscripts but not captured in this analysis
- Selected pharmaceutical companies were included based on their top 15 ranking from the Pharma 50 list of the largest pharmaceutical companies by revenue from the year before (2021)²
- This analysis was restricted to articles that included vague phrases. Articles that did not include vague phrases were not assessed. Therefore, it was not possible to evaluate what proportion of articles comply with MPIP recommendations #1 and #4

Conclusions

- Our findings suggest that a substantial number of industry-sponsored publications’ abstracts continue to include vague phrases to describe AEs
- Overly general statements, such as “well tolerated”, are ambiguous and do not provide specific and informative details about the overall safety profile of a drug
- Only 38% of the abstracts analyzed reported on one or more clinically relevant AEs
- Objective reporting of clinically relevant AE data could provide greater context and clarity for the application of trial results to daily clinical practice
- There are opportunities for further alignment within the industry to report specific AEs consistently, ensuring robust reporting of clinical trials

References

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Disclosures

IP is an employee of Takeda Development Center Americas, Inc., and holds stock and/or stock options. VD was, at the time the work was performed, a postdoctoral fellow employed full time by Northeastern University, and Takeda supported funding for the Fellowship. RZ is a postdoctoral fellow employed full time by Northeastern University, and Takeda supports funding for the Fellowship. SD is contracted by a third party to provide Publications Lead services to Takeda International UK. ME is a contractor providing Publications Lead services to Takeda Pharmaceuticals International AG. SW is an employee of Takeda Pharmaceuticals International AG and holds stock and/or stock options.

Funding

Takeda Development Center Americas, Inc., provided funding to Oxford PharmaGenesis, Oxford, UK for editorial assistance in formatting, proofreading, and copyediting.

Acknowledgments

The authors would like to thank Ericka Bueno and Sunita Setlur from Takeda Development Center Americas, Inc., for their contributions to the study design and the analysis of the data. We would also like to thank Aileen Lam of Takeda Development Center Americas, Inc., for providing medical writing support for this poster.

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Table S1. Articles by therapeutic area

Therapeutic area	No. of articles (n = 124)
Oncology	31
Dermatology	18
Infectious diseases	16
Endocrinology	11
Neurology	11
Immunology	6
Hematology	6
Pulmonology	6
Gastroenterology	5
Cardiology	4
Transplant	2
Urology	2
Rheumatology	2
Dental	1
Nephrology	1
Pain management	1
Vaccine	1

Table S2. Articles containing variations of the MPIP-defined AE vague phrases in the similar (“other”) category

Phrase	No. of articles (n = 124) ^a
Variations of “well tolerated/tolerated”	
well tolerated	61
generally well tolerated	24
tolerable	5
well tolerated with no new safety signals	2
not well tolerated	1
similar safety and tolerability profiles	1
favorable safety and tolerability profile	1
well tolerated with safety profiles consistent with known risks of individual agents	1
well tolerated with no safety concerns	1
tolerated	1
well tolerated with no unexpected toxicity	1
well tolerated with an acceptable safety profile	1
well tolerated with a manageable safety profile	1
well tolerated with a suitable safety profile	1
tolerance was good	1
tolerable dose	1
tolerable safety	1
safety and tolerability were consistent with the known profile of	1
safety and tolerability profile of ... was consistent with the known profiles for	1
good tolerability	1
less tolerable	1
acceptable tolerability	1
Other vague phrase modifications	
safe	6
acceptable safety profile	4
no [new/significant] safety concerns were identified	4
favorable safety profile	3
no new safety signals	3
safety was consistent with previous [studies/reports]	2
safety profile was consistent with [that of/the known]	2
similar safety [profile]	2
favorable risk-benefit profile	1
safety profile of ... was as expected for	1
adverse event profile similar to that previously seen	1
safety profile for ... was acceptable	1
safety profile was comparable to that seen in	1
an acceptable toxicity profile	1
displayed no marked safety findings	1
no new safety findings	1
overall safety profile was consistent with the current knowledge of	1
safety profile consistent with historical experiences	1

^aThe total number of phrases included in the similar (“other”) category (n = 146) was more than the total number of articles included in this category (n = 112) because articles could have contained one or more of these phrases. Phrases were counted as two separate phrases if they contained words in between (e.g., “well tolerated by patients with X disease, with no new safety signals”) or if they were separated by “and”, a comma, or a semicolon

AE, adverse event; MPIP, Medical Publishing Insights and Practices