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Lessons to learn from the reporting of adverse events in randomised controlled trials: a systematic review

Journal:	BMJ Open
Manuscript ID	bmjopen-2018-024537
Article Type:	Research
Date Submitted by the Author:	01-Jun-2018
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Keywords:	Randomised controlled trials, Harm data, Adverse drug reactions, Systematic review, Investigational drug, Adverse events < THERAPEUTICS



Lessons to learn from the reporting of adverse events in randomised controlled trials: a systematic
review
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Abstract

Objective

To ascertain current approaches to the collection, reporting and analysis of adverse events (AEs) in randomised controlled trials (RCTs).

Design

Systematic review of clinical trials of drug interventions from four high impact medical journals.

Data sources

Electronic contents table of the Lancet, the BMJ, the New England Journal of Medicine (NEJM) and the Journal of the American Medical Association (JAMA) were searched for reports of original RCTs published between September 2015 and September 2016.

Methods

A pre-piloted checklist was used and single data extraction was performed by three reviewers with independent check of a randomly sampled subset to verify quality. We extracted data on trial characteristics, collection methods, assessment of severity and causality, reporting criteria, analysis methods and presentation of AE data.

Results

We identified 184 eligible reports (BMJ n=3; JAMA n=38, Lancet n=62; and NEJM n=81). Sixty-two percent reported some form of spontaneous AE collection but only 29% included details of specific prompts used to ascertain AE data. Numbers that withdrew from the trial were well reported (80%),

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however only 35% of these reported whether the withdrawals were due to AEs. Results presented and analysis performed was predominantly on 'patients with at least 1 event' with 84% of studies ignoring repeated events. Despite a lack of power to undertake formal hypothesis testing, 47% performed such tests for binary outcomes.

Conclusions

This review highlighted that the collection, reporting and analysis of AE data in clinical trials is inconsistent and RCTs as a source of safety data are underutilised. Areas to improve include reducing information loss when analysing at patient level and inappropriate practice of underpowered multiple hypothesis testing. Implementation of standard reporting practices could enable a more accurate synthesis of safety data and development of guidance for statistical methodology to assess causality of AEs could facilitate better statistical practice.

Keywords

Randomised controlled trials; adverse events; harm data; adverse drug reactions; systematic review; investigational drug.

67.6

Article Summary

Strengths and Limitations of this study

- 1. This is the first systematic review to examine and quantify analysis practices for AEs in RCTs.
- 2. This review characterises what those leading the field in clinical trials are doing and provides some examples of good practice that could be adopted.
- 3. Articles included in this review were published in four of the top ranked medical journals therefore results are likely to be biased towards better findings than we would expect if we included all RCTs.
- 4. At present there is no guidance as to the best statistical methodology to assess causality of

AEs in RCTs.

INTRODUCTION

The methods to analyse and report beneficial effects from randomised controlled trials (RCTs) are well developed but this progress has not been matched for adverse event (AE) outcomes. An adverse event is defined as 'any untoward medical occurrence that may present during treatment with a pharmaceutical product but which does not necessarily have a causal relationship with this treatment'.¹ An adverse drug reaction (ADR) is defined as 'a response to a drug which is noxious and unintended ...' where a causal relationship is 'at least a reasonable possibility'.^{1, 2} RCTs provide an opportunity to compare rates of AEs between arms allowing causality to be evaluated. However current analysis and reporting practices are inadequate.

Previous studies have examined the methods for AE collection and presentation, and highlighted the inadequacies in AE reporting in journal articles.³⁻¹² In 2004 the Consolidated Standards of Reporting Trials (CONSORT) Group produced an extension to their guidelines for reporting trial results to cover the reporting of harms, however implementation of these guidelines has been shown to be poor.^{6, 10-13} Recently a joint pharmaceutical/journal collaboration published practical guidance and examples on what should be reported in journal articles and how it should be displayed to ensure transparency and aid clinical interpretation. They promote the use of clinical judgement in reporting rather than mandatory guidance.¹⁴ However there remains uncertainty about best practice for reporting, analysing and presenting AE data.

There are many challenges associated with analysing and reporting AEs in clinical trials. RCTs are typically designed to determine the efficacy of an intervention but are often underpowered to detect important differences in AEs between arms which may suggest an ADR. Often large numbers of AEs are reported during a study, sometimes exceeding the number of patients in the clinical trial.

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Performing hypothesis tests on these AEs would lead to issues of multiplicity, however any adjustment for multiplicity would make a 'finding untenable'.^{15, 16} The use of hypothesis testing may result in the medicinal product being deemed unsafe and a trial being halted too early due to a chance imbalance, or conversely deemed safe and not stopped early enough resulting in more patients than necessary suffering an ADR.^{15, 17, 18} Unlike efficacy outcomes which are well defined and restricted in number at the planning stage of a RCT, we collect numerous, undefined AEs in RCTs. Furthermore, AE collection requires additional information to be obtained on factors such as severity, timing and duration, number of occurrences and outcome, which for our efficacy outcomes would have all been predefined.

The aim of this review was to evaluate current best practice for collection, reporting and analysis of any arc AEs in RCTs. The aim being to identify and promote any areas of good practice, whilst highlighting any areas for improvement.

METHODS

Search strategy

Four high impact medical journals that publish clinical trials of drug interventions were selected: The Lancet (Impact Factor (IF) 44.00), the BMJ (IF 20.79), the New England Journal of Medicine (NEJM, IF 72.41) and the Journal of the American Medical Association (JAMA, IF 44.41). We manually searched the electronic contents table of the journals for reports of original RCTs published between September 2015 and September 2016, inclusive.

Selection criteria

The inclusion criteria were phase II-IV RCTs of drug interventions where the primary outcome was efficacy of the intervention. We did not restrict according to number of treatment arms and included both parallel and cluster RCTs. We excluded cross-over RCTs, RCTs with adaptive randomisation, observational studies, case reports, editorials and letters. We also excluded RCTs where the intervention was not a drug product (i.e. not classified as a clinical trial of an investigational medicinal product (CTIMP)). As the study aimed to assess how authors report and analyse AEs in efficacy trials, trials that were specifically designed to investigate safety as a primary outcome were not included.

Data extraction

Potentially eligible articles were identified based on titles and abstracts and the full text of these studies were retrieved. Supplementary material was also reviewed if readers were referred here from the main article for further results. Supplementary Table A1 lists all data items captured with guidance given to the reviewers for extraction. We focused on the following areas: how AE data was collected (mode of collection, timing) and defined (coding, attribution); how AEs were assessed in terms of severity of the event or relatedness to the medical intervention; if there was any planned AE analysis (final and interim monitoring plans and analysis populations); how events were selected for inclusion in the journal article; how summary event information was presented in the journal article and how AEs were analysed.⁷

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The data extraction sheet was piloted and then single data extraction was performed by three reviewers (RP, VC and LH) with 10% independent check of a randomly sampled subset to verify quality. Where specific items were flagged for poor agreement these were re-extracted. Agreement between authors was over 80%. Any queries during data extraction were shared and disagreements between reviewers were resolved through discussion.

Data analysis

The proportion of trials reporting each item, 3-4 and 8-34 in supplementary Table A1 were calculated and summary statistics (median and ranges) were calculated for items 5-7. All analyses were performed in Stata version 15.19 reliez on

RESULTS

Study characteristics

The search identified 184 eligible trial reports (BMJ n=3; JAMA n=38, Lancet n=62; and NEJM n=81) in which a total of 496911 participants were randomised with a median of 556 participants per trial (range 30, 205513; interquartile range (IQR) 281, 1704). The median trial follow-up was 52 weeks (range 48 hours to 10 years; IQR 24, 104 weeks) and 93% were multi-centre trials. Fifty-percent of studies had an active comparator and over 50% of trials received some element of industry funding (Table 1).

Characterist	ic	I	N=184	
		Median	(IQR)	min, max
Sample size		556	(281, 1704)	30, 205513
Centres ^a		35	(12, 100)	1, 1368
Trial duration	on (weeks) ^b	52	(24, 104)	0.3, 521
		n	%	
Journal				
BI	NJ	3	1.6	
JΑ	MA	81	44.0	
La	ncet	38	20.7	
N	EJM	62	33.7	
Funded by				
Ρι	ublic	70	38.3	
In	dustry	80	43.7	
Во	oth	33	18.0	
Centre				
Si	ngle-centre	12	7.0	
Μ	ulti-centre	161	93.0	
Control				
Pl	acebo	95	51.6	
A	ctive	80	43.5	
Во	oth	8	4.4	
N	either ^c	1	0.5	

Abbreviations: IQR = Inter-quartile range; min = minimum; and max = maximum

^a11 reports did not specify the number of centres

^b2 reports did not specify trial duration

^cOne trial compared interventional drug to behavioural change intervention

Collection and assessment methods

Sixty-two percent of reports made reference to some form of passive (e.g. spontaneously reported by patients) AE monitoring or collection methods but only 29% of reports included specific details (prompts e.g. questions about specific events or AEs in general, questionnaires, or diaries) regarding these collection methods (Table 2, examples 1-2).^{20, 21} The timing of collection was well documented

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(91%, 48 out of 53 reports) in the reports that included specific details about the prompts used to collect AEs. Although specific details on clinical examinations (e.g. vital signs and blood pressure) and laboratory tests were not widely reported (only 57% of reports (95 out of 166 reports with clinical examinations and/or laboratory results presented) included details on the timing of such assessments) it was often clear from the results presented that participants had undergone these assessments (83% and 79% of studies reported clinical and laboratory results respectively) (Table 3).

Example	Study	Example practice	Example
no.			
1	Litonjua et al. ²⁰	Description of AE collection method	"Study staff met with pregnant women monthly to administer a brief health questionnaire, assess medication use, and monitor for complications (via the questionnaire and medical record review) After delivery, children were monitored by telephone every 3 months and in-person annually for 3 years, during which time infants' health, respiratory symptoms, and medications were assessed"
2	Miller et al. ²¹	Description of AE collection method	"Safety evaluations included physical examinations, assessment of vital signs, clinical laboratory tests, and reporting of adverse events at each study visit"
3	Libman et al. ²²	Description of planned AE analysis	"The proportions of participants experiencing any adverse event, any related adverse event, any gastrointestinal event, any event other than a gastrointestinal event, at least 1 severe hypoglycaemic event, and at least 1 diabetic ketoacidosis event in each treatment group were compared using the Fisher exact test. The number of adverse events, new adverse events, serious adverse events, and non-serious adverse events were compared between groups using a Wilcoxon rank sumtest."
4	Gross et al. ²³	Description of planned AE analysis	"Safety analyses and secondary efficacy analyses used binomial regression, analysis of covariance, or the marginal Cox proportional hazards model as appropriate"

Table 2: Examples of reporting practice in reviewed articles

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Section	Component	Data item	N=	-184
Collection			n	%
	How was AE/harm information colle	cted?		
		Passive collection	114	62
		Prompted collection	53	28
		Active screening		
		Clinical examinations	153	83
		Laboratory tests	146	79
	Timing of prompted collection	specified (n=53)	48	90
	Timing of active collection spe	cified (n=166)	95	57
	Which if any dictionary was used to	o code AF data?		
	which, if any, alcohold y was used to		18	q
		MedDRA	43	23
		CTCAE and MedDRA	1	<u>د م</u>
		DAIDS	2	0. 1
		ICD-10	- 1	<u>۰</u>
		Researcher defined	2	1
		Other	3	1.
		No dictionary reported	114	62
Assessment				
	Who assigned attribution to study d	rug?		
		Blinded assessor	9	4.
		Unblinded assessor	7	3.
		Both	1	0.
		Not specified	164	89
		Not applicable ^a	3	1.
Analysis				
	Was any analysis for AEs specified in	the methods section?		
		Yes	57	31
	Was a population for AE analysis spe	ecified?		
		Yes	82	44
	Was there a planned interim analysi	s with stopping criteria?		
		No	138	75
		Yes for efficacy	24	13
		Yes for efficacy & futility	11	6.
		Yes for efficacy & safety	3	1.
		Yes for efficacy, futility &		
		safety	2	1.
		Yes but no other details		
		given	6	3.
Abbreviations: Dictionary for Diseases 10 th r	AE = Adverse event; CTCAE = Common Term Regulatory Activities; DAIDS = The Division o evision.	ninology Criteria for Adverse Events; N f AIDS; and ICD-10 = International Cla	1edDRA = ssificatior	Med n of
		and tatal samula		

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Prespecified analysis

Thirty-one percent of reports provided information on the planned analysis for AEs in the statistical analysis section of the paper and 45% pre-specified a safety population (Table 2, examples 3-4 and Table 3).^{22, 23} A quarter of trials reported planned interim analysis with stopping criteria (Table 3), five (2.7%) of which included specific criteria on stopping for a harmful event (Supplement Table A2).

Selection of AEs and reporting practices

Five trials did not report any information on AEs. Two of these reports made the following statements "there were no significant adverse events related to the procedure" and "no excess in mortality or major adverse events were found..." and three made no mention of AEs.²⁴⁻²⁸

Twenty-four (13%) trials only provided a summary of the number of AEs or serious AEs rather than listing the actual AEs that occurred. For example *"Six serious adverse events occurred in the acetaminophen group and 12 in the ibuprofen group."*²⁹ Of these 24 trials, 10 did provide specific details of the types of events in an appendix. This means 8% of trials either did not report AEs or only included a summary (Table 4).

Component	Data item	N=1	.84
· · ·		n	%
What was reported in the	manuscript?		
	Actual AE terms	73	39
	Summaries of AE type (e.g. AE, SAE)	24	13.
	Both	80	43
	Neither	7	3.
What was reported in the	appendix?		
•	Actual AE terms	76	41
	Summaries of AF type (e.g. AF SAF)	7	3
	Both	, 22	12
	Neither	2	1
		70	1.
		76	41
Which population was the	e AE analysis performed on?		
	All randomised	54	29
	Those that took at least a single dose	75	40
	Other	35	19
	Not specified	17	9.
	Not applicable ^b	3	1.
Were drop-outs/withdrav	vals reported?		
	No	33	17
	Yes by treatment arm	144	78
	Yes overall	2	1.
	Not applicable ^c	5	2.
Were withd	Irawals due to AEs reported? (n=146)		
	No	89	61
	Yes	51	32
	Not applicable ^d	6	4
Were speci	fic AEs causing withdrawals reported? (n=51)		
·	No	39	76
	Yes	12	23
How were binary AF outco	omes summarised by arm?		
	Not summarised ^e	6	3
	Number of people with an event	154	נ. גא
	Number of events	<u>1</u> 34 11	6
	Both	17	6. 5
	Unclear	1	0
Ware frequencies of AEs	enorted by arm?	T	0.
WEIE ILEQUEICLES ULAES I	No	Ę	r
	Nu Vos for somo	5 10	Z. -7
	Yes for sull	15	/.
	Yes for all	160	8/
	Not applicable [®]	6	3.
were percentages of AEs	reported by arm?		-
	No	18	9.
	Yes for some	25	13
	13		

1				
2		Vector ell	125	72.4
5 A		res ior all	135	75.4
4 5			6	3.3
6	Were between arm differences and 9	5% CI of AEs reported?		
7		No	141	76.6
8		Yes for some	18	9.8
9		Yes for all	19	10.3
10		Not applicable ^e	6	3.3
11	Were statistical significance tests bet	ween arms on AEs reported?		
12		No	92	50.0
13		Yes for some	31	16.9
14		Yes for all	55	29.9
15		Not applicable ^e	6	33
10	Were continuous AEs outcomes dicho	ntomised for summaries?	·	010
18	Were continuous ALS outcomes uten	No	10	51
19		No Vac for como	20	15.7
20		Yes for some	28	15.2
21		Yes for all	108	58.7
22		Not applicable	38	20.7
23	If continuous outcomes were left as o	continuous what between arm analyses was	performed?	(n=38)
24	Differences in measure	s of central tendency estimated with 95% CI		
25		No	23	60.5
26		Yes for some	1	2.6
27		Yes for all	14	36.8
20	Between arm hypothes	sis tests performed		
30		No	12	31.6
31		Yes for some	2	5.3
32		Yes for all	24	63.2
33	Were any 'signal detection' approach	es used?		
34	······································	No	184	100.0
35		Ves	0	0.0
36	Ware there any graphical presentation	ins of AE outcomes?	0	0.0
37	were there any graphical presentatio	No	100	00 0
38		NO	162	88.0
39 40		Yes	22	12.0
40	Were summaries of severity rating of	AEs reported?		
42		No	103	56.0
43		Yes for some	41	22.3
44		Yes for all	35	19.0
45		Not applicable ^f	5	2.7
46	Were number of serious AEs reported	1?		
47		No	44	23.9
48		Yes overall	2	1.1
49		Yes by treatment arm	132	71.7
5U 51		Not applicable ^g	6	3.3
52	For serious AFs was rel	atedness given? (n=134)	-	
53		No	77	57 5
54		Vos for somo	10	12 /
55			70	10.4 20.4
56		res for all	38	28.4
57				
58		14		
59				

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60

1				
2				
3		Yes overall	1	0.8
4	Were there any AEs where infor	mation on duration of events wa	s reported?	
5		No	175	95.1
0 7		Yes	9	4.9
7 8	Were there any AEs where infor	mation on the time of occurrence	e of events was reported?	
9		No	132	71.7
10		Yes	52	28.3
11	If any significance tests were pe	erformed on AEs was multiplicity	of events accounted for?	
12		No.	81	44 0
13		Yos	2	1 6
14		Not applicable	5 100	1.0 E / /
15			100	54.4
16	Did the report reference the CO	NSORT extension to harms		
17		No	184	100.0
18		Yes	0	0.0
19	Abbreviations: AE = Adverse Event; S	AE = Serious Adverse Event; CI = Conj	fidence Interval; and CONSOR	T =
20	Consolidated Standards for Reportin	g Trials.		
21	a Make no reference to the appendix			
22	⁹ 3 reports included no AE data			
25	5 reports indicate no withdrawals			
24	⁶ 6 reports specify the number of wi	hdrawals and reasons but none of th	e reasons are related to AEs	
25	[•] This includes 3 reports with no AE	lata (as per footnote °), 2 reports tha	t provide generic statements	regarding
20	AE data and 1 report that only report	ted continuous outcomes		
28	This includes 3 reports with no AE c	ata and 2 reports that provide gener	ic statements regarding AE da	ita (as per
29	^g 6 papers specifically state that pe	arious advorsa avants accurred		
30	6 papers specifically state that no s	erious adverse events occurred		
31				
32				
33	Eighty-nine percent of trials repo	rted a subset of all the AEs they c	ollected. How AEs are 'sele	cted'
34				
35	for inclusion in the article was no	t consistent or clear, and in 3% of	studies it was impossible t	0
36				
37	discern how the authors had sele	cted the AEs they presented for i	nclusion. Twenty-six percer	nt of
38				
39	reports selected events based or	a frequency threshold e.g. event	s experienced by greater th	ian x%
40				
41	in any group; 9% of reports used	a measure of severity to select ev	ents e.g. AEs of grade 3 or	higher;
42				
43 44	23% of reports included events b	ased on seriousness; and 8% inclu	uded AEs based on related	iess to
45				
46	treatment (percentages are not i	ndependent as the majority of rep	ports used several different	t
47				
48	criteria for selection). Supplemer	tary Table A3 provides full details	s of selection criteria used.	
49				
50				
51				
52				
53				
54				

100.0 0.0

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We found that 41% of trials analysed AEs in participants that received at least one dose, 29% of trials used all randomised participants and 9% did not specify the analysis population (Table 4). Further details on analysis populations used are given in supplementary Table A5.

Nearly 80% of trials reported the number of participants who withdrew from the trial; of these 35% (51 of 146 reports) reported whether the withdrawals were due to AEs and of these 24% (12 of 51 reports) reported the actual events that caused withdrawals. Results presented and analysis performed was predominantly on 'patients with at least 1 event' with 84% of reports providing no information on the number of events occurring. An example of how to incorporate information on number of events is presented in ³⁰. Forty-one percent of trials reported information on the severity of AEs. Five percent of trials include a report of at least one event with duration, but presenting such data is limited in the main report. The trials that did present this information did so in a variety of ways. For example incorporating the information into the AE table with summary statistics such as the mean duration of certain events or presenting it for a subgroup of events in the footnotes of AE tables e.g. *"One event of non-serious squamous cell carcinoma (day 210, resolved on day 215; adalimumab treatment was not interrupted*)."³¹⁻³³ Twenty-eight percent of reports included information on the timing of AEs (Table 4).

Serious adverse events were typically well documented (73%) and six reports (3%) explicitly stated that no serious events had occurred. However for forty-four reports (24%) it was not possible to discern if no serious events had occurred or whether they were simply omitted from the report. Forty-two percent (57 of 134 reports) of reports included details on whether the events had been classified as related to the intervention (Table 4).

Analysis of AE outcomes

Binary

The majority of trials summarised binary outcomes using frequencies (94%) and percentages (87%). Despite a lack of power to undertake formal hypothesis testing, 47% reported p-values for binary outcomes. For example "There were no between-group differences in the rate of patients with at least 1 adverse event (16.7% [14 patients] in the clopidogrel group vs 21.8% [19 patients] in the placebo group; difference, -5.2% [95% CI, -17% to 6.6%]; P = .44)." However with a total safety population of 171 such a test would have only had 13% power to detect such a difference and was therefore substantially underpowered. The conclusion that "No significant increase in adverse events was observed" makes no reference to the 95% confidence interval presented which indicates that the findings were in fact compatible with a 17% decrease in experiencing at least on AE as well as a near 7% increase.³⁴ iley

Continuous

There was a pervasive practise (59%) of categorising continuous clinical and laboratory outcomes. Of the trials that did not dichotomise continuous AE data nearly 70% performed some form of statistical significance testing (Table 4). Whilst continuous outcomes do not suffer to the same degree regarding lack of power, multiple testing is still a problem, however no multiplicity corrections for continuous outcomes were performed.

Of the trials that performed statistical significance testing on AE data, only three made an adjustment for multiplicity of tests (all three on dichotomised outcomes).^{31, 35, 36} Two of which used a Bonferroni correction and adjusted for the number of pairwise comparisons between each of the

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treatment groups for each individual event rather than the total number of significance tests performed. As such both analyses would have still been effected by issues of multiple testing.

Twelve percent of reports used graphs to illustrate AE data (Table 4). The CONSORT extension highlighted the value of graphs for summarising such data, especially for conveying information on time-to-event outcomes.³⁷ An example of such a plot is included in the supplement of ³⁸ (eFigure

2).

DISCUSSION

The safety profile of a medicinal product is established through evidence collected from several sources including clinical trials, observational studies and spontaneous reports.³⁹ The advantage of clinical trial data is that these provide a controlled comparison of the rate of AEs allowing causality to be evaluated but have the disadvantage that the sample size is often not large enough to detect rare ADRs.

To ensure that a useful and comprehensive picture of the safety profile is provided to all relevant parties clear reporting of AEs from clinical trials is required. Current research has shown the quality of reporting is substandard.³⁻¹² The aim of this study was to review best practice across four leading medical journals for AE collection, analysis and reporting practices, highlighting any areas for improvement and examples of good practice.

Principal Findings

Collection and assessment methods

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The CONSORT extension to harm was developed with the aim to improve reporting of safety data in RCTs.³⁷ Of the ten recommendations many were not well reported.¹³ This suggests that the CONSORT extension is not being routinely adopted by authors to aid their reporting. Most journals now request that authors include a completed CONSORT checklist when they submit their article but we are not aware of any journal that request the CONSORT harm extension to also be submitted. Of the four journals in this review the Lancet is the only journal that makes specific reference to the harm extension in their guidelines to authors. The CONSORT statement contains a single item related to safety, item 19: 'all important harms or unintended effects in each group' should be reported.³⁷ This may explain why some items listed on the CONSORT extension for harm were reported by so few trials. The adoption of CONSORT harms by journals may support better reporting.

We found that the method of AE collection was poorly reported. This has important implications for the type and frequency of AEs reported with "passive collection resulting in fewer recorded AEs".^{40,} ⁴¹ Where the method was given the timing of collection was typically also reported and we would recommend continuation of this practice. The frequency of AE collection has further important implications on the number of events reported. More frequent assessment and longer follow-up will result in more AEs reported.¹³ It is important to consider these factors when making conclusions about the safety profile. BMJ Open: first published as 10.1136/bmjopen-2018-024537 on 1 March 2019. Downloaded from http://bmjopen.bmj.com/ on June 11, 2025 at Agence Bibliographique de Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies.

The method of attribution between drug and AE was another area where reporting practice was inadequate. However the joint pharmaceutical/journal collaboration indicate that such attribution has 'limited value' given the 'inherent subjectivity in such attribution'.¹⁴

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Prespecified analysis

We found that formal assessments of AEs regarding stopping for emerging ADRs utilising statistical rules was rare. Subjective assessments of overwhelming amounts of data could easily lead to potential signals of harm being missed. There could be benefits to incorporating more objective methods alongside clinical review to monitor AE information, both for interim analysis by data monitoring committees (DMCs) and final trial analysis to help better identify drug harm relationships. Graphical displays have gone some way towards aiding interpretation.⁴²⁻⁴⁶

Selection of AEs and reporting practices

Due to space constraints in journal reports AE information is often included in the appendix. Whilst we encourage use of appendices and supplementary material for including additional detail on AEs, we caution authors against depositing all AE data into such documents without attempting to present a summary of the AE profile in the main article. It is important that the main report strikes a balance between efficacy and harm therefore allowing a risk-benefit assessment to be made solely from the article.

The failure to report any information on AEs restricts interpretation and prevents a risk-benefit assessment. We identified two reports that made generic summaries of the overall safety profile and it was clear in both that there had been harmful effects however the authors did not include any further information. Three reports contained no information leaving readers uninformed as to any additional information these studies may provide on the safety profile. Ambiguous reporting prevents building an accurate picture of the safety profile. As such profiles are developed on

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accumulating evidence, it is important that each study report to the same standard and information is not wasted.

We found that the selection criteria used by authors to decide what AEs to include in the report were arbitrary and inconsistent. This will have important implications when synthesising data across studies to construct safety profiles. Authors would benefit from guidance to facilitate consistency but currently research in this area is lacking. Lineberry et al. recommended clinically relevant events that should always be reported (deaths, SAEs and events leading to discontinuation of intervention) and criteria that should be considered when deciding what other AEs to report e.g. interest based on the disease(s) under investigation, comorbidities of the study population, intervention mechanism, trial duration.¹⁴ Standard outcomes for a drug class would be one potential solution to avoid issues of inconsistency suggested by Cornelius et al.⁷

CONSORT recommend that AE analyses should be performed on the intention-to-treat (ITT) population to maintain the random assignment.¹³ However it is clear from our review that this population label is not always appropriately and consistently applied. There is a tendency for studies to make modifications to the ITT population. Using the ITT or modified-ITT population is likely to underestimate the risk by inflating the denominator with participants who may have never received the study drug.⁴⁷ Such estimates are appropriate for health economic evaluations where estimates of the cost-effectiveness will inform policy level decisions regarding how to treat the population. However a more appropriate population for AE analysis to inform prescriber and patient decisions may be those that receive at least one dose. It is important that authors are clear about what they are estimating and how this affects their conclusions.

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Proxy outcomes can be used as a measure of the impact of AEs on patients. Examples include the number of withdrawal due to any reason, withdrawals due to AEs, the number of events an individual experiences, the severity of the AE and the duration. A high proportion of trials reported withdrawal for any reason and this is likely to be as a result of the CONSORT recommendations.³⁷ The other outcomes were not frequently reported and increasing this could facilitate interpretation.¹³ This information would permit better evaluation of the impact of AEs and the tolerability of the intervention to inform patients' and clinicians' treatment decisions. Reporting numbers that experience at least one event only and not providing information on repeated events masks valuable information that may be important to the patient and the cost-effectiveness evaluation. For example, chronic, repeated headaches over an extended duration will have an important impact for patients compared to a single headache or headaches over a short duration but it is not possible to distinguish between these two scenarios when reported as 'at least one event'.¹⁴ Severity of events was also an important aspect that was often not differentiated. For example there would be different impact on patients' quality-of-life with mild compared to severe nausea and which could lead to changes in dosing regimens. Displaying such information for all AEs in tables would soon become overwhelming and make interpretation difficult. Graphical approaches have been suggested as a solution to aid review. Examples of such a plots can be found in ⁴⁸. Online appendices and supplementary material provide more opportunity to include this important information.

For serious adverse events information on the time of likely onset can be useful information to inform patient monitoring plans. For example the documented risk of suicide and suicidal ideation within the first few weeks of starting anti-depressant allows patients and prescribers to remain alert and monitor closely for this period. Nearly a third of reports included such information and we would encourage authors to adopt this practice.

Analysis of AE outcomes

The majority of trials in this review included a balanced report of AEs alongside benefit. However many included generic statements regarding the safety profile such as 'the intervention was well tolerated' or 'the intervention exhibited a good safety profile' and these were frequently based on post-hoc statistical tests. Guidelines caution against such tests.¹⁴ The results of which are difficult to interpret as a lack of significance does not indicate that the intervention is safe and conversely multiple testing without adjustment will increase the number of significant differences due to chance.^{49, 50}

Graphs are an efficient method to convey and interpret large amounts of data and can make it easier to flag potential safety signals.^{45, 46, 48} Twenty-two studies included in the review used graphs to present AE data and an example of one such report is given in the supplementary eTable of ⁵¹.

Limitations of trials

Trials are a valuable source for high quality adverse event data but compared to observational studies have smaller sample size, follow-up periods and generalisability which restrict the ability to detect rare ADRs, ADRs with long latency and drug interactions in complex populations. The typical duration of a trial means there is often insufficient follow-up to fully characterise the safety profile as it provides limited information on long-term exposure. Stringent inclusion criteria restrict the

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population the intervention is assessed in and so limited information on drug-interactions is obtained.¹⁷

Limitations of this study

Articles included in this review were published in four of the top ranked medical journals therefore results are likely to be biased towards better findings than we would expect if we included all RCTs. However this review characterises what those leading the field are doing and provides some examples of good practice that could be adopted.

Conclusions and recommendations for future work

RCTs are a valuable source of information establishing the safety profile of medicinal products. Our review has demonstrated that data is not currently being fully utilised. Analysis of AE data is frequently inappropriate and reports often provide insufficient and inconsistent information to allow a comprehensive summary of the safety profile to be established.

This research has identified two areas that would benefit from future research. i) Improving the consistency of reporting important AE outcomes across trials to facilitate comparison and synthesis. This is in line with work from the COMET Initiative group (<u>http://www.comet-initiative.org/</u>). The development of CORE safety outcomes by drug class could be considered.⁷ ii) Evaluation of methods to analyse AEs in RCTs.

None declared.

FUNDING

This research was supported by the NIHR grant number DRF-2017-10-131.

DATA SHARING STATEMENT

No additional data are available.

AUTHOR STATEMENT

RP conceived the idea for this review, conducted the search, carried out data extraction and analysis, and wrote the manuscript. VC conceived the idea for the review, performed data extraction and critical revision of the manuscript. LH performed data extraction and critical revision of the

manuscript. OS performed critical revision of the manuscript.

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Table A1: Data	items extracte	d from pu	Dications	Instructi	
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Study details		3	Funding source: public, private, both or unspecified.	Studies av explicate	$\frac{3}{6}$ will be assumed to be funded by industry only if this is $\sqrt{6}$ tated.
		4	Control: placebo, active or both	Selectoria should be at least or receivant	Belected for trials with multiple arms where there is group receiving no active treatment and one group an active treatment.
characteristics		5	Number of centres	ata	
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Deta how outc were (coo	Details of how AE outcomes were defined (coding, attribution)	8	Describe the collection method: passive surveillance, patient prompted, clinical examinations (e.g. vital signs or urine samples), and laboratory tests. (Select all that apply)	Passinge: 1 study with was passi Prompted questions questions	Fauthors state that AEs were collected throughout the fino further information we will assume that collection Prompted methods include, but are not limited to babout both specific events and AEs in generation pares, or diaries.
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Planned analysis	Details of any	12	Describe analysis for AE outcomes in the statistical methods.	Reterence harm eve analysed.	emust be made to harmful events e.g. AEs or a specification of the simply how binary events will b
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3 4 5 6 7 8 9 10 11 12 13		Details of what was reported and where	15	What was reported in the main paper: summaries of type of AEs (e.g. AE, SAE, AR, ADR), actual AE terms, both, neither or not applicable?	Not applicable is relevant when for example authors explicitly state there are no events or there is only one event so summaries are inappropriate.
			16	What was reported in the appendix: summaries of type of AEs (e.g. AE, SAE, AR, ADR), actual AE terms, both, neither or not applicable?	Not applied ble is relevant when for example authors explicitly state that there are no events or there is only one event so summaries are inappropriate. We will only search the appendix/supplementary material for AE dotation the main article makes reference to it.
14 15			17	Who was the AE analysis performed on: all randomised, participants who took at least a single dose, other or not specified?	t and d
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20 21 22	Results		19	Were drop-outs/withdrawals due to AEs reported: Yes, no or not applicable?	Not applicable if drop-outs/withdrawals are not reported or if it is reparted that there are no drop-outs/withdrawals.
23 24 25			20	Were specific AEs causing withdrawals reported: Yes, no or not applicable?	Not applicable if drop-outs/withdrawals due to AEs are not reported of if it is reported that there are no drop- outs/Bithdrawals due to AEs.
26 27 28 29			21	What was the selection criteria for the AEs reported?	Free text esponse where possibilities can include for example: most dependent, above a severity threshold, SAEs. Include defails of what's in the main journal article and what is in the appendix separately.
30 31 32 33 34		Details of how AEs were summarised and presented - binary outcomes		What summary information was given. Number of people, number of	Only celect 'number of events' if presented for each individual events of events. Not applicable is only relevant when report that there are no
35 36			22	events, both, unclear, not summarised or not applicable?	AES. G
37 38			23	What analysis was performed: frequencies, percentages, differences and 95% confidence intervals, significance tests, other? (Select all that apply)	Bibli
39 40					ygraphic
41 42				2	d d
43				For peer review only - http://bmjopen.bmj.com/site/about/guideline	es.xhtml 📮

			BMJ Open	bmjopen-2018 J by copyright,	Page 34 of 4
D hu su au	Details of how AEs were summarised and presented	24	Were continuous outcomes dichotomised: Yes for all, yes for some, no or not applicable?	This Encloses me contiguous and th blood pressure etc.	asures that will have been captured as en dichotomised for example blood levels,
- 01	continuous utcomes	25	performed: differences in measures of central tendency, significance tests, other? (Select all that apply)	rch 20 Enseig ses rel	
D he	Details of how AEs	26 27	Were signal detection methods used?	19. Dov nemen ated to	
w sı aı	vere ummarised nd presented	28	Were severity ratings given: Yes for all, yes for some, no or not applicable? Were numbers of agricus quests presented: Yes by tractment arm use	wnloadeg tt Superig text and	d as part of the officery outcome it is not
		29	overall, no or not applicable?	enough foconstitut a AB a B a B	a as part of the efficacy outcome it is not reporting serious events.
		30	Were serious events coded as treatment related: Yes for all, yes for some, no or not applicable?	http://bn ES) . lining, /	
		31	Provided information on the duration of events?	This reference to the le	ngth of the actual AE i.e. how long did it last.
		32	Provided information on the timing of events?	This geferent to the ti	me of onset of the AE.
		33 34	Referenced CONSORT extension for harms?	and s	
			3	on June 11, 2025 at Agence Bibliographique de milar technologies.	
			For peer review only - http://bmiopen.bmi.com/site/about/guideline	s.xhtml 💾	

Table A2: Stopping	criteria fo	r safety
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Study	Main article text	Appendix text
Myles et	"O'Brien–Fleming stopping boundaries were used to	
al.55	assess efficacy, and <u>a less stringent boundary was</u>	
Billings et al. ⁵⁴	<u>used to assess harm</u> ." "The data and safety monitoring board (DSMB) reviewed patient recruitment practices, safety reporting, and data quality after 30 patients completed the study; performed an interim analysis after 277 patients had completed the study to assess <u>safety of the intervention</u> ; and performed a second interim analysis after 546 patients had completed the study to assess the safety, efficacy, and futility of the intervention. The DSMB made recommendations based on qualitative assessments of the safety, efficacy, and futility of the intervention"	 "Suspend enrolment in any study arm due to safety concerns based on study intervention. Safety concerns include: Increase in in-hospital all-cause mortality in subjects randomized to A or B such that the DSMB deems the increase is excessive compared to A or B. Increased treatment toxicity in either treatment group deemed excessive. Toxicity is defined as moderate or severe myalgias. Increased severity of adverse events deemed "Probably Related" or "Possibly Related" to study intervention in either treatment group. Itemized adverse event reports separated by treatment will be
		provided. • Increased AKI incidence in either treatment group deemed excessive. • Increased incidence of stroke or hemodialysis requirement in either group (secondary endpoints) deemed excessive."
Beardsley et al. ⁵⁵	"An independent data and safety monitoring committee oversaw trial safety and analyzed unblinded data after every 50 deaths, according to its charter"	"The Haybittle-Peto boundary, requiring p<0.001 at interim analysis to consider stopping for efficacy, will be used as guidance. <u>A level of significance of 1% will</u> <u>be used as a quide for stopping the trial early because</u> <u>of a detected harm of dexamethasone</u> . In addition, the DMEC will receive conditional power curves to assess whether it remains realistic that the trial will demonstrate superiority of dexamethasone conditional on the data accrued up to the point of the interim analysis. Importantly, the DMEC recommendations will not be based purely on statistical tables but will also use clinical judgment."
Kor et al. ⁵⁶	"In addition to statistical criteria for significance, the study included a priori "go-no-go" definitions for recommending continuation to phase 3 study Briefly, continuation to phase 3 would occur with a positive primary outcome finding along with an acceptable safety profile. An acceptable safety profile was defined as a serious adverse event profile for aspirin that was not statistically worse than placebo (95% CI for the relative risk of any serious adverse event covers the null value of relative risk = 1.0). The "no-go decision" was defined as early termination by the data and safety monitoring board for safety or unfavorable risk/benefit ratio. An indeterminate case in which there was a non-statistically significant effect but this effect was in a clinically meaningful direction was also defined."	Initiate Phase III Study: Demonstrated efficacy signal in addition to adequate safety profile Criteria: Early termination for benefit at interim analysis or p<0.08885 at final analysis (alpha=0.10 for study). <u>Serious adverse event profile of ASA not statistically</u> <u>worse than placebo (95% confidence interval for the</u> <u>relative risk of any SAE covers the null value of</u> <u>RR=1.0).</u> Further Development Potentially Required: Weak efficacy signal Criteria: Primary endpoint did not achieve a priori level of significance but there were at least a general consistency of secondary endpoints indicating propensity for efficacy with a larger sample size and/or more specific primary endpoint. Abandon Treatment Platform: Harm (in efficacy or safety endpoints) Criteria: Study terminated early per recommendation <u>by DSMB for safety and/or</u> <u>risk/benefit ratio concerns</u> (i.e., stop for futility, harm, unaccentable rick profile etc.)

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Nichol al. ⁵⁷	et	We used a group sequential statistical approach to do two equally spaced pre-planned interim analyses (at 33% and 67% of total recruitment) to assess accumulated safety data (differential proportions of deep venous thrombosis and total mortality). This <u>approach was chosen to provide for early stopping for</u> <u>probable harm</u> or strong evidence of benefit. We applied the Haybittle-Peto criterion ($ Zk \ge 3$) for early	
		stopping at these analyses.	

for occurrence with a second

2				
4	Table A3: Selection criteria used to select AEs presented in the main journal report		0/	_
5		20	10.97	-
6	All AES presented AEs in greater than x% in any group	20	10.87	
/ 8	As in greater than x % in treatment group	10	5.43	
9	As in greater than $x/0$ in cleatment group	4	2.17	
10	Aestingreater than x% in an patients	1	0.54	
11	Most common (no criteria specified)	9	4.89	
12	Predetined AES	26	14.13	
13	SAEs	15	8.15	
14 15	AEs leading to study drug discontinuation/interruption	3	1.63	Pr
15 16	Treatment related AEs	5	2.72	ote
10	Grade 3>= events	9	4.89	cteo
18	AEs in greater than x% in any group & predefined/special interest AEs	4	2.17	р р
19	AEs in greater than x% in any group & frequency between groups differed by more than y% &) CC
20	predefined/special interest AEs	1	0.54	py
21	AEs in greater than x% in all patients & predefined/special interest AEs	3	1.63	righ
22	AEs in greater than x% in treatment group & AEs of special interest	2	1.09	,∓ ≕
23 24	AEs in greater than x% in any group & all SAEs	2	1.09	nclu
25	AEs in greater than x% in all patients & all SAEs	1	0.54	Jdir
26	AEs in greater than x% in any group & SAEs related to treatment	1	0.54	ן חם f
27	Most common (no criteria specified) & predefined/special interest AEs	3	1.63	or I
28	Most common (no criteria specified) & all SAEs	4	2.17	Jse
29	Most common (no criteria specified) & all SAEs & AEs leading to study drug discontinuation/interruption	1	0.54	sei s re
30 21	Most common (no criteria specified) & treatment related SAEs	1	0.54) elat
32	AEs where frequency between groups differed by more than y% & all SAEs	1	0.54	ed t
33	AEs of special interest	6	3 26	0 nt c
34	Grade \geq 3 AEs in greater than x% of patients	1	0.54	Sup
35	Grade \geq 3 AFs in greater than x% in intervention & v% in control	1	0.54	anc
36	Most common (no criteria specified) grade 3>= AFs	1	0.54	eur da
37	Most common SAEs (no criteria specified)	T	0.54	ta r
38	SAEs & AE of special interest	1	0.54	nin
40	Treatment related AEs in greater than x% of nationts	1	0.54	ing
41	Treatment related AEs in greater than x% of patients	1	0.54	, ≥
42	Treatment related AEs in greater than x% in any group	1	0.54	tra
43	AEs in greater than x% in treatment group & SAEs	1	0.54	inir
44	AEs in greater than x% in treatment group & SAEs & predefined AEs	2	1.09	, ĝ
45	AEs in greater than x% in any group & significantly different & SAEs	1	0.54	and
40 47	AEs in greater than x% in any group & treatment related AEs/SAEs	2	1.09	sir
48	AEs in greater than x% in treatment group & treatment related AEs & SAEs	1	0.54	nila
49	AEs in greater than x% in treatment group & treatment related AEs in greater than y% in all patients	1	0.54	ır te
50	AEs in greater than x% in any group & Grade 3>= events	1	0.54) chi
51	AEs in greater than x% in all patients & Grade 3>= events	1	0.54	nolo
52	AEs in greater than x% in all patients & Grade 2>= treatment related AEs	1	0.54	ogie
53	AEs in greater than x% in any group & Grade 3>= events in greater than y% in any group	1	0.54	S.
55	AEs in greater than x% in any group & SAEs in treatment group	1	0.54	
56	AEs in greater than x% in any group & AEs of special interest & most common (no criteria specified) AEs	-		
57	leading to treatment discontinuation/interruption & predefined AEs	1	0.54	
58	AEs in greater than x% in any group, AEs of special interest in greater than y% in treatment group &			
59	treatment related deaths	1	0.54	
60				

AEs in greater than x% in treatment group & SAEs in greater than y% in any group	1	0 54
AEs and SAEs occurring more often in treatment group than control	1	0.54
AEs in greater than x% in treatment group & occurred more often in treatment group than control &	-	0.01
predefined/special interest AEs	1	0.54
AEs in greater than x% in any group & frequency between groups differed by more than y%, SAEs in greater than z% in any group & all grade >=3 AEs	1	0.54
AEs in greater than x% patients & more than y% difference between treatment groups & AEs leading to		
treatment discontinuation/interruption & most common SAEs (no criteria specified) & death	1	0.54
Predefined AEs, AEs leading to hospitalisation/death/study drug discontinuation/interruption & SUSARS	2	1.09
Some form of overall summary	6	3.26
Not specified how selected	6	3.26
Not summarised in main paper	11	5.98
		,
		(
		(
		(

Selection criteria		n
All AEs	1	18
SAEs	1	18
All AEs & SAEs		4
AEs in greater than x% in any group		7
AEs in greater than x% in treatment group		2
AEs in greater than x% in all patients		1
AEs in greater than x% in any group & all SAEs		2
AEs in greater than x% in treatment group & all SAEs		1
AEs in greater than x% in all patients & all SAEs		3
AEs in greater than x% in treatment group & all SAEs		1
AEs in greater than x% in treatment group & greater than in control group & all	SAEs	1
SAEs in greater than x% in any group		1
AEs in greater than x% in any group & SAEs in greater than y% in any group		1
AEs in greater than x% in any group & AEs of special interest		2
Treatment related AEs		5
Freatment related AEs in greater than x% in any group		2
Grade 3>= events		2
Predefined AEs		8
AEs of special interest		1
As leading to study drug discontinuation/interruption		2
As leading to study drug discontinuation & SAEs		1
Grade 3>= events leading to study drug discontinuation & grade 3>= laboratory	results	1
reatment related AEs & AEs leading to study drug discontinuation		1
AEs in greater than x% in all patients leading to treatment discontinuations, SAI group, serious predefined/special interest AEs and clinically significant laborate	Es in greater than x% in any ory results	1
AEs in greater than x% in any group, treatment related AEs in greater than x% in	n any group, treatment	1
Clinical Jahoratory data		1
Predefined AFs. AFs leading to hospitalisation/death/study drug discontinuation	n/interruption & SUSARS	т З
Deaths	,	2
Some form of overall summary		5
Not specified how selected		2
Not summarised in the appendix	٤	84

Table A5: Population used for AE analysis

Those that took at least a single dose	n	%
	75	40.
All randomised	54	29.3
Randomised and not withdrawn/ineligible	19	10.3
Not specified	17	9.2
Not applicable	3	1.6
Took a single dose and underwent AE/toxicity assessment	3	1.6
Active treatment groups	2	1.0
Completed treatment and assessed for primary outcome	2	1.0
Other	2	1.0
Patients who treatment was at least attempted on	1	0.5
Intention-to-treat population	1	0.5
Randomised and assessed for primary outcome	1	0.5
Randomised and attended at least on follow-up visit	1	0.5
Randomised and remained in follow-up	1	0.5
Randomised and underwent AE/toxicity assessment	1	0.5
Randomised, eligible and received at least a single dose	1	0.5

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Reporting checklist for systematic review and meta-analysis.

Based on the PRISMA guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the PRISMA reporting guidelines, and cite them as:

Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement

		Reporting Item	Page Number
	#1	Identify the report as a systematic review,	1
		meta-analysis, or both.	
Structured	#2	Provide a structured summary including, as	2
summary		applicable: background; objectives; data	
		sources; study eligibility criteria, participants,	
		and interventions; study appraisal and	
		synthesis methods; results; limitations;	
		conclusions and implications of key findings;	
		systematic review registration number	
Rationale	#3	Describe the rationale for the review in the	5-6
		context of what is already known.	
Objectives	#4	Provide an explicit statement of questions	6
		being addressed with reference to	
		participants, interventions, comparisons,	
		outcomes, and study design (PICOS).	
Protocol and	#5 Fo	Indicate if a review protocol exists, if and or peer review only - http://bmjopen.bmj.com/site/about/guid	n/a - review protocol was not delines.xhtml

1 2 3 4	registration		where it can be accessed (e.g., Web address) and, if available, provide registration information including the registration number.	published
5 6 7 8 9 10 11 12	rEEligibility criteria	#6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rational	6-7 Protecte
13 14 15 16 17 18 19	Information sources	#7	Describe all information sources in the search (e.g., databases with dates of coverage, contact with study authors to identify additional studies) and date last searched.	d by copyright, incl
20 21 22 23 24 25 26	Search	#8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	n/a - we manually searched the electronic contents table of the journals for reports of original RCTs
27 28 29 30 31 32 33	Study selection	#9	State the process for selecting studies (i.e., for screening, for determining eligibility, for inclusion in the systematic review, and, if applicable, for inclusion in the meta-analysis).	ted to text and data
34 35 36 37 38 39 40 41	Data collection process	#10	Describe the method of data extraction from reports (e.g., piloted forms, independently by two reviewers) and any processes for obtaining and confirming data from investigators.	mining, Al training, and
42 43 44 45 46 47 48	Data items	#11	List and define all variables for which data were sought (e.g., PICOS, funding sources), and any assumptions and simplifications made.	d similar technologi
49 50 51 52 53 54 55 56 57 58 59 60	Risk of bias in individual studies	#12 Fo	Describe methods used for assessing risk of bias in individual studies (including specification of whether this was done at the study or outcome level, or both), and how this information is to be used in any data synthesis.	n/a – the review was to identify current practice, we did not look at and synthesize the actual results of individual studies and as such this assessment was not relevant

1 2 3	Summary measures	#13	State the principal summary measures (e.g., risk ratio, difference in means).	8 C C Pen.
4 5 7 8 9 10	Planned methods of analyis	#14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I2) for each meta-analysis.	8 Pr
11 12 13 14 15 16 17	Risk of bias across studies	#15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	n/a – please see item #12cted by copyrig
18 19 20 21 22 23 24	Additional analyses	#16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta- regression), if done, indicating which were pre-specified.	n/a – no such analysis was performed for use berformed for use
25 26 27 28 29 30 31	Study selection	#17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	n/a – manual search resulted related in only eligible articles beinged to downloaded to the Super- to the Super-to the Super-to the Super-to the Super-to the Super-to the
32 33 34 35 36 37 38	Study characteristics	#18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citation.	ieur (ABES) . d data mining, Al tra 8
39 40 41 42 43	Risk of bias within studies	#19	Present data on risk of bias of each study and, if available, any outcome-level assessment (see Item 12).	n/a – please see item #12ing, and sim
44 45 46 47 48 49 50 51	Results of individual studies	#20	For all outcomes considered (benefits and harms), present, for each study: (a) simple summary data for each intervention group and (b) effect estimates and confidence intervals, ideally with a forest plot.	n/a – only simple descriptive statistics are presented to describe current practice s.
52 53 54 55 56 57 58 59 60	Synthesis of results	#21 Fo	Present the main results of the review. If meta-analyses are done, include for each, confidence intervals and measures of consistency.	elines.xhtml

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Risk of bias across studies	#22	Present results of any assessment of risk of bias across studies (see Item 15).	n/a – please see item #12
Additional analysis	#23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta- regression [see Item 16]).	n/a – please see item #16
Summary of Evidence	#24	Summarize the main findings, including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., health care providers, users, and policy makers	13-18 trotected by copyrig
Limitations	#25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias).	nt, including for use
Conclusions	#26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	35 18-19 18 ted to te
Funding	#27	Describe sources of funding or other support (e.g., supply of data) for the systematic review; role of funders for the systematic review.	tt and data 4d data mining
The PRISMA cl CC-BY. This ch made by the EC	hecklist hecklist v QUATOF	is distributed under the terms of the Creative Convas completed on 29. May 2018 using <u>http://www. R Network</u> in collaboration with <u>Penelope.ai</u>	A tranng and similar technologies.
	Fo	r peer review only - http://bmjopen.bmj.com/site/about/guidel	lines.xhtml

BMJ Open

Analysis and reporting of adverse events in randomised controlled trials: a review

Journal:	BMJ Open
Manuscript ID	bmjopen-2018-024537.R1
Article Type:	Research
Date Submitted by the Author:	17-Oct-2018
Complete List of Authors:	Phillips, Rachel; Imperial College London, Faculty of Medicine, School of Public Health Hazell, Lorna; Drug Safety Research Unit, Clinical Research; University of Portsmouth, Associate Dept. of Pharmacy and Biomedical Sciences Sauzet, Odile; Universität Bielefeld, Cornelius, Victoria; Imperial College London Faculty of Medicine, School of Public Health
Primary Subject Heading :	Research methods
Secondary Subject Heading:	Medical publishing and peer review
Keywords:	Randomised controlled trials, Harm data, Adverse drug reactions, Systematic review, Investigational drug, Adverse events < THERAPEUTICS



Analysis and reporting of adverse events in randomised controlled trials: a review

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Word Count: 4204

Objective

To ascertain current approaches to the collection, reporting and analysis of adverse events (AEs) in

randomised controlled trials (RCTs) with a primary efficacy outcome.

Design

A review of clinical trials of drug interventions from four high impact medical journals.

Data sources

Electronic contents table of the BMJ, the Journal of the American Medical Association, the Lancet, and the New England Journal of Medicine were searched for reports of original RCTs published between September 2015 and September 2016.

Methods

A pre-piloted checklist was used and single data extraction was performed by three reviewers with independent check of a randomly sampled subset to verify quality. We extracted data on collection methods, assessment of severity and causality, reporting criteria, analysis methods and presentation of AE data.

Results

We identified 184 eligible reports (BMJ n=3; JAMA n=38, Lancet n=62; and NEJM n=81). Sixty-two percent reported some form of spontaneous AE collection but only 29% included details of specific prompts used to ascertain AE data. Numbers that withdrew from the trial were well reported (80%), however only 35% of these reported whether withdrawals were due to AEs. Results presented and analysis performed was predominantly on 'patients with at least 1 event' with 84% of studies ignoring repeated events. Despite a lack of power to undertake formal hypothesis testing, 47% performed such tests for binary outcomes.

Conclusions

This review highlighted that the collection, reporting and analysis of AE data in clinical trials is inconsistent and RCTs as a source of safety data are underutilised. Areas to improve include reducing information loss when analysing at patient level and inappropriate practice of underpowered multiple hypothesis testing. Implementation of standard reporting practices could enable a more accurate synthesis of safety data and development of guidance for statistical methodology to assess causality of AEs could facilitate better statistical practice. BMJ Open: first published as 10.1136/bmjopen-2018-024537 on 1 March 2019. Downloaded from http://bmjopen.bmj.com/ on June 11, 2025 at Agence Bibliographique de Enseignement Superieur (ABES)

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Keywords

Randomised controlled trials; adverse events; harm data; adverse drug reactions; review; investigational drug.

Article Summary

Strengths and Limitations of this study

- 1. This is the first review to examine and quantify AE analysis practice in RCTs published in high impact journals.
- 2. This review identifies weakness that need to be addressed as well as good practice that could be

adopted.

3. Articles included in this review were published in four of the top ranked general medical revi. Its are likely to u.

journals therefore results are likely to be biased towards better practice.

INTRODUCTION

The methods to analyse and report outcomes to measure benefit from randomised controlled trials (RCTs) are well developed but this progress has not been matched for adverse event (AE) outcomes. An adverse event is defined as 'any untoward medical occurrence that may present during treatment with a pharmaceutical product but which does not necessarily have a causal relationship with this treatment'.¹ An adverse drug reaction (ADR) is defined as 'a response to a drug which is noxious and unintended ...' where a causal relationship is 'at least a reasonable possibility'.^{1, 2} RCTs provide an opportunity to compare rates of AEs between arms allowing causality to be evaluated. However current analysis and reporting practices are inadequate.

There are many challenges associated with analysing and reporting AEs in clinical trials. RCTs are typically designed to determine the efficacy of an intervention but are often underpowered to detect important differences in AEs between arms which may suggest an ADR. Often large numbers of AEs are reported during a study, sometimes exceeding the number of patients in the clinical trial. Performing hypothesis tests on these AEs would lead to issues of multiplicity, however any adjustment for multiplicity would make a 'finding untenable'.^{3, 4} The use of hypothesis testing may result in the medicinal product being deemed unsafe and a trial being halted too early due to a chance imbalance, or conversely deemed safe and not stopped early enough resulting in more patients than necessary suffering an ADR.^{3, 5, 6} Unlike efficacy outcomes which are well defined and restricted in number at the planning stage of a RCT, we collect numerous, undefined AEs in RCTs. Furthermore, AE collection

requires additional information to be obtained on factors such as severity, timing and duration, number of occurrences and outcome, which for our efficacy outcomes would have all been predefined.

Previous studies have examined the methods for AE collection and presentation only, and highlighted the inadequacies in AE reporting in journal articles.⁷⁻¹⁶ In 2004 the Consolidated Standards of Reporting Trials (CONSORT) Group produced an extension to their guidelines for reporting trial results to cover the reporting of harms, however implementation of these guidelines has been shown to be poor.^{10, 14-17} Recently a joint pharmaceutical/journal collaboration published practical guidance and examples on what should be reported in journal articles and how it should be displayed to ensure transparency and aid clinical interpretation. They promote the use of clinical judgement in reporting rather than mandatory guidance.¹⁸ Whilst this work has been undertaken there remains uncertainty about practice for reporting and presenting AE data, and in addition the analysis practice for AEs remains a neglected area for review.

The aim of this review was to evaluate current practice for collection, reporting and analysis of AEs in RCTs where the primary outcome was efficacy. The aim being to identify and promote any areas of good practice, whilst highlighting any areas for improvement.

METHODS

Search strategy

The top four general medical journals as ranked by impact factors that publish clinical trials of drug interventions were selected: The BMJ (Impact Factor 20.79), the Journal of the American Medical Association (JAMA, IF 44.41), the Lancet (IF 47.83), and the New England Journal of Medicine (NEJM, IF 72.41). Impact factors quoted are from 2016 to reflect the time period from which the articles were drawn. One reviewer manually searched the electronic contents table of the journals for reports of original RCTs published between September 2015 and September 2016, inclusive. Any queries regarding eligibility were reviewed and discussed with a second reviewer.

Selection criteria

The inclusion criteria were phase II-IV RCTs of drug interventions where the primary outcome was efficacy of the intervention. We did not restrict according to number of treatment arms and included both parallel and cluster RCTs. We excluded cross-over RCTs, RCTs with adaptive randomisation, observational studies, case reports, editorials and letters. We also excluded RCTs where the intervention was not a drug product (i.e. not classified as a clinical trial of an investigational medicinal product (CTIMP)). As the study aimed to assess how authors report and analyse AEs in studies where the primary outcome was efficacy, trials that were specifically designed to investigate safety as a primary outcome were not included. BMJ Open: first published as 10.1136/bmjopen-2018-024537 on 1 March 2019. Downloaded from http://bmjopen.bmj.com/ on June 11, 2025 at Agence Bibliographique de Enseignement Superieur (ABES)

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Data extraction

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Potentially eligible articles were identified based on titles and abstracts and the full text of these studies were retrieved. Supplementary material was also reviewed if readers were referred here from the main article for further results. Supplementary Table A1 lists all data items captured with guidance given to the reviewers for extraction. We focused on the following areas: how AE data was collected (mode of collection, timing) and defined (coding, attribution); how AEs were assessed in terms of severity of the event or relatedness to the medical intervention; if there was any planned AE analysis (final and interim monitoring plans and analysis populations); how events were selected for inclusion in the journal article; how summary event information was presented in the journal article and how AEs were analysed.¹¹

The items to be extracted were based on the work by Cornelius et al. and the CONSORT Harms extension with new items added to capture more specific information on analysis practices.^{11, 17} A data extraction sheet was piloted and then single data extraction was performed by three reviewers (RP, VC and LH) with 10% independent check of a randomly sampled subset to verify quality. Queries were also informally discussed between reviewers on an ongoing basis. Where specific items were flagged for poor agreement these were re-extracted. Any queries during data extraction were shared and disagreements between reviewers were resolved through discussion.

Data analysis

The proportion of trials reporting each item, 3-4 and 8-34 in supplementary Table A1 were calculated and summary statistics (median and ranges) were calculated for items 5-7. All analyses were performed

in Stata version 15.¹⁹ A risk of bias assessment was not undertaken as this study aimed to describe best practice and not evaluate outcomes.

Patient and public involvement

This review forms part of a wider research project that was developed with input from a range of patient representatives. There were no study participants directly involved in this review but the original proposal and patient and public involvement (PPI) strategy were reviewed by service user representatives (with experience as clinical trial participants and PPI advisors) who provided advice specifically with regard to communication and dissemination to patient and public groups.

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RESULTS

Data extraction

A total of 585 items were extracted twice across all three reviewers to check the quality of the data extraction. A total of 95 discrepancies were identified. This gave agreement of 84%. During this independent check several items were flagged for potential poor agreement. These items were 100% independently extracted by one author and verified. The items were: study duration; the AE collection method; timing of collection; how binary harm outcomes were summarised; whether continuous outcomes were dichotomised; if continuous outcomes were left as continuous how they were analysed.

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Study characteristics

The search identified 184 eligible trial reports (BMJ n=3; JAMA n=38, Lancet n=62; and NEJM n=81) in which a total of 496911 participants were randomised with a median of 556 participants per trial (range 30, 205513; interquartile range (IQR) 281, 1704). The median trial follow-up was 52 weeks (range 48 hours to 10 years; IQR 24, 104 weeks) and 93% were multi-centre trials. Fifty-percent of studies had an active comparator and over 50% of trials received some element of industry funding (Table 1).

Characteristic		N=184	
	Median	(IQR)	min, max
Sample size	556	(281, 1704)	30, 205513
Centres ^a	35	(12, 100)	1, 1368
Trial duration (weeks	s) ⁵ 52	(24, 104)	0.3, 521
	n	0/	•
lournal		/0	
BMI	3	1.6	
JAMA	81	44.0	
Lancet	38	20.7	
NEJM	62	33.7	
Funded by			
Public	70	38.3	
Industry	80	43.7	
Both	33	18.0	
Centre			
Single-cent	re 12	7.0	
Multi-cent	re 161	93.0	
Control			
Placebo	95	51.6	
Active	80	43.5	
Both	8	4.4	
Neither	1	0.5	

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Abbreviations: *IQR = Inter-quartile range; min = minimum; and max = maximum* ^a11 reports did not specify the number of centres ^b2 reports did not specify trial duration ^cOne trial compared interventional drug to behavioural change intervention

Collection and assessment methods

Sixty-two percent (n=114) of reports made reference to some form of passive (e.g. spontaneously reported by patients) AE monitoring or collection methods. Of these only 46.5% (53/114) or 29% of total reports included specific details (prompts e.g. questions about specific events or AEs in general, questionnaires, or diaries) regarding these collection methods (Table 2, examples 1-2).^{20, 21} The timing of collection was well documented (91%, 48 out of 53 reports) in the reports that included specific details about the prompts used to collect AEs. Although specific details on clinical examinations (e.g. vital signs and blood pressure) and laboratory tests were not widely reported (only 57% of reports (95 out of 166 reports with clinical examinations and/or laboratory results presented) included details on the timing of such assessments) it was often clear from the results presented that participants had undergone these assessments (83% and 79% of studies reported clinical and laboratory results respectively) (Table 3).

Table 2: Examples of reporting practice in reviewed articles

Example	Study	Example practice	Example
no.			
1	Litonjua et al. ²⁰	Description of AE collection method	"Study staff met with pregnant women monthly to administer a brief health questionnaire, assess medication use, and monitor for complications (via the questionnaire and medical record review) After delivery, children were monitored by telephone every 3 months and in-person annually for 3 years, during which time infants' health, respiratory symptoms, and medications were assessed"

2	Miller et al. ²¹	Description of AE collection method	"Safety evaluations included physical examinations, assessment of vital signs, clinical laboratory tests, and reporting of adverse events at each study visit"
3	Libman et al. ²²	Description of planned AE analysis	"The proportions of participants experiencing any adverse event, any related adverse event, any gastrointestinal event, any event other than a gastrointestinal event, at least 1 severe hypoglycaemic event, and at least 1 diabetic ketoacidosis event in each treatment group were compared using the Fisher exact test. The number of adverse events, new adverse events, serious adverse events, and non-serious adverse events were compared between groups using a Wilcoxon rank sumtest."
4	Gross et al. ²³	Description of planned AE analysis	"Safety analyses and secondary efficacy analyses used binomial regression, analysis of covariance, or the marginal Cox proportional hazards model as appropriate"

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Section	Component	Data item	N=	-184
Collection			n	Ģ
	How was AE/harm information collect	ed?		
		Passive collection	114	6
		Prompted collection (n=114)	53	4
		No method of collection reported	70	z
	Did they undertake proactive	No method of concetion reported	70	5
	screening?			
	bereening.	Clinical examinations	153	8
		Laboratory tests	1/6	7
			140	,
	Timing of prompted collection s	pecified (n=53)	48	9
	Timing of active collection speci	fied (n=166)	95	5
	Which, if any, dictionary was used to c	code AE data?		
		CTCAE	18	g
		MedDRA	43	2
		CTCAE and MedDRA	1	(
		DAIDS	2	1
		ICD-10	1	(
		Researcher defined	2	1
		Other	3	1
		No dictionary reported	114	6
Assessment	L			
	Who assigned attribution to study dru	g?		
		Blinded assessor	9	2
		Unblinded assessor	7	3
		Both	1	(
		Not specified	164	8
		Not applicable ^a	3	1
Analysis		ha wath all a start		
	was any analysis for AEs specified in the	ne methods section?	F 7	n
	Was a nonulation for AE analysis area	ites	57	3
	was a population for AE analysis speci		ຊາ	л
	Was there a planned interim analysis y	with stonning criteria?	02	4
	was there a plained interim analysis i		128	7
		Ves for efficacy	130 7/	1
		Ves for efficacy & futility	∠4 11	ـــــــــــــــــــــــــــــــــــــ
		Ves for efficacy & safety	5 TT	1
		Ves for efficacy futility & safety	נ ר	1
		Ves but no other details given	2	2
Abbreviations	· AE - Adverse event: CTCAE - Common Tormin	pology Criteria for Adverse Events: MadDP/	0 h = Mad	
Dictionary for	Regulatory Activities: DAIDS = The Division of A	AIDS: and ICD-10 = International Classificat	ion of D	iser
10 th revision.				

NOTE: Denominator specified in item column if it differs from total sample ^a3 reports made no reference to AE data throughout the article

Prespecified analysis

Thirty-one percent of reports provided information on the planned analysis for AEs in the statistical analysis section of the paper and 45% pre-specified a safety population (Table 2, examples 3-4 and Table 3).^{22, 23} A quarter of trials reported planned interim analysis with stopping criteria (Table 3), five (2.7%) of which included specific criteria on stopping for a harmful event (Supplement Table A2 ²⁴⁻²⁸).

Selection of AEs and reporting practices

Two reports only made generic statements regarding AE data: *"there were no significant adverse events related to the procedure"* and *"no excess in mortality or major adverse events were found..."*. Three reports made no mention of AEs throughout the manuscript.²⁹⁻³³

Twenty-four (13%) trials only provided a summary of the number of AEs or serious AEs rather than listing the actual AEs that occurred. For example "*Six serious adverse events occurred in the acetaminophen group and 12 in the ibuprofen group.*"³⁴ Of these 24 trials, 10 did provide specific details of the types of events in an appendix. This means 8% of trials either did not report AEs or only included a summary (Table 4).

Component	Data item	N=1	184
		n	%
What was reported in the	manuscript?		
	Actual AE terms	73	39.7
	Summaries of AF type (e.g. AF, SAF)	24	13.0
	Both	80	13.0
	Neither	80 7	
M/hat was reported in the		7	5.0
what was reported in the a	appendix?	70	11 ·
	Actual AE terms	76	41.:
	Summaries of AE type (e.g. AE, SAE)	7	3.8
	Both	22	12.0
	Neither	3	1.6
	Not applicable ^a	76	41.3
Which population was the	AE analysis performed on?		
	- All randomised	54	29.
	Those that took at least a single dose	75	40
	Other	75	40.
	Other	35	19.0
	Not specified	1/	9.2
	Not applicable ^b	3	1.6
Were drop-outs/withdraw	als reported?		
	No	33	17.
	Yes by treatment arm	144	78.3
	Yes overall	2	1.1
	Not applicable ^c	5	2.7
Were withdr	rawals due to AEs reported? (n=146)		
	No	89	61
	Vec	51	34
	Not applicabled	51	. 1
		D	4.1
were specifi	c AEs causing withdrawais reported? (n=51)		-
	No	39	76.
	Yes	12	23.
How were binary AE outco	mes summarised by arm?		
	Not summarised ^e	6	3.3
	Number of people with an event	154	83.
	Number of events	11	6.0
	Both	12	6.5
	Unclear	1	0.5
Were frequencies of AFs re	eported by arm?	-	210
	No.	5	7 ר כ
	Ves for some	10	2.7
		13	/.1
	res for all	100	87.0
	Not applicable ^e	6	3.3
	15		
	15		
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2				
3	Were percentages of AEs reported	by arm?		
4		No	18	9.8
5		Yes for some	25	13.6
7		Vec for all	125	72 /
, 8		tes for all	135	75.4
9		Not applicable ^c	6	3.3
10	Were between arm differences and	1 95% CI of AEs reported?		
11		No	141	76.6
12		Yes for some	18	9.8
13		Yes for all	19	10.3
14		Not applicable ^e	6	3.3
15	Were statistical significance tests h	etween arms on AFs reported?	-	
10 17		No	0.2	EO 0
18			92	30.0
19		Yes for some	31	16.9
20		Yes for all	55	29.9
21		Not applicable ^e	6	3.3
22	Were continuous AEs outcomes die	hotomised for summaries?		
23		No	10	5.4
24		Yes for some	28	15.2
25		Ves for all	108	58.7
20 27		Not applicable	20	20.7
27	If continuous outcomes were left a	s continuous what between arm analy	JO Jose was parformed	20.7 20.7
29		s continuous what between ann analy	yses was performed	f (11-50)
30	Differences in measu	ires of central tendency estimated wit	in 95% Cl	
31		No	23	60.5
32		Yes for some	1	2.6
33		Yes for all	14	36.8
34	Between arm hypoth	nesis tests performed		
35		No	12	31.6
30 37		Ves for some	2	53
38		Vec for all	2	5.5 62 2
39		restor all	24	03.2
40	Were any 'signal detection' approa	ches used?		
41		No	184	100.0
42		Yes	0	0.0
43	Were there any graphical presenta	tions of AE outcomes?		
44		No	162	88.0
45		Yes	22	12.0
40 47	Were summaries of severity rating	of AFs reported?		
48		No	103	56.0
49		Vector come	105	20.0
50		Yes for some	41	22.3
51		Yes for all	35	19.0
52		Not applicable ^f	5	2.7
53	Were number of serious AEs report	ted?		
54		No	44	23.9
55		Yes overall	2	1.1
00 57				
58		16		
50		10		

	Yes by treatment arm	132	71.7
	Not applicable ^g	6	3.3
For serious AEs wa	s relatedness given? (n=134)		
	No	77	57.5
	Ves for some	18	13 /
	Vos for all	20	10.4 20.4
		50	20.4
	Yes overall	1	0.8
Were there any AEs where inform	mation on duration of events was repor	ted?	
	No	175	95.1
	Yes	9	4.9
Were there any AEs where infor	mation on the time of occurrence of eve	ents was reported?	
	No	132	71.7
	Yes	52	28.3
If any significance tests were pe	rformed on AEs was multiplicity of even	nts accounted for?	
	< No	81	44.0
	Yes	3	1.6
	Not applicable	100	54.4
Did the report reference the CON	SORT extension to harms		
blu the report reference the cor	No	10/	100.0
	No	104	100.0
Abbas istisas AC Advance French C	AE Cariana Advance Events Cl., Canfidance		0.0
^d 6 reports specify the number of wit ^e This includes 3 reports with no AE of AE data and 1 report that only report ^f This includes 3 reports with no AE d	hdrawals and reasons but none of the reaso lata (as per footnote ^b), 2 reports that provid ted continuous outcomes ata and 2 reports that provide generic states	ns are related to AEs le generic statements ments regarding AE da	regarding ita (as per
footnote ^e) ^g 6 papers specifically state that no so	erious adverse events occurred		
Eighty-nine percent of trials report	ed a subset of all the AEs they collected	. How AEs are 'selec	ted' for
inclusion in the article was not con	sistent or clear, and in 3% of studies it w	vas impossible to dis	cern how
the authors had selected the AEs t	hey presented for inclusion. Twenty-six	percent of reports s	elected
events based on a frequency thres	hold e.g. events experienced by greater	than x% in any grou	p; 9% of
reports used a measure of severity	to select events e.g. AEs of grade 3 or h	igher; 23% of report	s included
events based on seriousness; and a	3% included AEs based on relatedness to	o treatment (percent	ages are
	17		

not independent as the majority of reports used several different criteria for selection). Supplementary Tables A3 and A4 provide full details of selection criteria used.

We found that 41% of trials analysed AEs in participants that received at least one dose, 29% of trials used all randomised participants and 9% did not specify the analysis population (Table 4). Further details on analysis populations used are given in supplementary Table A5.

Nearly 80% of trials reported the number of participants who withdrew from the trial; of these 35% (51 of 146 reports) reported whether the withdrawals were due to AEs and of these 24% (12 of 51 reports) reported the actual events that caused withdrawals. Results presented and analysis performed was predominantly on 'patients with at least 1 event' with 84% of reports providing no information on the number of events occurring. An example of how to incorporate information on number of events is presented in ³⁵. Forty-one percent of trials reported information on the severity of AEs. Five percent of trials include a report of at least one event with duration, but presenting such data is limited in the main report. The trials that did present this information did so in a variety of ways. For example incorporating the information into the AE table with summary statistics such as the mean duration of certain events or presenting it for a subgroup of events in the footnotes of AE tables e.g. *"One event of non-serious squamous cell carcinoma (day 210, resolved on day 215; adalimumab treatment was not interrupted)."*³⁶⁻³⁸ Twenty-eight percent of reports included information on the timing of AEs (Table 4).

Serious adverse events were typically well documented (73%) and six reports (3%) explicitly stated that no serious events had occurred. However for forty-four reports (24%) it was not possible to discern if no

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serious events had occurred or whether they were simply omitted from the report. Forty-two percent (57 of 134 reports) of reports included details on whether the events had been classified as related to the intervention (Table 4).

Analysis of AE outcomes

Binary

The majority of trials summarised binary outcomes using frequencies (94%) and percentages (87%). Despite a lack of power to undertake formal hypothesis testing, 47% reported p-values for binary outcomes. For example *"There were no between-group differences in the rate of patients with at least 1 adverse event* (16.7% [14 patients] in the clopidogrel group vs 21.8% [19 patients] in the placebo group; *difference,* -5.2% [95% Cl, -17% to 6.6%]; P = .44)." However with a total safety population of 171 such a test would have only had 13% power to detect such a difference and was therefore substantially underpowered. The conclusion that *"No significant increase in adverse events was observed"* makes no reference to the 95% confidence interval presented which indicates that the findings were in fact compatible with a 17% decrease in experiencing at least on AE as well as a near 7% increase.³⁹ BMJ Open: first published as 10.1136/bmjopen-2018-024537 on 1 March 2019. Downloaded from http://bmjopen.bmj.com/ on June 11, 2025 at Agence Bibliographique de Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies.

Continuous

There was a pervasive practise (59%) of categorising continuous clinical and laboratory outcomes. Of the trials that did not dichotomise continuous AE data nearly 70% performed some form of statistical significance testing (Table 4). Whilst continuous outcomes do not suffer to the same degree regarding

lack of power, multiple testing is still a problem, however no multiplicity corrections for continuous outcomes were performed.

Of the trials that performed statistical significance testing on AE data, only three made an adjustment for multiplicity of tests (all three on dichotomised outcomes).^{36, 40, 41} Two of which used a Bonferroni correction and adjusted for the number of pairwise comparisons between each of the treatment groups for each individual event rather than the total number of significance tests performed. As such both analyses would have still been effected by issues of multiple testing.

Twelve percent of reports used graphs to illustrate AE data (Table 4). The CONSORT extension highlighted the value of graphs for summarising such data, especially for conveying information on time-to-event outcomes.⁴² An example of such a plot is included in the supplement of reference ⁴³ (eFigure 2).

We assessed any reference to the CONSORT Harm extension and found that none of the included studies mentioned it. Of the four journals included in the review, the Lancet was the only journal that made specific reference to the harm extension in their guidelines to authors.

DISCUSSION

The safety profile of a medicinal product is established through evidence collected from several sources including clinical trials, observational studies and spontaneous reports.⁴⁴ The advantage of clinical trial

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data is that these provide a controlled comparison of the rate of AEs allowing causality to be evaluated but have the disadvantage that the sample size is often not large enough to detect rare ADRs.

To ensure that a useful and comprehensive picture of the safety profile is provided to all relevant parties clear reporting of AEs from clinical trials is required. Current research has shown the quality of reporting is substandard.⁷⁻¹⁶ The aim of this study was to review current practice across four leading medical journals for AE collection, analysis and reporting practices, highlighting any areas for improvement and examples of good practice.

Collection and assessment methods

The CONSORT extension to harm was developed with the aim to improve reporting of safety data in RCTs.⁴² None of the included studies referenced the CONSTORT HARM extension and of the items in our review that are covered in CONSORT many were not well reported.¹⁷ This suggests that the CONSORT extension is not being routinely adopted by authors to aid their reporting. Most journals now request that authors include a completed CONSORT checklist when they submit their article but we are not aware of any journal that request the CONSORT harm extension to also be submitted. Of the four journals in this review the Lancet is the only journal that makes specific reference to the harm extension in their guidelines to authors. The CONSORT statement contains a single item related to safety, item 19: 'all important harms or unintended effects in each group' should be reported.⁴² This may explain why some items listed on the CONSORT extension for harm were reported by so few trials. The adoption of CONSORT harms by journals may support better reporting.

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We found that the method of AE collection was poorly reported. This has important implications for the type and frequency of AEs reported with "passive collection resulting in fewer recorded AEs".^{45, 46} Where the method was given the timing of collection was typically also reported and we would recommend continuation of this practice. The frequency of AE collection has further important implications on the number of events reported. More frequent assessment and longer follow-up will result in more AEs reported.¹⁷ It is important to consider these factors when making conclusions about the safety profile.

The method of attribution between drug and AE was another area where reporting practice was inadequate. However the joint pharmaceutical/journal collaboration indicate that such attribution has 'limited value' given the 'inherent subjectivity in such attribution'.¹⁸

Prespecified analysis

We found that formal assessments of AEs regarding stopping for emerging ADRs utilising statistical rules was rare. Subjective assessments of overwhelming amounts of data could easily lead to potential signals of harm being missed. There could be benefits to incorporating more objective methods alongside clinical review to monitor AE information, both for interim analysis by data monitoring committees (DMCs) and final trial analysis to help better identify drug harm relationships. Graphical displays have gone some way towards aiding interpretation.⁴⁷⁻⁵¹

Selection of AEs and reporting practices

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Due to space constraints in journal reports AE information is often included in the appendix. Whilst we encourage use of appendices and supplementary material for including additional detail on AEs, we caution authors against depositing all AE data into such documents without attempting to present a summary of the AE profile in the main article. It is important that the main report strikes a balance between efficacy and harm therefore allowing a risk-benefit assessment to be made solely from the article.

The failure to report any information on AEs restricts interpretation and prevents a risk-benefit assessment. We identified two reports that made generic summaries of the overall safety profile and it was clear in both that there had been harmful effects however the authors did not include any further information. Three reports contained no information leaving readers uninformed as to any additional information these studies may provide on the safety profile. Ambiguous reporting prevents building an accurate picture of the safety profile. As such profiles are developed on accumulating evidence, it is important that each study report to the same standard and information is not wasted. BMJ Open: first published as 10.1136/bmjopen-2018-024537 on 1 March 2019. Downloaded from http://bmjopen.bmj.com/ on June 11, 2025 at Agence Bibliographique de Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies.

We found that the selection criteria used by authors to decide what AEs to include in the report were arbitrary and inconsistent. This will have important implications when synthesising data across studies to construct safety profiles. Authors would benefit from guidance to facilitate consistency but currently research in this area is lacking. Lineberry et al. recommended clinically relevant events that should always be reported (deaths, SAEs and events leading to discontinuation of intervention) and criteria that should be considered when deciding what other AEs to report e.g. interest based on the disease(s) under investigation, comorbidities of the study population, intervention mechanism, trial duration.¹⁸

Standard outcomes for a drug class would be one potential solution to avoid issues of inconsistency suggested by Cornelius et al.¹¹

CONSORT recommend that AE analyses should be performed on the intention-to-treat (ITT) population to maintain the random assignment.¹⁷ However it is clear from our review that this population label is not always appropriately and consistently applied. There is a tendency for studies to make modifications to the ITT population. Using the ITT or modified-ITT population is likely to underestimate the risk by inflating the denominator with participants who may have never received the study drug.⁵² Such estimates are appropriate for health economic evaluations where estimates of the cost-effectiveness will inform policy level decisions regarding how to treat the population. However a more appropriate population for AE analysis to inform prescriber and patient decisions may be those that receive at least one dose. It is important that authors are clear about what they are estimating and how this affects their conclusions.

Proxy outcomes can be used as a measure of the impact of AEs on patients. Examples include the number of withdrawal due to any reason, withdrawals due to AEs, the number of events an individual experiences, the severity of the AE and the duration. A high proportion of trials reported withdrawal for any reason and this is likely to be as a result of the CONSORT recommendations.⁴² The other outcomes were not frequently reported and increasing this could facilitate interpretation.¹⁷ This information would permit better evaluation of the impact of AEs and the tolerability of the intervention to inform patients' and clinicians' treatment decisions. Reporting numbers that experience at least one event only and not providing information on repeated events masks valuable information that may be important to the patient and the cost-effectiveness evaluation. For example, chronic, repeated headaches over an

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extended duration will have an important impact for patients compared to a single headache or headaches over a short duration but it is not possible to distinguish between these two scenarios when reported as 'at least one event'.¹⁸ Severity of events was also an important aspect that was often not differentiated. For example there would be different impact on patients' quality-of-life with mild compared to severe nausea and which could lead to changes in dosing regimens. Displaying such information for all AEs in tables would soon become overwhelming and make interpretation difficult. Graphical approaches have been suggested as a solution to aid review. Examples of such a plots can be found in ⁵³. Online appendices and supplementary material provide more opportunity to include this important information.

For serious adverse events information on the time of likely onset can be useful information to inform patient monitoring plans. For example the documented risk of suicide and suicidal ideation within the first few weeks of starting anti-depressant allows patients and prescribers to remain alert and monitor closely for this period. Nearly a third of reports included such information and we would encourage authors to adopt this practice. BMJ Open: first published as 10.1136/bmjopen-2018-024537 on 1 March 2019. Downloaded from http://bmjopen.bmj.com/ on June 11, 2025 at Agence Bibliographique de Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies.

Analysis of AE outcomes

The majority of trials in this review included a balanced report of AEs alongside benefit. However many included generic statements regarding the safety profile such as 'the intervention was well tolerated' or 'the intervention exhibited a good safety profile' and these were frequently based on post-hoc statistical tests. Guidelines caution against such tests.¹⁸ The results of which are difficult to interpret as a lack of

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significance does not indicate that the intervention is safe and conversely multiple testing without adjustment will increase the number of significant differences due to chance.^{54, 55}

Graphs are an efficient method to convey and interpret large amounts of data and can make it easier to flag potential safety signals.^{50, 51, 53} Twenty-two studies included in the review used graphs to present AE data and an example of one such report is given in the supplementary eTable of ⁵⁶.

Limitations of trials

Trials are a valuable source for high quality adverse event data but compared to observational studies have smaller sample size, follow-up periods and generalisability which restrict the ability to detect rare ADRs, ADRs with long latency and drug interactions in complex populations. The typical duration of a trial means there is often insufficient follow-up to fully characterise the safety profile as it provides limited information on long-term exposure. Stringent inclusion criteria restrict the population the intervention is assessed in and so limited information on drug-interactions is obtained.⁵

Limitations of this study

Articles included in this review were published in four of the top ranked medical journals therefore results are likely to be biased towards better findings than we would expect if we included all RCTs and are only for year 2015-2016. We also acknowledge that only completing 10% independent check of

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extracted data would not have removed subjectivity from the data extraction but are happy that ongoing discussion between authors to clarify any queries would have kept this to a minimum. However this review characterises what those leading the field are doing and provides some examples of good practice that could be adopted.

Conclusions and recommendations for future work

RCTs are a valuable source of information establishing the safety profile of medicinal products. Our review has demonstrated that data is not currently being fully utilised. Analysis of AE data is frequently inappropriate and reports often provide insufficient and inconsistent information to allow a comprehensive summary of the safety profile to be established. RCTs that have been published over a recent period in examples of high impact general medicine journals are deficient.

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This research has identified two areas that would benefit from future research. i) Improving the consistency of reporting important AE outcomes across trials to facilitate comparison and synthesis. This is in line with work from the COMET Initiative group (<u>http://www.comet-initiative.org/</u>). The development of CORE safety outcomes by drug class could be considered.⁷ ii) Evaluation of methods to analyse AEs in RCTs.

COMPETING INTERESTS

None declared.

FUNDING

This research was supported by the NIHR grant number DRF-2017-10-131.

DATA SHARING STATEMENT

No additional data are available.

AUTHOR STATEMENT

RP conceived the idea for this review, conducted the search, carried out data extraction and analysis, and wrote the manuscript. VC conceived the idea for the review, performed data extraction and critical revision of the manuscript. LH performed data extraction and critical revision of the manuscript. OS performed critical revision of the manuscript. BMJ Open: first published as 10.1136/bmjopen-2018-024537 on 1 March 2019. Downloaded from http://bmjopen.bmj.com/ on June 11, 2025 at Agence Bibliographique de l Enseignement Superieur (ABES) .

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Supple	mentary mater	rial		-024537 , includii
Table A1: Data	items extracte	d from pu	blications	
			Items collected	Instructions
		1	Study number	sen
Study details		2	Journal	relagn
		3	Funding source: public, private, both or unspecified.	Studie Studie Studie Stated.
Study		4	Control: placebo, active or both	Selection Selected for trials with multiple arms where there is at least and group receiving no active treatment and one group receiver an active treatment
characteristics		5	Number of centres	ta Am
		6	Number randomised	
		7	Study duration (length of trial follow-up)	
Methods	Details of how AE outcomes were defined (coding, attribution)	8	Describe the collection method: passive surveillance, patient prompted, clinical examinations (e.g. vital signs or urine samples), and laboratory tests. (Select all that apply)	<i>Passize</i> : Eauthors state that AEs were collected throughout the study with no further information we will assume that collection was passive. <i>Promoted</i> : Prompted methods include, but are not limited to questions about both specific events and AEs in general question numbers, or diaries.
Withous	and were	9	Stated the timing of collection.	mi on
	collected (mode of	10	Mention dictionary for coding of events: Researcher defined, MedDRA, CTCAE, WHO-ART, COSTART, ICD-10, other or not applicable	June ar tec
	collection, timing)	11	Describe who undertook the assessment of attribution to study drug: blinded assessor, unblinded assessor or not specified.	11, 20 hnolo
Planned	Details of any	12	Describe analysis for AE outcomes in the statistical methods.	Reference nust be made to harmful events e.g. AEs or a specific harm event, this cannot be simply how binary events will be analysed.
analysis	analysing AE	13	Define a 'safety' population for analysis.	
-	outcomes	14	Specify a planned interim analysis with stopping criteria: based on efficacy, based on safety, based on both efficacy and safety, yes but no other details given, no planned interim analysis or unclear	Criteria for stopping must be set out, it is not enough to say the DMC eviewed the data.
			1 For peer review only - http://bmjopen.bmj.com/site/about/guideline	nique de es.xhtml –

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3 4 5 6		Details of what was reported and where	15	What was reported in the main paper: summaries of type of AEs (e.g. AE, SAE, AR, ADR), actual AE terms, both, neither or not applicable?	Not applied state that summaries	ble is relevant when for example authors explicitly there are no events or there is only one event so are inappropriate.
7 8 9 10					Not applied state angle and summare angle	ble is relevant when for example authors explicitly there are no events or there is only one event so are inappropriate.
11 12 13			16	What was reported in the appendix: summaries of type of AEs (e.g. AE, SAE, AR, ADR), actual AE terms, both, neither or not applicable?	AE data Su	the main article makes reference to it.
14 15			17	Who was the AE analysis performed on: all randomised, participants who took at least a single dose, other or not specified?	t and d	
16 17 18 19			18	How were number of drop-outs/withdrawals reported: By treatment arm, overall, not reported or not applicable?	Not and A	cable is relevant when there are no drop- rawals. tot include discontinuation of treatment.
20 21 22	Results		19	Were drop-outs/withdrawals due to AEs reported: Yes, no or not applicable?	Not applic	able if drop-outs/withdrawals are not reported or if it that there are no drop-outs/withdrawals.
23 24 25			20	Were specific AEs causing withdrawals reported: Yes, no or not applicable?	Not applie reported of outs/ditho	able if drop-outs/withdrawals due to AEs are not if it is reported that there are no drop- awals due to AEs.
26 27 28				0	Free text to most Heqt	sponse where possibilities can include for example: ent, above a severity threshold, SAEs.
29			21	What was the selection criteria for the AEs reported?	Include de	ails of what's in the main journal article and what is addix separately.
30 31 32		Details of how AEs were			Only Gelec event not	'number of events' if presented for each individual est overall number of events.
33 34 35		summarised and presented	22	What summary information was given: Number of people, number of events, both, unclear, not summarised or not applicable?	Not applic AEs.	able is only relevant when report that there are no
36 37 38		outcomes	23	What analysis was performed: frequencies, percentages, differences and 95% confidence intervals, significance tests, other? (Select all that apply)		
39 40 41					ograpniqu	
42 43				2	s xhtml	

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1				n-2018-C pyright, i
3 4 5 6	Details of how AEs were summarised	24	Were continuous outcomes dichotomised: Yes for all, yes for some, no or not applicable?	This cructures measures that will have been captured as continuous and then dichotomised for example blood levels, blood pressure etc.
7 8 9	and presented - continuous outcomes	25	If continuous outcomes were analysed as continuous what analysis was performed: differences in measures of central tendency, significance tests, other? (Select all that apply)	March 20 uses reig
10	Details of	26	Were signal detection methods used?	atec
12	how AEs	27	Were any graphical summaries of AEs presented?	to
13 14	summarised and presented	28	Were severity ratings given: Yes for all, yes for some, no or not applicable?	text a
15 16 17		29	Were numbers of serious events presented: Yes by treatment arm, yes overall, no or not applicable?	If define reported as part of the efficacy outcome it is not enough to constitute reporting serious events.
18 19 20		30	Were serious events coded as treatment related: Yes for all, yes for some, no or not applicable?	ES) . hining, A
21		31	Provided information on the duration of events?	This refer to the length of the actual AE i.e. how long did it last.
23		32	Provided information on the timing of events?	This reference to the time of onset of the AE.
24		33	Accounted for multiplicity of statistical tests?	
25		34	Referenced CONSORT extension for harms?	si m
27 28 29 30 31 32 33 34				on June 11, 2025 at Age nilar technologies.
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Table A2: Stopping criteria for safety

Study	Main article text	Appendix text	
Myles et al. ²⁴	"O'Brien–Fleming stopping boundaries were used to assess efficacy, and <u>a less stringent boundary was</u> used to assess harm."		
Billings et al. ²⁵	"The data and safety monitoring board (DSMB) reviewed patient recruitment practices, safety reporting, and data quality after 30 patients completed the study; performed an interim analysis after 277 patients had completed the study to assess <u>safety of the intervention</u> ; and performed a second interim analysis after 546 patients had completed the study to assess the safety, efficacy, and futility of the intervention. The DSMB made recommendations based on qualitative assessments of the safety, efficacy, and futility of the intervention"	 "Suspend enrolment in any study arm due to safety concerns based on study intervention. Safety concerns include: Increase in in-hospital all-cause mortality in subjects randomized to A or B such that the DSMB deems the increase is excessive compared to A or B. Increased treatment toxicity in either treatment group deemed excessive. Toxicity is defined as moderate or severe myalgias. Increased severity of adverse events deemed "Probably Related" or "Possibly Related" to study intervention in either treatment group. Itemized adverse event reports separated by treatment will be provided. Increased AKI incidence in either treatment group deemed excessive. 	Protected by copyright, including for
Beardsley et al. ²⁶	"An independent data and safety monitoring committee oversaw trial safety and analyzed unblinded data after every 50 deaths, according to its charter"	"The Haybittle-Peto boundary, requiring p<0.001 at interim analysis to consider stopping for efficacy, will be used as guidance. <u>A level of significance of 1% will</u> <u>be used as a quide for stopping the trial early because</u> <u>of a detected harm of dexamethasone</u> . In addition, the DMEC will receive conditional power curves to assess whether it remains realistic that the trial will demonstrate superiority of dexamethasone conditional on the data accrued up to the point of the interim analysis. Importantly, the DMEC recommendations will not be based purely on statistical tables but will also use clinical judgment."	r uses related to text and data mining
Kor et al. ²⁷	"In addition to statistical criteria for significance, the study included a priori "go-no-go" definitions for recommending continuation to phase 3 study Briefly, continuation to phase 3 would occur with a positive primary outcome finding along with an acceptable safety profile. An acceptable safety profile was defined as a serious adverse event profile for aspirin that was not statistically worse than placebo (95% CI for the relative risk of any serious adverse event covers the null value of relative risk = 1.0). The "no-go decision" was defined as early termination by the data and safety monitoring board for safety or unfavorable risk/benefit ratio. An indeterminate case in which there was a non–statistically significant effect but this effect was in a clinically meaningful direction was also defined."	Initiate Phase III Study: Demonstrated efficacy signal in addition to adequate safety profile Criteria: Early termination for benefit at interim analysis or p<0.08885 at final analysis (alpha=0.10 for study). <u>Serious adverse event profile of ASA not statistically</u> <u>worse than placebo (95% confidence interval for the</u> <u>relative risk of any SAE covers the null value of</u> <u>RR=1.0).</u> Further Development Potentially Required: Weak efficacy signal Criteria: Primary endpoint did not achieve a priori level of significance but there were at least a general consistency of secondary endpoints indicating propensity for efficacy with a larger sample size and/or more specific primary endpoint. Abandon Treatment Platform: Harm (in efficacy or safety endpoints) Criteria: Study terminated early per recommendation <u>by DSMB for safety and/or</u> <u>risk/benefit ratio concerns</u> (i.e., stop for futility, harm, unacceptable risk profile, etc.)	, AI training, and similar technologies.

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Nichol et al. ²⁸	We used a group sequential statistical approach to do two equally spaced pre-planned interim analyses (at 33% and 67% of total recruitment) to assess accumulated safety data (differential proportions of deep venous thrombosis and total mortality). This approach was chosen to provide for early stopping for probable harm or strong evidence of benefit. We applied the Haybittle-Peto criterion ($ Zk \ge 3$) for early stopping at these analyses.

Selection criteria	n	%
All AEs presented	20	10.87
AEs in greater than x% in any group	10	5.43
AEs in greater than x% in treatment group	4	2.17
AEs in greater than x% in all patients	1	0.54
Most common (no criteria specified)	9	4.89
Predefined AEs	26	14.13
SAEs	15	8.15
AEs leading to study drug discontinuation/interruption	3	1.63
Treatment related AEs	5	2.72
Grade 3>= events	9	4.89
AEs in greater than x% in any group & predefined/special interest AEs	4	2.17
AEs in greater than x% in any group & frequency between groups differed by more than y% &		
predefined/special interest AEs	1	0.54
AEs in greater than x% in all patients & predefined/special interest AEs	3	1.63
AEs in greater than x% in treatment group & AEs of special interest	2	1.09
AEs in greater than x% in any group & all SAEs	2	1.09
AEs in greater than x% in all patients & all SAEs	1	0.54
AEs in greater than x% in any group & SAEs related to treatment	1	0.54
Most common (no criteria specified) & predefined/special interest AEs	3	1.63
Most common (no criteria specified) & all SAEs	4	2.17
Most common (no criteria specified) & all SAEs & AEs leading to study drug discontinuation/interruption	1	0.54
Most common (no criteria specified) & treatment related SAEs	1	0.54
AEs where frequency between groups differed by more than y% & all SAEs	1	0.54
AEs of special interest	6	3.26
Grade >=3 AEs in greater than x% of patients	1	0.54
Grade >=3 AEs in greater than x% in intervention & y% in control	1	0.54
Most common (no criteria specified) grade 3>= AEs	1	0.54
Most common SAEs (no criteria specified)	1	0.54
SAEs & AE of special interest	1	0.54
Treatment related AEs in greater than x% of patients	1	0.54
Treatment related AEs in greater than x% in any group	1	0.54
AEs in greater than x% in treatment group & SAEs	1	0.54
AEs in greater than x% in treatment group & SAEs & predefined AEs	2	1.09
AEs in greater than x% in any group & significantly different & SAEs	1	0.54
AEs in greater than x% in any group & treatment related AEs/SAEs	2	1.09
AEs in greater than x% in treatment group & treatment related AEs & SAEs	1	0.54
AEs in greater than x% in treatment group & treatment related AEs in greater than y% in all patients	1	0.54
AEs in greater than x% in any group & Grade 3>= events	1	0.54
AEs in greater than x% in all patients & Grade 3>= events	-	0.54
AEs in greater than x% in all patients & Grade 2>= treatment related AEs	-	0.54
AEs in greater than x% in any group & Grade 3>= events in greater than y% in any group	1	0.54
AEs in greater than x% in any group & SAEs in treatment group	- 1	0.54
AEs in greater than x% in any group & AEs of special interest & most common (no criteria specified) AEs leading to treatment discontinuation/interruption & predefined AEs	1	0.54
AEs in greater than x% in any group, AEs of special interest in greater than v% in treatment group &	Т	0.54
treatment related deaths	1	0.54

3	AEs in greater than v% in treatment group & SAEs in greater than v% in any group	4	0.54
4	Als and SAEs occurring more often in treatment group than control	1	0.54
5	Als and SALS occurring more often in treatment group than control	1	0.54
6	AES in greater than X% in treatment group & occurred more often in treatment group than control &		
7	predefined/special interest AES	1	0.54
8	AEs in greater than x% in any group & frequency between groups differed by more than y%, SAEs in		
9	greater than z% in any group & all grade >=3 AEs	1	0.54
10	AEs in greater than x% patients & more than y% difference between treatment groups & AEs leading to		
11	treatment discontinuation/interruption & most common SAEs (no criteria specified) & death	1	0.54
12	Predefined AFs, AFs leading to hospitalisation/death/study drug discontinuation/interruption & SUSARS	- -	1 00
14	Some form of overall summary	2	1.09
15		6	3.26
16	Not specified now selected	6	3.26
17	Not summarised in main paper	11	5.98
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Table A4: Selection criteria used to select AEs presented in the appendix

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All AEs	18	9
SAEs	18	9
All AEs & SAEs	4	2
AEs in greater than x% in any group	7	3
AEs in greater than x% in treatment group	2	1
AEs in greater than x% in all patients	1	0
AEs in greater than x% in any group & all SAEs	2	1
AEs in greater than x% in treatment group & all SAEs	1	0
AEs in greater than x% in all patients & all SAEs	3	1
AEs in greater than x% in treatment group & all SAEs	1	0
AEs in greater than x% in treatment group & greater than in control group & all SAEs	1	0
SAEs in greater than x% in any group	1	0
AEs in greater than x% in any group & SAEs in greater than y% in any group	1	0
AEs in greater than x% in any group & AEs of special interest	2	1
Freatment related AEs	5	2
Freatment related AEs in greater than x% in any group	2	1
Grade 3>= events	2	1
Predefined AEs	8	4
AEs of special interest	1	0
AEs leading to study drug discontinuation/interruption	2	1
AEs leading to study drug discontinuation & SAEs	1	0
Grade 3>= events leading to study drug discontinuation & grade 3>= laboratory results	1	0
Freatment related AEs & AEs leading to study drug discontinuation	1	0
AEs in greater than x% in all patients leading to treatment discontinuations, SAEs in greater than x% in any group, serious predefined/special interest AEs and clinically significant laboratory results	1	0
AEs in greater than x% in any group, treatment related AEs in greater than x% in any group, treatment		
related SAEs and select AEs	1	0
Clinical laboratory data	1	0
Predefined AEs, AEs leading to hospitalisation/death/study drug discontinuation/interruption & SUSARS	3	1
Deaths	2	1
some form of overall summary	5	2
Not specified how selected	2	1
Not summarised in the appendix	84	4.

Table A5	Population	used for	AE analysis
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Analysis population	n	%
Those that took at least a single dose	75	40.7
All randomised	54	29.3
Randomised and not withdrawn/ineligible	19	10.3
Not specified	17	9.24
Not applicable	3	1.63
Took a single dose and underwent AE/toxicity assessment	3	1.6
Active treatment groups	2	1.0
Completed treatment and assessed for primary outcome	2	1.0
Other	2	1.0
Patients who treatment was at least attempted on	1	0.5
Intention-to-treat population	1	0.5
Randomised and assessed for primary outcome	1	0.5
Randomised and attended at least on follow-up visit	1	0.5
Randomised and remained in follow-up	1	0.5
Randomised and underwent AE/toxicity assessment	1	0.5
Randomised, eligible and received at least a single dose	1	0.5

Reporting checklist for systematic review and meta-analysis.

Based on the PRISMA guidelines.

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Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the PRISMA reporting guidelines, and cite them as:

Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement

		Reporting Item	Page Number
	#1	Identify the report as a systematic review, meta-analysis, or both.	1
Structured	#2	Provide a structured summary including, as	2
summary		applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number	
Rationale	#3	Describe the rationale for the review in the context of what is already known.	5-6
Objectives	#4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	6

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1 2 3 4 5 6 7	Protocol and registration	#5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address) and, if available, provide registration information including the registration number.	n/a - review protocol was not published
9 10 11 12 13 14 15 16	rEEligibility criteria	#6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rational	6-7 6-7
17 18 19 20 21 22 23 24	Information sources	#7	Describe all information sources in the search (e.g., databases with dates of coverage, contact with study authors to identify additional studies) and date last searched.	6 6
25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59	Search	#8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	n/a - we manually searched the electronic contents table of the journals for reports of original RCTs
	Study selection	#9	State the process for selecting studies (i.e., for screening, for determining eligibility, for inclusion in the systematic review, and, if applicable, for inclusion in the meta-analysis).	7 7
	Data collection process	#10	Describe the method of data extraction from reports (e.g., piloted forms, independently by two reviewers) and any processes for obtaining and confirming data from investigators.	, and similar technolog
	Data items	#11	List and define all variables for which data were sought (e.g., PICOS, funding sources), and any assumptions and simplifications made.	7 ⁵
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1 2 3 4 5 6 7 8 9 10	Risk of bias in individual studies	#12	Describe methods used for assessing risk of bias in individual studies (including specification of whether this was done at the study or outcome level, or both), and how this information is to be used in any data synthesis.	n/a – the review was to identify current practice, we did not look at and synthesize the actual results of individual studies and as such this assessment was not relevant	MJ Open: first published as 1 Pr
11 12	-				0.11; otec
13 14 15	Summary measures	#13	State the principal summary measures (e.g., risk ratio, difference in means).	8	36/bmjop ted by c:
16 17 18 19 20 21	Planned methods of analyis	#14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I2) for each meta-analysis.	8	oen-2018-024537 on opyright, including
22 23 24 25 26 27 28	Risk of bias across studies	#15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	n/a – please see item #12	1 March 2019. Dow Enseignement for uses related to
29 30	Additional	#16	Describe methods of additional analyses	n/a – no such analysis was	Inloa Sup text
31 32 33 34 35	analyses		(e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	performed	aded from http: erieur (ABES) and data minin
36 37	Study selection	#17	Give numbers of studies screened,	n/a – manual search	q, A
38	-		assessed for eligibility, and included in the	resulted in only eligible	ope trai
39 40 41 42			review, with reasons for exclusions at each stage, ideally with a flow diagram.	articles being downloaded	1.bmj.con 1ing, and
42 43 44 45 46 47 48 49	Study characteristics	#18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citation.	9	n/ on June 11, 2025 a similar technologies
50 51 52 53 54	Risk of bias within studies	#19	Present data on risk of bias of each study and, if available, any outcome-level assessment (see Item 12).	n/a – please see item #12	at Agence Biblic 3.
55 56	Results of	#20	For all outcomes considered (benefits and	n/a – only simple descriptive	ograp
57	individual		harms), present, for each study: (a) simple	statistics are presented to	ohiq
58 59 60	studies	For	summary data for each intervention group peer review only - http://bmjopen.bmj.com/site/about/guid	describe current practice	ue de l

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		and (b) effect estimates and confidence intervals, ideally with a forest plot.	
Synthesis of results	#21	Present the main results of the review. If meta-analyses are done, include for each, confidence intervals and measures of consistency.	9-13
Risk of bias across studies	#22	Present results of any assessment of risk of bias across studies (see Item 15).	n/a – please see item #12
Additional analysis	#23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	n/a – please see item #16
Summary of Evidence	#24	Summarize the main findings, including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., health care providers, users, and policy makers	13-21
Limitations	#25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias).	26/27
Conclusions	#26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	27
Funding	#27	Describe sources of funding or other support (e.g., supply of data) for the systematic review; role of funders for the systematic review.	28
The PRISMA chec CC-BY. This chec made by the <u>EQU</u>	cklist is klist wi	a distributed under the terms of the Creative Con as completed on 29. May 2018 using <u>http://www</u> <u>Network</u> in collaboration with <u>Penelope.ai</u>	nmons Attribution License <u>agoodreports.org/</u> , a tool
	For	peer review only - http://bmjopen.bmj.com/site/about/guide	lines.xhtml

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Analysis and reporting of adverse events in randomised controlled trials: a review

Journal:	BMJ Open
Manuscript ID	bmjopen-2018-024537.R2
Article Type:	Research
Date Submitted by the Author:	21-Dec-2018
Complete List of Authors:	Phillips, Rachel; Imperial College London, Faculty of Medicine, School of Public Health Hazell, Lorna; Drug Safety Research Unit, Clinical Research; University of Portsmouth, Associate Dept. of Pharmacy and Biomedical Sciences Sauzet, Odile; Universität Bielefeld, Cornelius, Victoria; Imperial College London Faculty of Medicine, School of Public Health
Primary Subject Heading :	Research methods
Secondary Subject Heading:	Medical publishing and peer review
Keywords:	Randomised controlled trials, Harm data, Adverse drug reactions, Systematic review, Investigational drug, Adverse events < THERAPEUTICS
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Word Count: 4319

Abstract

Objective

To ascertain current approaches to the collection, reporting and analysis of adverse events (AEs) in randomised controlled trials (RCTs) with a primary efficacy outcome.

Design

A review of clinical trials of drug interventions from four high impact medical journals.

Data sources

Electronic contents table of the BMJ, the Journal of the American Medical Association, the Lancet, and the New England Journal of Medicine were searched for reports of original RCTs published between September 2015 and September 2016.

Methods

A pre-piloted checklist was used and single data extraction was performed by three reviewers with independent check of a randomly sampled subset to verify quality. We extracted data on collection methods, assessment of severity and causality, reporting criteria, analysis methods and presentation of AE data.

Results

We identified 184 eligible reports (BMJ n=3; JAMA n=38, Lancet n=62; and NEJM n=81). Sixty-two percent reported some form of spontaneous AE collection but only 29% included details of specific prompts used to ascertain AE data. Numbers that withdrew from the trial were well reported (80%),

however only 35% of these reported whether withdrawals were due to AEs. Results presented and analysis performed was predominantly on 'patients with at least 1 event' with 84% of studies ignoring repeated events. Despite a lack of power to undertake formal hypothesis testing, 47% performed such tests for binary outcomes.

Conclusions

This review highlighted that the collection, reporting and analysis of AE data in clinical trials is inconsistent and RCTs as a source of safety data are underutilised. Areas to improve include reducing information loss when analysing at patient level and inappropriate practice of underpowered multiple hypothesis testing. Implementation of standard reporting practices could enable a more accurate synthesis of safety data and development of guidance for statistical methodology to assess causality of AEs could facilitate better statistical practice.

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Keywords

Randomised controlled trials; adverse events; harm data; adverse drug reactions; review;

investigational drug.

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Article Summary

Strengths and Limitations of this study

- 1. This is the first review to examine and quantify AE analysis practice in RCTs published in high impact journals.
- 2. This review identifies weakness that need to be addressed as well as good practice that could be adopted.
- 3. Articles included in this review were published in four of the top ranked general medical journals therefore results are likely to be biased towards better practice and are only for year 2015-2016 and as such may not reflect the most current practice.

INTRODUCTION

The methods to analyse and report outcomes to measure benefit from randomised controlled trials (RCTs) are well developed but this progress has not been matched for adverse event (AE) outcomes. An adverse event is defined as 'any untoward medical occurrence that may present during treatment with a pharmaceutical product but which does not necessarily have a causal relationship with this treatment'.¹ An adverse drug reaction (ADR) is defined as 'a response to a drug which is noxious and unintended ...' where a causal relationship is 'at least a reasonable possibility'.^{1, 2} RCTs provide an opportunity to compare rates of AEs between arms allowing causality to be evaluated. However, current analysis and reporting practices are inadequate.

There are many challenges associated with analysing and reporting AEs in clinical trials. RCTs are typically designed to determine the efficacy of an intervention but are often underpowered to detect important differences in AEs between arms which may suggest an ADR. Often large numbers of AEs are reported during a study, sometimes exceeding the number of patients in the clinical trial. Performing hypothesis tests on these AEs would lead to issues of multiplicity, however any adjustment for multiplicity would make a 'finding untenable'.^{3, 4} The use of hypothesis testing may result in the medicinal product being deemed unsafe and a trial being halted too early due to a chance imbalance, or conversely deemed safe and not stopped early enough resulting in more patients than necessary suffering an ADR.^{3, 5, 6} Unlike efficacy outcomes which are well defined and restricted in number at the planning stage of a RCT, we collect numerous, undefined AEs in RCTs. Furthermore, AE collection requires additional information to be obtained on factors such as severity, timing and duration, number of occurrences and outcome, which for our efficacy outcomes would have all been predefined.

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Previous studies have examined the methods for AE collection and presentation only, and highlighted the inadequacies in AE reporting in journal articles.⁷⁻¹⁶ In 2004 the Consolidated Standards of Reporting Trials (CONSORT) Group produced an extension to their guidelines for reporting trial results to cover the reporting of harms, however implementation of these guidelines has been shown to be poor.^{10, 14-17} Recently a joint pharmaceutical/journal collaboration published practical guidance and examples on what should be reported in journal articles and how it should be

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displayed to ensure transparency and aid clinical interpretation. They promote the use of clinical judgement in reporting rather than mandatory guidance.¹⁸ Whilst this work has been undertaken there remains uncertainty about practice for reporting and presenting AE data, and in addition the analysis practice for AEs remains a neglected area for review.

The aim of this review was to evaluate current practice for collection, reporting and analysis of AEs in RCTs where the primary outcome was efficacy. The aim being to identify and promote any areas of good practice, whilst highlighting any areas for improvement.

METHODS

Search strategy

The top four general medical journals as ranked by impact factors that publish clinical trials of drug interventions were selected: The BMJ (Impact Factor 20.79), the Journal of the American Medical Association (JAMA, IF 44.41), the Lancet (IF 47.83), and the New England Journal of Medicine (NEJM, IF 72.41). Impact factors quoted are from 2016 to reflect the time period from which the articles were drawn. High impact journals were chosen as we would expect practice in these journals to be of high standard as they include statistical and methodological review. We limited the search to four

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journals after an initial scoping review revealed around 100 studies would be eligible for inclusion, which was a feasible number to review given the time and resources available and would provide a sufficient number to evaluate practice. One reviewer manually searched the electronic contents table of the journals for reports of original RCTs published between September 2015 and September 2016, inclusive. Any queries regarding eligibility were reviewed and discussed with a second reviewer.

Selection criteria

The inclusion criteria were phase II-IV RCTs of drug interventions where the primary outcome was efficacy of the intervention. We did not restrict according to number of treatment arms and included both parallel and cluster RCTs. We excluded cross-over RCTs, RCTs with adaptive randomisation, observational studies, case reports, editorials and letters. We also excluded RCTs where the intervention was not a drug product (i.e. not classified as a clinical trial of an investigational medicinal product (CTIMP)). As the study aimed to assess how authors report and analyse AEs in studies where the primary outcome was efficacy, trials that were specifically designed to investigate safety as a primary outcome were not included. Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies.

Data extraction

Potentially eligible articles were identified based on titles and abstracts and the full text of these studies were retrieved. Supplementary material was also reviewed if readers were referred here from the main article for further results. Supplementary Table A1 lists all data items captured with guidance given to the reviewers for extraction. The items to be extracted were based on the work by

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Cornelius et al. and the CONSORT harm extension with additional items added to capture more specific information on analysis practices.^{11, 17} Specifically we focused on the following areas: how AE data was collected (mode of collection, timing) and defined (coding, attribution); how AEs were assessed in terms of severity of the event or relatedness to the medical intervention; if there was any planned AE analysis (final and interim monitoring plans and analysis populations); how events were selected for inclusion in the journal article; how summary event information was presented in the journal article and how AEs were analysed.¹¹ A more detailed rationale for the choice of items extracted is provided in the supplementary material (Table A2).

A data extraction sheet was piloted and then single data extraction was performed by three reviewers (RP, VC and LH) with 10% independent check of a randomly sampled subset to verify quality. Queries were also informally discussed between reviewers on an ongoing basis. Where specific items were flagged for poor agreement these were re-extracted. Any queries during data extraction were shared and disagreements between reviewers were resolved through discussion.

Data analysis

The proportion of trials reporting each item, 3-4 and 8-34 in supplementary Table A1 were calculated and summary statistics (median and ranges) were calculated for items 5-7. All analyses were performed in Stata version 15.¹⁹ A risk of bias assessment was not undertaken as this study aimed to describe best practice and not evaluate outcomes.

Patient and public involvement

This review forms part of a wider research project that was developed with input from a range of patient representatives. There were no study participants directly involved in this review but the

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original proposal and patient and public involvement (PPI) strategy were reviewed by service user representatives (with experience as clinical trial participants and PPI advisors) who provided advice specifically with regard to communication and dissemination to patient and public groups.

RESULTS

Data extraction

A total of 585 items were extracted twice across all three reviewers to check the quality of the data extraction. A total of 95 discrepancies were identified. This gave agreement of 84%. During this independent check several items were flagged for potential poor agreement. These items were 100% independently extracted by one author and verified. The items were: study duration; the AE collection method; timing of collection; how binary harm outcomes were summarised; whether continuous outcomes were dichotomised; if continuous outcomes were left as continuous how they were analysed.

Study characteristics

The search identified 184 eligible trial reports (BMJ n=3; JAMA n=38, Lancet n=62; and NEJM n=81) in which a total of 496911 participants were randomised with a median of 556 participants per trial (range 30, 205513; interquartile range (IQR) 281, 1704). The median trial follow-up was 52 weeks (range 48 hours to 10 years; IQR 24, 104 weeks) and 93% were multi-centre trials. Fifty-percent of

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studies had an active comparator and over 50% of trials received some element of industry funding

(Table 1).

Table 1: Characteristics of included studies					
Characteristic	1	N=184			
	Median	(IQR)	min, max		
Sample size	556	(281, 1704)	30, 205513		
Centres ^a	35	(12, 100)	1, 1368		
Trial duration (weeks) ^b	52	(24, 104)	0.3, 521		
	n	%			
Journal					
BMJ	3	1.6			
JAMA	81	44.0			
Lancet	38	20.7			
NEJM	62	33.7			
Funded by					
Public	70	38.3			
Industry	80	43.7			
Both	33	18.0			
Centre					
Single-centre	12	7.0			
Multi-centre	161	93.0			
Control					
Placebo	95	51.6			
Active	80	43.5			
Both	8	4.4			
Neither	1	0.5			

Abbreviations: *IQR* = *Inter-quartile range; min* = *minimum; and max* = *maximum*

°11 reports did not specify the number of centres

^b2 reports did not specify trial duration

^cOne trial compared interventional drug to behavioural change intervention

Collection and assessment methods

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Sixty-two percent (n=114) of reports made reference to some form of passive (e.g. spontaneously reported by patients) AE monitoring or collection methods. Of these only 46.5% (53/114) or 29% of total reports included specific details (prompts e.g. questions about specific events or AEs in general, questionnaires, or diaries) regarding these collection methods (Supplementary Table A3, examples 1-2).^{20, 21} The timing of collection was well documented (91%, 48 out of 53 reports) in the reports that included specific details about the prompts used to collect AEs. Although specific details on clinical examinations (e.g. vital signs and blood pressure) and laboratory tests were not widely reported (only 57% of reports (95 out of 166 reports with clinical examinations and/or laboratory results presented) included details on the timing of such assessments) it was often clear from the reported clinical and laboratory results respectively) (Table 2).

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Section	Component Data item			N=184	
Collection			n	%	
	How was AE/harm information collected?				
	Passive co	llection	114	62	
	Prom	pted collection (n=114)	53	46	
	No metho	d of collection reported	70	38	
	Did they undertake proactive screening?				
	Clinical ex	aminations	153	83	
	Laborator	y tests	146	79	
	Timing of prompted collection specified (n=53)	48	9	
	Timing of active collection specified (n=166)	,	95	5	
	Which if any dictionary was used to code AE data?				
			18	c	
	MedDBA		13	2	
	CTCAE and			2	
			2	1	
	MedDRA 43 CTCAE and MedDRA 1 DAIDS 2 ICD-10 1 Researcher defined 2 Other 3 No dictionary reported 114 MedDRA 1 DAIDS 2 ICD-10 1 Researcher defined 2 Other 3 No dictionary reported 114 Mot assessor 9 Unblinded assessor 9 Unblinded assessor 7 Both 1 Not specified 164 Not applicable ^a 3	ر ر			
	Researche	r defined	2	1	
	Other		3	1	
	No diction	ary reported	114	6	
Assessment		,		-	
	Who assigned attribution to study drug?				
	Blinded as	sessor	9	Z	
	Unblinded	assessor	7	3	
	Both		1	C	
	Not specif	ied	164	8	
	Not applic	ableª	3	1	
Analysis	Ö				
	Was any analysis for AEs specified in the methods se	ection?			
	Yes		57	3	
	Was a population for AE analysis specified?				
	Yes		82	4	
	Was there a planned interim analysis with stopping	criteria?			
	No		138	7.	
	Yes for eff	icacy	24	1	
	Yes for eff	icacy & futility	11	6	
	Yes for eff	icacy & safety	3	1	
	Yes for eff	icacy, futility & safety	2	1	
	Yes but no	other details given	6	3	

10th revision.

NOTE: Denominator specified in item column if it differs from total sample

°3 reports made no reference to AE data throughout the article

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Prespecified analysis

Thirty-one percent of reports provided information on the planned analysis for AEs in the statistical analysis section of the paper and 45% pre-specified a safety population (Supplementary Table A3, examples 3-4 and Table 2).^{22, 23} A quarter of trials reported planned interim analysis with stopping criteria (Table 2), five (2.7%) of which included specific criteria on stopping for a harmful event (Supplement Table A4²⁴⁻²⁸).

Selection of AEs and reporting practices

Two reports only made generic statements regarding AE data: *"there were no significant adverse events related to the procedure"* and *"no excess in mortality or major adverse events were found..."*. Three reports made no mention of AEs throughout the manuscript.²⁹⁻³³

Twenty-four (13%) trials only provided a summary of the number of AEs or serious AEs rather than listing the actual AEs that occurred. For example *"Six serious adverse events occurred in the acetaminophen group and 12 in the ibuprofen group."*³⁴ Of these 24 trials, 10 did provide specific details of the types of events in an appendix. This means 8% of trials either did not report AEs or only included a summary (Table 3).

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Component	Data item	N=184	
		n	%
What was reported in the r	nanuscript?		
	Actual AE terms	73	39
	Summaries of AE type (e.g. AE, SAE)	24	13
	Both	80	43
	Neither	7	3.
What was reported in the a	ippendix?		
	Actual AE terms	76	41
	Summaries of AE type (e.g. AE, SAE)	7	3.
	Both	22	12
	Neither	3	1.
	Not applicable ^a	76	41
Which population was the	AE analysis performed on?		
	All randomised	54	29
	Those that took at least a single dose	75	40
	Other	35	19
	Not specified	17	9.
	Not applicable ^b	3	1.
Were drop-outs/withdrawa	als reported?		
	No	33	17
	Yes by treatment arm	144	78
	Yes overall	2	1
	Not applicable ^c	5	2
Were withdr	awals due to AEs reported? (n=146)		
	No	89	61
	Yes	51	34
	Not applicable ^d	6	4
Were specific	c AEs causing withdrawals reported? (n=51)		
	No	39	76
	Yes	12	23
How were binary AE outco	mes summarised by arm?		
•	Not summarised ^e	6	3
	Number of people with an event	154	83
	Number of events	11	6
	Both	12	6
	Unclear	1	0.
Were frequencies of AEs re	ported by arm?		
	No	5	2.
	Yes for some	13	7.
	Yes for all	160	87
	Not applicable ^e	6	3.
Were percentages of AEs re	eported by arm?		
	No	18	9.
	Yes for some	25	13
			-

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З Д		Yes for all	135	73.4
5		Not applicable ^e	6	3.3
6	Were between arm differences and	95% CI of AEs reported?		
7		No	141	76.6
8		Yes for some	18	9.8
9		Yes for all	19	10.3
10		Not applicable ^e		2 2
11	Wara statistical significance tasts h	atwoon arms on AEs reported?	0	5.5
13	were statistical significance tests b	No.	02	50.0
14			92	50.0
15		Yes for some	31	16.9
16		Yes for all	55	29.9
17		Not applicable ^e	6	3.3
18	Were continuous AEs outcomes dic	hotomised for summaries?		
19		No	10	5.4
20		Yes for some	28	15.2
22		Yes for all	108	58.7
23		Not applicable	38	20.7
24	If continuous outcomes were left as	s continuous what between arm analy	ses was performed	? (n=38)
25	Differences in measu	res of central tendency estimated with	h 95% Cl	. (11 50)
26	Differences in measu	No	22	C0 F
27		NO	23	60.5
20		Yes for some	1	2.6
30		Yes for all	14	36.8
31	Between arm hypoth	esis tests performed		
32		No	12	31.6
33		Yes for some	2	5.3
34		Yes for all	24	63.2
35 36	Were any 'signal detection' approa	ches used?		
37	, , , , , , , , , , , , , , , , , , , ,	No	184	100.0
38		Yes	0	0.0
39	Were there any graphical presentat	tions of AF outcomes?	C C	0.0
40	Were there any graphical presentat	No.	167	00 N
41		No	102	12.0
42		res	22	12.0
45 44	were summaries of severity rating	of AEs reported?		
45		No	103	56.0
46		Yes for some	41	22.3
47		Yes for all	35	19.0
48		Not applicable ^f	5	2.7
49	Were number of serious AEs report	ed?		
50		No	44	23.9
57		Yes overall	2	1.1
53		Yes by treatment arm	132	71.7
54		Not applicable ^g	6	22
55	Ear carious A Faura	alatadaass givan 2 (n=124)	0	5.5
56	FOR SERIOUS AES WAS R	elateulless givell: (II=134)		
57		INO	//	57.5
58 50		Yes for some	18	13.4
59 60		Yes for all	38	28.4
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	Yes overall	1	0.8
Were there any AEs where in	formation on duration of events was re	ported?	
	No	175	95.1
	Yes	9	4.9
Were there any AEs where in	formation on the time of occurrence of	events was reported?	
	No	132	71.7
	Yes	52	28.3
If any significance tests were	e performed on AEs was multiplicity of e	events accounted for?	
	No	81	44.0
	Yes	3	1.6
	Not applicable	100	54.4
Did the report reference the	CONSORT extension to harms		
	No	184	100.0
	Yes	0	0.0

Abbreviations: AE = Adverse Event; SAE = Serious Adverse Event; CI = Confidence Interval; and CONSORT = Consolidated Standards for Reporting Trials.

^a Make no reference to the appendix

^b 3 reports made no reference to AE data throughout the article

^c 5 reports indicate no withdrawals

^d 6 reports specify the number of withdrawals and reasons but none of the reasons are related to AEs

^e This includes 3 reports with no AE data (as per footnote ^b), 2 reports that provide generic statements regarding AE data and 1 report that only reported continuous outcomes

^f This includes 3 reports with no AE data and 2 reports that provide generic statements regarding AE data (as per footnote ^e)

^g 6 papers specifically state that no serious adverse events occurred

Eighty-nine percent of trials reported a subset of all the AEs they collected. How AEs are 'selected' for inclusion in the article was not consistent or clear, and in 3% of studies it was impossible to discern how the authors had selected the AEs they presented for inclusion. Twenty-six percent of reports selected events based on a frequency threshold e.g. events experienced by greater than x% in any group; 9% of reports used a measure of severity to select events e.g. AEs of grade 3 or higher; 23% of reports included events based on seriousness; and 8% included AEs based on relatedness to treatment (percentages are not independent as the majority of reports used several different criteria for selection). Supplementary Tables A5 and A6 provide full details of selection criteria used.

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We found that 41% of trials analysed AEs in participants that received at least one dose, 29% of trials used all randomised participants and 9% did not specify the analysis population (Table 3). Further details on analysis populations used are given in supplementary Table A7.

Nearly 80% of trials reported the number of participants who withdrew from the trial; of these 35% (51 of 146 reports) reported whether the withdrawals were due to AEs and of these 24% (12 of 51 reports) reported the actual events that caused withdrawals. Results presented and analysis performed was predominantly on 'patients with at least 1 event' with 84% of reports providing no information on the number of events occurring. An example of how to incorporate information on number of events is presented in reference ³⁵. Forty-one percent of trials reported information on the severity of AEs. Five percent of trials include a report of at least one event with duration, but presenting such data is limited in the main report. The trials that did present this information did so in a variety of ways. For example incorporating the information into the AE table with summary statistics such as the mean duration of certain events or presenting it for a subgroup of events in the footnotes of AE tables e.g. *"One event of non-serious squamous cell carcinoma (day 210, resolved on day 215; adalimumab treatment was not interrupted*)."³⁶⁻³⁸ Twenty-eight percent of reports included information on the timing of AEs (Table 3).

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Serious adverse events were typically well documented (73%) and six reports (3%) explicitly stated that no serious events had occurred. However, for forty-four reports (24%) it was not possible to discern if no serious events had occurred or whether they were simply omitted from the report. Forty-two percent (57 of 134 reports) of reports included details on whether the events had been classified as related to the intervention (Table 3).

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Analysis of AE outcomes

Binary

The majority of trials summarised binary outcomes using frequencies (94%) and percentages (87%). Despite a lack of power to undertake formal hypothesis testing, 47% reported p-values for binary outcomes. For example "There were no between-group differences in the rate of patients with at least 1 adverse event (16.7% [14 patients] in the clopidogrel group vs 21.8% [19 patients] in the placebo group; difference, -5.2% [95% Cl, -17% to 6.6%]; P = .44)." However, with a total safety population of 171 such a test would have only had 13% power to detect such a difference and was therefore substantially underpowered. The conclusion that "No significant increase in adverse events was observed" makes no reference to the 95% confidence interval presented which indicates that the findings were in fact compatible with a 17% decrease in experiencing at least on AE as well as a near 7% increase.39 ilen

Continuous

There was a pervasive practise (59%) of categorising continuous clinical and laboratory outcomes. Of the trials that did not dichotomise continuous AE data nearly 70% performed some form of statistical significance testing (Table 3). Whilst continuous outcomes do not suffer to the same degree regarding lack of power, multiple testing is still a problem, however no multiplicity corrections for continuous outcomes were performed.

Of the trials that performed statistical significance testing on AE data, only three made an adjustment for multiplicity of tests (all three on dichotomised outcomes).^{36, 40, 41} Two of which used a Bonferroni correction and adjusted for the number of pairwise comparisons between each of the

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treatment groups for each individual event rather than the total number of significance tests performed. As such both analyses would have still been effected by issues of multiple testing.

Twelve percent of reports used graphs to illustrate AE data (Table 3). The CONSORT extension highlighted the value of graphs for summarising such data, especially for conveying information on time-to-event outcomes.⁴² An example of such a plot is included in the supplement of reference ⁴³ (eFigure2).

We assessed any reference to the CONSORT harm extension and found that none of the included studies mentioned it. Of the four journals included in the review, the Lancet was the only journal that made specific reference to the harm extension in their guidelines to authors.

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DISCUSSION

The safety profile of a medicinal product is established through evidence collected from several sources including clinical trials, observational studies and spontaneous reports.⁴⁴ The advantage of clinical trial data is that these provide a controlled comparison of the rate of AEs allowing causality to be evaluated but have the disadvantage that the sample size is often not large enough to detect rare ADRs.

To ensure that a useful and comprehensive picture of the safety profile is provided to all relevant parties clear reporting of AEs from clinical trials is required. Current research has shown the quality of reporting is substandard.⁷⁻¹⁶ The aim of this study was to review current practice across four

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leading medical journals for AE collection, analysis and reporting practices, highlighting any areas for improvement and examples of good practice.

Collection and assessment methods

The CONSORT extension to harm was developed with the aim to improve reporting of safety data in RCTs.⁴² None of the included studies referenced the CONSTORT harm extension and of the items in our review that are covered in CONSORT many were not well reported.¹⁷ This suggests that the CONSORT extension is not being routinely adopted by authors to aid their reporting. Most journals now request that authors include a completed CONSORT checklist when they submit their article but we are not aware of any journal that request the CONSORT harm extension to also be submitted. Of the four journals in this review the Lancet is the only journal that makes specific reference to the harm extension in their guidelines to authors. The CONSORT statement contains a single item related to safety, item 19: 'all important harms or unintended effects in each group' should be reported.⁴² This may explain why some items listed on the CONSORT extension for harm were reported by so few trials. The mandatory submission of CONSORT harms by journals may support better reporting.

We found that the method of AE collection was poorly reported. This has important implications for the type and frequency of AEs reported with "passive collection resulting in fewer recorded AEs".^{45,} ⁴⁶ Where the method was given the timing of collection was typically also reported and we would recommend continuation of this practice. The frequency of AE collection has further important implications on the number of events reported. More frequent assessment and longer follow-up will result in more AEs reported.¹⁷ It is important to consider these factors when making conclusions about the safety profile.

The method of attribution between drug and AE was another area where reporting practice was inadequate. However, the joint pharmaceutical/journal collaboration indicate that such attribution has 'limited value' given the 'inherent subjectivity in such attribution'.¹⁸

Prespecified analysis

We found that formal assessments of AEs regarding stopping for emerging ADRs utilising statistical rules was rare. Subjective assessments of overwhelming amounts of data could easily lead to potential signals of harm being missed. There could be benefits to incorporating more objective statistical methods alongside clinical review to assist the evaluation of AE information to help better identify drug harm relationships. Graphical displays have gone some way towards aiding interpretation.⁴⁷⁻⁵¹

Selection of AEs and reporting practices

Due to space constraints in journal reports AE information is often included in the appendix. Whilst we encourage use of appendices and supplementary material for including additional detail on AEs, we caution authors against depositing all AE data into such documents without attempting to present a summary of the AE profile in the main article. It is important that the main report strikes a balance between efficacy and harm therefore allowing a risk-benefit assessment to be made solely from the article. Enseignement Superieur (ABES) Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies.

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The failure to report any information on AEs restricts interpretation and prevents a risk-benefit assessment. We identified two reports that made generic summaries of the overall safety profile and it was clear in both that there had been harmful effects. However, the authors did not include any further information. Three reports contained no information leaving readers uninformed as to any additional information these studies may provide on the safety profile. Ambiguous reporting prevents building an accurate picture of the safety profile. As such profiles are developed on accumulating evidence, it is important that each study report to the same standard and information is not wasted.

We found that the selection criteria used by authors to decide what AEs to include in the report were arbitrary and inconsistent. This will have important implications when synthesising data across studies to construct safety profiles. Authors would benefit from guidance to facilitate consistency but currently research in this area is lacking. Lineberry et al. recommended clinically relevant events that should always be reported (deaths, SAEs and events leading to discontinuation of intervention) and criteria that should be considered when deciding what other AEs to report e.g. interest based on the disease(s) under investigation, comorbidities of the study population, intervention mechanism, trial duration.¹⁸ Standard outcomes for a drug class would be one potential solution to avoid issues of inconsistency suggested by Cornelius et al.¹¹

CONSORT recommend that AE analyses should be performed on the intention-to-treat (ITT) population to maintain the random assignment.¹⁷ However it is clear from our review that this population label is not always appropriately and consistently applied. There is a tendency for studies to make modifications to the ITT population. Using the ITT or modified-ITT population is likely to underestimate the risk by inflating the denominator with participants who may have never received the study drug.⁵² Such estimates are appropriate for health economic evaluations where estimates

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of the cost-effectiveness will inform policy level decisions regarding how to treat the population. However, a more appropriate population for AE analysis to inform prescriber and patient decisions may be those that receive at least one dose. It is important that authors clearly define and specify a suitable safety analysis population and consider how this affects their conclusions.

Proxy outcomes can be used as a measure of the impact of AEs on patients. Examples include the number of withdrawals due to any reason, withdrawals due to AEs, the number of events an individual experiences, the severity of the AE and the duration. A high proportion of trials reported withdrawal for any reason and this is likely to be as a result of the CONSORT recommendations.⁴² The other outcomes were not frequently reported and increasing this could facilitate interpretation.¹⁷ This information would permit better evaluation of the impact of AEs and the tolerability of the intervention to inform patients' and clinicians' treatment decisions. Reporting numbers that experience at least one event only and not providing information on repeated events masks valuable information that may be important to the patient and the cost-effectiveness evaluation. For example, chronic, repeated headaches over an extended duration will have an important impact for patients compared to a single headache or headaches over a short duration but it is not possible to distinguish between these two scenarios when reported as 'at least one event'.¹⁸ Severity of events was also an important aspect that was often not differentiated. For example, there would be a different impact on patients' quality-of-life with mild compared to severe nausea, which could lead to changes in dosing regimens. Displaying such information for all AEs in tables would soon become overwhelming and make interpretation difficult. Graphical approaches have been suggested as a solution to aid review. Examples of such a plots can be found in reference ⁵³. Online appendices and supplementary material provide more opportunity to include this important information.

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For serious adverse events information on the time of likely onset can be useful information to inform patient monitoring plans. For example, the documented risk of suicide and suicidal ideation within the first few weeks of starting anti-depressant allows patients and prescribers to remain alert and monitor closely for this period. Nearly a third of reports included such information and we would encourage authors to adopt this practice.

Analysis of AE outcomes

The majority of trials in this review included a balanced report of AEs alongside benefit. However many included generic statements regarding the safety profile such as 'the intervention was well tolerated' or 'the intervention exhibited a good safety profile' and these were frequently based on post-hoc statistical tests. Guidelines caution against such tests.¹⁸ The results of which are difficult to interpret as a lack of significance does not indicate that the intervention is safe and conversely multiple testing without adjustment will increase the number of significant differences due to chance.^{54, 55}

Graphs are an efficient method to convey and interpret large amounts of data and can make it easier to flag potential safety signals.^{50, 51, 53} Twelve percent of studies included in the review used graphs to present AE data and an example of one such report is given in the supplementary eTable of reference ⁵⁶.

Recommendations for consideration for immediate adoption by the clinical trial community are summarised in Table 4.

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Table 4: Recommendations to improve adverse event analysis and reporting in clinical trial report
publications

	Recommendation		
Analysis	Incorporate objective statistical methods to assist the		
	evaluation of adverse event information.		
	Consider avoiding dichotomising continuous data.		
	When count outcomes are available (such as repeated events		
	within participants) use appropriate statistical methods.		
	Clearly define exposure and specify a suitable safety analysis		
	population.		
	Use graphical approaches to help summarise large amounts of		
	data.		
Reporting	Report adverse event data according to the CONSORT harm		
	checklist.		
	Increase the uptake of mandatory submission of CONSORT		
	harm by journals.		
	Include a relevant summary of the adverse event profile in the		
	main article. Resist depositing all adverse event data into		
	appendices without summarising.		

Limitations of trials

Trials are a valuable source for high quality adverse event data but compared to observational studies have smaller sample size, follow-up periods and generalisability, which restrict the ability to detect rare ADRs, ADRs with long latency and drug interactions in complex populations. The typical duration of a trial means there is often insufficient follow-up to fully characterise the safety profile as it provides limited information on long-term exposure. Stringent inclusion criteria restrict the population the intervention is assessed in and so limited information on drug-interactions is obtained.⁵

Limitations of this study

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Articles included in this review were published in four of the top ranked medical journals therefore results are likely to be biased towards better findings than we would expect if we included all RCTs. Articles are only for year 2015-2016 and as such may not reflect the most current practice. We also acknowledge that only completing 10% independent check of extracted data would not have removed subjectivity from the data extraction but are happy that ongoing discussion between authors to clarify any queries would have kept this to a minimum. Despite these limitations, this review characterises what those leading the field are doing and provides some examples of good practice that could be adopted.

Conclusions and recommendations for future work

RCTs are a valuable source of information establishing the safety profile of medicinal products. Our review has demonstrated that data is not currently being fully utilised. Analysis of AE data is frequently inappropriate and reports often provide insufficient and inconsistent information to allow a comprehensive summary of the safety profile to be established. RCTs that have been published over a recent period in examples of high impact general medicine journals are deficient.

This research has identified two areas that would benefit from future research. i) Improving the consistency of reporting important AE outcomes across trials to facilitate comparison and synthesis. This is in line with work from the COMET Initiative group (<u>http://www.comet-initiative.org/</u>). The development of CORE safety outcomes by drug class could be considered.⁷ ii) Evaluation of methods to analyse AEs in RCTs.

COMPETING INTERESTS

None declared.

FUNDING

This research was supported by the NIHR grant number DRF-2017-10-131.

DATA SHARING STATEMENT

No additional data are available.

AUTHOR STATEMENT

RP conceived the idea for this review, conducted the search, carried out data extraction and analysis, and wrote the manuscript. VC conceived the idea for the review, performed data extraction, critical revision of the manuscript and supervised the project. LH performed data extraction and critical revision of the manuscript. OS performed critical revision of the manuscript.

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Table A1: Data	items extracte	a from pu	Directions	Instruction	s S DS
		1	Study number	uses) t
Starday data ila		2	Journal	n 20 seig s rel	5 5 5
Study details		3	Funding source: public, private, both or unspecified.	Studies avil explicately of	be assumed to be funded by industry only if this is ated.
		4	Control: placebo, active or both	Selections	ebo if no active treatment is given, else active. Both elected for trials with multiple arms where there is group receiving no active treatment and one group n active treatment.
characteristics		5	Number of centres	(Allata	
		6	Number randomised	min	
		7	Study duration (length of trial follow-up)	ing,	
	Details of how AE outcomes were defined (coding,	8	Describe the collection method: passive surveillance, patient prompted, clinical examinations (e.g. vital signs or urine samples), and laboratory tests. (Select all that apply)	Passive: Is study with was passive Promoted questions questionna	authors state that AEs were collected throughout the no further information we will assume that collection e. Prompted methods include, but are not limited to about both specific events and AEs in generatives, or diaries.
li cuious	and were	9	Stated the timing of collection.	on imil	
	collected (mode of	10	Mention dictionary for coding of events: Researcher defined, MedDRA, CTCAE, WHO-ART, COSTART, ICD-10, other or not applicable	June 1 ar tech	
	timing)	11	Describe who undertook the assessment of attribution to study drug: blinded assessor, unblinded assessor or not specified	nok	<u>د</u>
Planned analysis	Details of any	12	Describe analysis for AE outcomes in the statistical methods.	Reference harm even analysed.	nust be made to harmful events e.g. AEs or a specifi t, this cannot be simply how binary events will b
	analysing AE	13	Define a 'safety' population for analysis.	е с	5
	outcomes	14	Specify a planned interim analysis with stopping criteria: based on efficacy, based on safety, based on both efficacy and safety, yes but no other details given, no planned interim analysis or unclear	Criteria for the DMC	stopping must be set out, it is not enough to say the eviewed the data.
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3 4 5 6		Details of what was reported and where	15	What was reported in the main paper: summaries of type of AEs (e.g. AE, SAE, AR, ADR), actual AE terms, both, neither or not applicable?	Not applicable is relevant when for example authors explicitly state there are no events or there is only one event so summaries are inappropriate.
/ 8 9 10 11 12 13			16	What was reported in the appendix: summaries of type of AEs (e.g. AE, SAE, AR, ADR), actual AE terms, both, neither or not applicable?	Not applied ble is relevant when for example authors explicitly state that there are no events or there is only one event so summaries are inappropriate. We will only search the appendix/supplementary material for AE dotation the main article makes reference to it.
14 15			17	Who was the AE analysis performed on: all randomised, participants who took at least a single dose, other or not specified?	t and d
16 17 18 19			18	How were number of drop-outs/withdrawals reported: By treatment arm, overall, not reported or not applicable?	Not book to be a constructed by the construction of the constructi
20 21 22	Results		19	Were drop-outs/withdrawals due to AEs reported: Yes, no or not applicable?	Not applicable if drop-outs/withdrawals are not reported or if it is reparted that there are no drop-outs/withdrawals.
23 24 25			20	Were specific AEs causing withdrawals reported: Yes, no or not applicable?	Not applicable if drop-outs/withdrawals due to AEs are not reported of if it is reported that there are no drop- outs/Bithdrawals due to AEs.
26 27 28 29			21	What was the selection criteria for the AEs reported?	Free text esponse where possibilities can include for example: most dependent, above a severity threshold, SAEs. Include defails of what's in the main journal article and what is in the appendix separately.
30 31 32 33 34		Details of how AEs were summarised		What summary information was given. Number of people, number of	Only celect 'number of events' if presented for each individual events of events. Not applicable is only relevant when report that there are no
35 36		- binary	22	events, both, unclear, not summarised or not applicable?	AES. G
37 38		outcomes	23	What analysis was performed: frequencies, percentages, differences and 95% confidence intervals, significance tests, other? (Select all that apply)	Bibli
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Details of how AEs were summarised	24	Were continuous outcomes dichotomised: Yes for all, yes for some, no or not applicable?	This Encloyed and then contiguous and then blood pressure etc.	sures that will have been captured as dichotomised for example blood levels,
and presented - continuous outcomes	25	If continuous outcomes were analysed as continuous what analysis was performed: differences in measures of central tendency, significance tests, other? (Select all that apply)	/arch 20 Enseig uses rel	
Details of	26	Were signal detection methods used?	19. [nem ated	
now AES were	27	Were any graphical summaries of AEs presented?	bown to t	
summarised	28	Were severity ratings given: Yes for all, yes for some, no or not applicable?	ווסמכ Supe ext a	
and presented	29	Were numbers of serious events presented: Yes by treatment arm, yes overall, no or not applicable?	If dealing reported enough to constitute	as part of the efficacy outcome it is not reporting serious events.
	30	Were serious events coded as treatment related: Yes for all, yes for some, no or not applicable?	http://bm ES) . hining, A	
	31	Provided information on the duration of events?	This reference to the leng	th of the actual AE i.e. how long did it last.
	32	Provided information on the timing of events?	This Beferento the time	e of onset of the AE.
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Table A2: Rationale for items extracted

Item	Rationale
How AE data was	Variation in the collection and definition of events could explain differences in
collected (mode of	the incidence of observed events. ^{13, 14} For example specifically asking
collection, timing) and	participants about an event of interest in one treatment group whilst relying on
defined (coding,	patient report in another is likely to lead to a disparity in incidence of events
attribution) during the	unlikely to be related to the medicinal product.
study.	
Assessment practices of	Attribution of causality by an unblinded assessor allows for subjectivity and
severity of the event or	bias (even if subconscious) to enter into their decision which can have
relatedness to the	important implications on the risk-benefit assessment.
medicinal product.	
Planned AE analysis (final	For example, the intention-to-treat population is likely to underestimate the
and interim monitoring	AE risk by inflating the denominator. Therefore, this needs to be considered
plans and analysis	when making conclusions about a drug's safety profile.
populations).	
How events were	Due to the space constraints in journal articles it is not always feasible to
selected for inclusion in	report all AEs experienced by participants. Therefore, articles often only
the journal article.	report a subset of AEs and how these are selected for inclusion has important
	implications for the safety evaluation. Arbitrary selection criteria can lead to
	inconsistencies in what is presented across trials for the same disease and/or
	drug. This prevents an accurate overview of the AEs experienced and
	invalidates any potential systematic review of events.
How and what summary	For example, the number of events and duration of events provides insight
event information was	into the impact of AEs, with repeated or longer events potentially having far
presented in the journal	wider clinical implications than a single, shorter event for both patients and
article.	prescribers.
How AEs were analysed.	There are many challenges to be considered when analysing AEs in clinical
	trials. For example, inappropriate statistical testing can lead to misleading
	conclusions e.g. failure to find a statistically significant result leading authors
	to conclude that the medicinal product is safe or chance imbalance could lead
	the authors to erroneously stopping a trial too early. ³⁻⁶

Table A3: Examples	of reporting	practice in	reviewed	articles
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Example	Study	Example practice	Example
no.		• •	•
1	Litonjua et al. ²⁰	Description of AE collection method	"Study staff met with pregnant women monthly to administer a brief health questionnaire, assess medication use, and monitor for complications (via the questionnaire and medical record review) After delivery, children were monitored by telephone every 3 months and in-person annually for 3 years, during which time infants' health, respiratory symptoms, and medications were assessed"
2	Miller et al. ²¹	Description of AE collection method	"Safety evaluations included physical examinations, assessment of vital signs, clinical laboratory tests, and reporting of adverse events at each study visit"
3	Libman et al. ²²	Description of planned AE analysis	"The proportions of participants experiencing any adverse event, any related adverse event, any gastrointestinal event, any event other than a gastrointestinal event, at least 1 severe hypoglycaemic event, and at least 1 diabetic ketoacidosis event in each treatment group were compared using the Fisher exact test. The number of adverse events, new adverse events, serious adverse events, and non-serious adverse events were compared between groups using a Wilcoxon rank sumtest."
4	Gross et al. ²³	Description of planned AE analysis	"Safety analyses and secondary efficacy analyses used binomial regression, analysis of covariance, or the marginal Cox proportional hazards model as appropriate"

Table A4:	Stopping	criteria	for	safety
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Study	Main article text	Appendix text
Myles et al. ²⁴	"O'Brien–Fleming stopping boundaries were used to assess efficacy, and <u>a less stringent boundary was</u> <u>used to assess harm</u> ."	
Billings et al. ²⁵	"The data and safety monitoring board (DSMB) reviewed patient recruitment practices, safety reporting, and data quality after 30 patients completed the study; performed an interim analysis after 277 patients had completed the study to assess <u>safety of the intervention</u> ; and performed a second interim analysis after 546 patients had completed the study to assess the safety, efficacy, and futility of the intervention. The DSMB made recommendations based on qualitative assessments of the safety, efficacy, and futility of the intervention"	 "Suspend enrolment in any study arm due to safety concerns based on study intervention. Safety concerns include: Increase in in-hospital all-cause mortality in subjects randomized to A or B such that the DSMB deems the increase is excessive compared to A or B. Increased treatment toxicity in either treatment group deemed excessive. Toxicity is defined as moderate or severe myalgias. Increased severity of adverse events deemed "Probably Related" or "Possibly Related" to study intervention in either treatment group. Itemized adverse event reports separated by treatment will be provided. Increased AKI incidence in either treatment group (secondary endpoints) deemed excessive."
Beardsley et al. ²⁶	"An independent data and safety monitoring committee oversaw trial safety and analyzed unblinded data after every 50 deaths, according to its charter"	"The Haybittle-Peto boundary, requiring p<0.001 at interim analysis to consider stopping for efficacy, will be used as guidance. <u>A level of significance of 1% will</u> <u>be used as a quide for stopping the trial early because</u> <u>of a detected harm of dexamethasone</u> . In addition, the DMEC will receive conditional power curves to assess whether it remains realistic that the trial will demonstrate superiority of dexamethasone conditional on the data accrued up to the point of the interim analysis. Importantly, the DMEC recommendations will not be based purely on statistical tables but will also use clinical judgment."
Kor et al. ²⁷	"In addition to statistical criteria for significance, the study included a priori "go-no-go" definitions for recommending continuation to phase 3 study Briefly, continuation to phase 3 would occur with a positive primary outcome finding along with an acceptable safety profile. An acceptable safety profile was defined as a serious adverse event profile for aspirin that was not statistically worse than placebo (95% CI for the relative risk of any serious adverse event covers the null value of relative risk = 1.0). The "no-go decision" was defined as early termination by the data and safety monitoring board for safety or unfavorable risk/benefit ratio. An indeterminate case in which there was a non-statistically significant effect but this effect was in a clinically meaningful direction was also defined."	Initiate Phase III Study: Demonstrated efficacy signal in addition to adequate safety profile Criteria: Early termination for benefit at interim analysis or p<0.08885 at final analysis (alpha=0.10 for study). <u>Serious adverse event profile of ASA not statistically</u> <u>worse than placebo (95% confidence interval for the</u> <u>relative risk of any SAE covers the null value of</u> <u>RR=1.0).</u> Further Development Potentially Required: Weak efficacy signal Criteria: Primary endpoint did not achieve a priori level of significance but there were at least a general consistency of secondary endpoints indicating propensity for efficacy with a larger sample size and/or more specific primary endpoint. Abandon Treatment Platform: Harm (in efficacy or safety endpoints) Criteria: Study terminated early per recommendation <u>by DSMB for safety and/or</u> <u>risk/benefit ratio concerns</u> (i.e., stop for futility, harm, unacceptable risk profile, etc.)

Nichol e al. ²⁸	et	We used a group sequential statistical approach to do two equally spaced pre-planned interim analyses (at 33% and 67% of total recruitment) to assess accumulated safety data (differential proportions of deep venous thrombosis and total mortality). This <u>approach was chosen to provide for early stopping for</u> <u>probable harm</u> or strong evidence of benefit. We applied the Haybittle-Peto criterion (17k1>3) for early	
		applied the Haybittle-Peto criterion $(Zk \ge 3)$ for early stopping at these analyses.	

to peet terier only

2 3	Table A5: Selection criteria used to select AFs presented in the main journal report			
4	Selection criteria	n	%	-
5	All AEs presented	20	10.87	-
7	AEs in greater than x% in any group	10	5.43	
8	AEs in greater than x% in treatment group	4	2.17	
9	AEs in greater than x% in all patients	1	0.54	
10	Most common (no criteria specified)	9	4.89	
11	Predefined AEs	26	14.13	
12	SAEs	15	8.15	
14	AEs leading to study drug discontinuation/interruption	3	1.63	т
15	Treatment related AEs	5	2 72	rot
16	Grade 3>= events	9	4 89	ecte
17	AEs in greater than x% in any group & predefined/special interest AEs	4	2 17	a pe
10 19	AEs in greater than x% in any group & frequency between groups differed by more than y% &	-	2.17	o V
20	predefined/special interest AEs	1	0.54	^o p
21	AEs in greater than x% in all patients & predefined/special interest AEs	3	1.63	/rig
22	AEs in greater than x% in treatment group & AEs of special interest	2	1.09	hť, i
23	AEs in greater than x% in any group & all SAEs	2	1.09	ncl
24 25	AEs in greater than x% in all patients & all SAEs	1	0.54	udi
26	AEs in greater than x% in any group & SAEs related to treatment	1	0.54	ng 1
27	Most common (no criteria specified) & predefined/special interest AEs	3	1.63	ior i
28	Most common (no criteria specified) & all SAEs	4	2.17	use En
29	Most common (no criteria specified) & all SAEs & AEs leading to study drug discontinuation/interruption	1	0.54	s re
30 31	Most common (no criteria specified) & treatment related SAEs	1	0.54	gne
32	AEs where frequency between groups differed by more than y% & all SAEs	1	0.54	ed t
33	AEs of special interest	6	3.26	onto
34	Grade >=3 AEs in greater than x% of patients	1	0.54	хt а
35	Grade >=3 AEs in greater than x% in intervention & y% in control	1	0.54	and
36 27	Most common (no criteria specified) grade 3>= AEs	1	0.54	dat
38	Most common SAEs (no criteria specified)	1	0.54	a A n B
39	SAEs & AE of special interest	-	0.54	inii
40	Treatment related AEs in greater than x% of patients	1	0.54	ŋġ, .
41	Treatment related AEs in greater than x% in any group	1	0.54	₽ t
42	AEs in greater than x% in treatment group & SAEs	1	0.54	rair
43 44	AEs in greater than x% in treatment group & SAEs & predefined AEs	2	1 09	ning
45	AEs in greater than x% in any group & significantly different & SAEs	1	0.54	j, ar
46	AEs in greater than x% in any group & treatment related AEs/SAEs	2	1 09	s pt
47	AEs in greater than x% in treatment group & treatment related AEs & SAEs	1	0.54	imi
48	AEs in greater than x% in treatment group & treatment related AEs in greater than v% in all patients	1	0.54	lar
49 50	AFs in greater than x% in any group & Grade 3>= events	1	0.54	fec
51	AFs in greater than x% in all patients & Grade 3>= events	1	0.54	hno
52	AFs in greater than x% in all patients & Grade $2>=$ treatment related AFs	1	0.54	log
53	AFs in greater than x% in any group & Grade $3 \ge $ events in greater than x% in any group	1	0.54	ies.
54	As in greater than y % in any group & SAEs in treatment group	T	0.54	-
55 56	AFs in greater than x% in any group & AFs of special interest & most common (no criteria specified) AFs	T	0.54	
57	leading to treatment discontinuation/interruption & predefined AEs	1	0 5 4	
58	AEs in greater than x% in any group. AEs of special interest in greater than v% in treatment group &	Ŧ	0.54	
59	treatment related deaths	1	0.54	
60				

As in greater than $y^{0/2}$ in treatment group 9. SASs in greater than $y^{0/2}$ in any group		
AEs and SAEs accurring more often in treatment group & SAEs in greater than your any group	1	0.54
Also and SALS occurring more often in treatment group than control	1	0.54
predefined/special interest AEs		
Also in greater than $y^{(0)}$ in any group & frequency between groups differed by more than $y^{(0)}$. SAEs in	1	0.54
greater than z% in any group & all grade >=3 AEs	1	0.54
AEs in greater than x% patients & more than x% difference between treatment groups & AEs leading to	T	0.54
treatment discontinuation/interruption & most common SAEs (no criteria specified) & death	1	0 54
Predefined AEs, AEs leading to hospitalisation/death/study drug discontinuation/interruption & SUSARS	2	1.09
Some form of overall summary	6	3.26
Not specified how selected	6	3.26
Not summarised in main paper	11	5.98
		c.
		9
		(

Selection criteria	n
All AEs	1
SAEs	1
All AEs & SAEs	4
AEs in greater than x% in any group	-
AEs in greater than x% in treatment group	
AEs in greater than x% in all patients	
AEs in greater than x% in any group & all SAEs	
AEs in greater than x% in treatment group & all SAEs	
AEs in greater than x% in all patients & all SAEs	
AEs in greater than x% in treatment group & all SAEs	
AEs in greater than x% in treatment group & greater than in control group & all SAEs	
SAEs in greater than x% in any group	
AEs in greater than x% in any group & SAEs in greater than y% in any group	
AEs in greater than x% in any group & AEs of special interest	
Treatment related AEs	
Treatment related AEs in greater than x% in any group	
Grade 3>= events	
Predefined AEs	
AEs of special interest	
AEs leading to study drug discontinuation/interruption	
AEs leading to study drug discontinuation & SAEs	
Grade 3>= events leading to study drug discontinuation & grade 3>= laboratory results	
Treatment related AEs & AEs leading to study drug discontinuation	
AEs in greater than x% in all patients leading to treatment discontinuations, SAEs in greater than x% in any group, serious predefined (special interest AEs and clinically significant laboratory results	
group, serious predenined, special interest AES and clinically significant laboratory results	
AEs in greater than x% in any group, treatment related AEs in greater than x% in any group, treatment	
Clinical laboratory data	
Predefined AFs. AFs leading to hospitalisation/death/study drug discontinuation/interruption & SUSARS	
Deaths	
Some form of overall summary	
Not specified how selected	
Not summarised in the annendix	

r technologies.

Table A7: Population used for AE analysis

Analysis population	n	%
Those that took at least a single dose	75	40.7
All randomised	54	29.3
Randomised and not withdrawn/ineligible	19	10.3
Not specified	17	9.24
Not applicable	3	1.63
Took a single dose and underwent AE/toxicity assessment	3	1.63
Active treatment groups	2	1.09
Completed treatment and assessed for primary outcome	2	1.09
Other	2	1.09
Patients who treatment was at least attempted on	1	0.54
Intention-to-treat population	1	0.54
Randomised and assessed for primary outcome	1	0.54
Randomised and attended at least on follow-up visit	1	0.54
Randomised and remained in follow-up	1	0.54
Randomised and underwent AE/toxicity assessment	1	0.54
Randomised, eligible and received at least a single dose	1	0.54

Reporting checklist for systematic review and meta-analysis.

Based on the PRISMA guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the PRISMA reporting guidelines, and cite them as:

Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement

		Reporting Item	Page Number
	#1	Identify the report as a systematic review,	1
		meta-analysis, or both.	
Structured	#2	Provide a structured summary including, as	2
summary		applicable: background; objectives; data	
		sources; study eligibility criteria,	
		participants, and interventions; study	
		appraisal and synthesis methods; results;	
		limitations; conclusions and implications of	
		key findings; systematic review registration	
		number	
Rationale	#3	Describe the rationale for the review in the	5-6
		context of what is already known.	
Objectives	#4	Provide an explicit statement of questions	6
		being addressed with reference to	
		participants, interventions, comparisons,	
		outcomes, and study design (PICOS).	
	Foi	r peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml	

	Protocol and registration	#5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address) and, if available, provide registration information including the registration number.	n/a - review protocol was not published
0 1 2 3 4 5 6	rEEligibility criteria	#6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rational	6-7
7 8 9 0 1 2 3 4	Information sources	#7	Describe all information sources in the search (e.g., databases with dates of coverage, contact with study authors to identify additional studies) and date last searched.	6 6 view of uses
5 7 8 9 0	Search	#8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	n/a - we manually searched the electronic contents table of the journals for reports of original RCTs
2 3 4 5 5 7 7 8 9	Study selection	#9	State the process for selecting studies (i.e., for screening, for determining eligibility, for inclusion in the systematic review, and, if applicable, for inclusion in the meta-analysis).	7 a 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1
) 2 3 4 5 5 7	Data collection process	#10	Describe the method of data extraction from reports (e.g., piloted forms, independently by two reviewers) and any processes for obtaining and confirming data from investigators.	g, and similar technolog
2 9 1 2 3 4 5 5 7 8 9	Data items	#11	List and define all variables for which data were sought (e.g., PICOS, funding sources), and any assumptions and simplifications made.	7 , j
0		For	peer review only - http://bmjopen.bmj.com/site/about/guic	delines.xhtml

1 2 3 4 5 6 7 8 9 10 11	Risk of bias in individual studies	#12	Describe methods used for assessing risk of bias in individual studies (including specification of whether this was done at the study or outcome level, or both), and how this information is to be used in any data synthesis.	n/a – the review was to identify current practice, we did not look at and synthesize the actual results of individual studies and as such this assessment was not relevant
12 13 14	Summary measures	#13	State the principal summary measures (e.g., risk ratio, difference in means).	8 8 8
16 17 18 19 20 21	Planned methods of analyis	#14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I2) for each meta-analysis.	opyright, including
22 23 24 25 26 27 28	Risk of bias across studies	#15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	n/a – please see item #12
29 30 31 32 33 34 35	Additional analyses	#16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	n/a – no such analysis was and performed data minin
36 37 38 39 40 41 42	Study selection	#17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	n/a – manual search A resulted in only eligible articles being downloaded g
43 44 45 46 47 48 49	Study characteristics	#18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citation.	9 9
50 51 52 53 54	Risk of bias within studies	#19	Present data on risk of bias of each study and, if available, any outcome-level assessment (see Item 12).	n/a – please see item #12
55 56 57 58 59 60	Results of individual studies	#20 For	For all outcomes considered (benefits and harms), present, for each study: (a) simple summary data for each intervention group peer review only - http://bmjopen.bmj.com/site/about/guid	n/a – only simple descriptive statistics are presented to describe current practice elines.xhtml

		BMJ Open	Page 4
		and (b) effect estimates and confidence intervals, ideally with a forest plot.	
Synthesis of results	#21	Present the main results of the review. If meta-analyses are done, include for each, confidence intervals and measures of consistency.	9-13
Risk of bias across studies	#22	Present results of any assessment of risk of bias across studies (see Item 15).	n/a – please see item #12
Additional analysis	#23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	n/a – please see item #16
Summary of Evidence	#24	Summarize the main findings, including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., health care providers, users, and policy makers	13-21
Limitations	#25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias).	26/27
Conclusions	#26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	27
Funding	#27	Describe sources of funding or other support (e.g., supply of data) for the systematic review; role of funders for the systematic review.	28
The PRISMA che C-BY. This che nade by the <u>EQ</u>	ecklist is cklist w <u>JATOR</u>	s distributed under the terms of the Creative Com as completed on 29. May 2018 using <u>http://www Network</u> in collaboration with <u>Penelope.ai</u>	nmons Attribution License .goodreports.org/, a tool
	For	peer review only - http://bmjopen.bmj.com/site/about/guidel	ines.xhtml

BMJ Open

Analysis and reporting of adverse events in randomised controlled trials: a review

Journal:	BMJ Open
Manuscript ID	bmjopen-2018-024537.R3
Article Type:	Research
Date Submitted by the Author:	15-Jan-2019
Complete List of Authors:	Phillips, Rachel; Imperial College London, Faculty of Medicine, School of Public Health Hazell, Lorna; Drug Safety Research Unit, Clinical Research; University of Portsmouth, Associate Dept. of Pharmacy and Biomedical Sciences Sauzet, Odile; Universität Bielefeld, Cornelius, Victoria; Imperial College London Faculty of Medicine, School of Public Health
Primary Subject Heading :	Research methods
Secondary Subject Heading:	Medical publishing and peer review
Keywords:	Randomised controlled trials, Harm data, Adverse drug reactions, Systematic review, Investigational drug, Adverse events < THERAPEUTICS



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Word Count: 4362

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Abstract

Objective

To ascertain contemporary approaches to the collection, reporting and analysis of adverse events

(AEs) in randomised controlled trials (RCTs) with a primary efficacy outcome.

Design

A review of clinical trials of drug interventions from four high impact medical journals.

Data sources

Electronic contents table of the BMJ, the Journal of the American Medical Association, the Lancet, and the New England Journal of Medicine were searched for reports of original RCTs published between September 2015 and September 2016.

Methods

A pre-piloted checklist was used and single data extraction was performed by three reviewers with independent check of a randomly sampled subset to verify quality. We extracted data on collection methods, assessment of severity and causality, reporting criteria, analysis methods and presentation of AE data.

Results

We identified 184 eligible reports (BMJ n=3; JAMA n=38, Lancet n=62; and NEJM n=81). Sixty-two percent reported some form of spontaneous AE collection but only 29% included details of specific prompts used to ascertain AE data. Numbers that withdrew from the trial were well reported (80%),

however only 35% of these reported whether withdrawals were due to AEs. Results presented and analysis performed was predominantly on 'patients with at least 1 event' with 84% of studies ignoring repeated events. Despite a lack of power to undertake formal hypothesis testing, 47% performed such tests for binary outcomes.

Conclusions

This review highlighted that the collection, reporting and analysis of AE data in clinical trials is inconsistent and RCTs as a source of safety data are underutilised. Areas to improve include reducing information loss when analysing at patient level and inappropriate practice of underpowered multiple hypothesis testing. Implementation of standard reporting practices could enable a more accurate synthesis of safety data and development of guidance for statistical methodology to assess causality of AEs could facilitate better statistical practice.

21/0

Keywords

Randomised controlled trials; adverse events; harm data; adverse drug reactions; review;

investigational drug.

Article Summary

Strengths and Limitations of this study

- This is the first review to examine and quantify the methods used for AE analysis in RCTs published in high impact general medical journals.
- This review identifies methodological weakness that need to be addressed as well as good practice that could be adopted.
- *3.* Articles included in this review were published in four of the top ranked general medical journals therefore results are likely to be biased towards better practice.
- 4. Included articles are only for year 2015-2016 and as such may not reflect current practice.
INTRODUCTION

The methods to analyse and report outcomes to measure benefit from randomised controlled trials (RCTs) are well developed but this progress has not been matched for adverse event (AE) outcomes. An adverse event is defined as 'any untoward medical occurrence that may present during treatment with a pharmaceutical product but which does not necessarily have a causal relationship with this treatment'.¹ An adverse drug reaction (ADR) is defined as 'a response to a drug which is noxious and unintended ...' where a causal relationship is 'at least a reasonable possibility'.^{1, 2} RCTs provide an opportunity to compare rates of AEs between arms allowing causality to be evaluated. However, contemporary analysis and reporting practices are inadequate.

There are many challenges associated with analysing and reporting AEs in clinical trials. RCTs are typically designed to determine the efficacy of an intervention but are often underpowered to detect important differences in AEs between arms which may suggest an ADR. Often large numbers of AEs are reported during a study, sometimes exceeding the number of patients in the clinical trial. Performing hypothesis tests on these AEs would lead to issues of multiplicity, however any adjustment for multiplicity would make a 'finding untenable'.^{3, 4} The use of hypothesis testing may result in the medicinal product being deemed unsafe and a trial being halted too early due to a chance imbalance, or conversely deemed safe and not stopped early enough resulting in more patients than necessary suffering an ADR.^{3, 5, 6} Unlike efficacy outcomes which are well defined and restricted in number at the planning stage of a RCT, we collect numerous, undefined AEs in RCTs. Furthermore, AE collection requires additional information to be obtained on factors such as severity, timing and duration, number of occurrences and outcome, which for our efficacy outcomes would have all been predefined.

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> Previous studies have examined the methods for AE collection and presentation only, and highlighted the inadequacies in AE reporting in journal articles.⁷⁻¹⁶ In 2004 the Consolidated Standards of Reporting Trials (CONSORT) Group produced an extension to their guidelines for reporting trial results to cover the reporting of harms, however implementation of these guidelines has been shown to be poor.^{10, 14-17} Recently a joint pharmaceutical/journal collaboration published practical guidance and examples on what should be reported in journal articles and how it should be displayed to ensure transparency and aid clinical interpretation. They promote the use of clinical judgement in reporting rather than mandatory guidance.¹⁸ Whilst this work has been undertaken there remains uncertainty about practice for reporting and presenting AE data, and in addition the analysis practice for AEs remains a neglected area for review.

The aim of this review was to evaluate contemporary practice for collection, reporting and analysis of AEs in RCTs where the primary outcome was efficacy. The aim being to identify and promote any areas of good practice, whilst highlighting any areas for improvement.

METHODS

Search strategy

The top four general medical journals as ranked by impact factors that publish clinical trials of drug interventions were selected: The BMJ (Impact Factor 20.79), the Journal of the American Medical Association (JAMA, IF 44.41), the Lancet (IF 47.83), and the New England Journal of Medicine (NEJM, IF 72.41). Impact factors quoted are from 2016 to reflect the time period from which the articles were drawn. High impact journals were chosen as we would expect practice in these journals to be of high standard as they include statistical and methodological review. We limited the search to four

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journals after an initial scoping review revealed around 100 studies would be eligible for inclusion, which was a feasible number to review given the time and resources available and would provide a sufficient number to evaluate practice. One reviewer manually searched the electronic contents table of the journals for reports of original RCTs published between September 2015 and September 2016, inclusive. Any queries regarding eligibility were reviewed and discussed with a second reviewer.

Selection criteria

The inclusion criteria were phase II-IV RCTs of drug interventions where the primary outcome was efficacy of the intervention. We did not restrict according to number of treatment arms and included both parallel and cluster RCTs. We excluded cross-over RCTs, RCTs with adaptive randomisation, observational studies, case reports, editorials and letters. We also excluded RCTs where the intervention was not a drug product (i.e. not classified as a clinical trial of an investigational medicinal product (CTIMP)). As the study aimed to assess how authors report and analyse AEs in studies where the primary outcome was efficacy, trials that were specifically designed to investigate safety as a primary outcome were not included. Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies.

Data extraction

Potentially eligible articles were identified based on titles and abstracts and the full text of these studies were retrieved. Supplementary material was also reviewed if readers were referred here from the main article for further results. Supplementary Table A1 lists all data items captured with guidance given to the reviewers for extraction. The items to be extracted were based on the work by

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Cornelius et al. and the CONSORT harm extension with additional items added to capture more specific information on analysis practices.^{11, 17} Specifically we focused on the following areas: how AE data was collected (mode of collection, timing) and defined (coding, attribution); how AEs were assessed in terms of severity of the event or relatedness to the medical intervention; if there was any planned AE analysis (final and interim monitoring plans and analysis populations); how events were selected for inclusion in the journal article; how summary event information was presented in the journal article and how AEs were analysed.¹¹ A more detailed rationale for the choice of items extracted is provided in the supplementary material (Table A2).

A data extraction sheet was piloted and then single data extraction was performed by three reviewers (RP, VC and LH) with 10% independent check of a randomly sampled subset to verify quality. Queries were also informally discussed between reviewers on an ongoing basis. Where specific items were flagged for poor agreement these were re-extracted. Any queries during data extraction were shared and disagreements between reviewers were resolved through discussion.

Data analysis

The proportion of trials reporting each item, 3-4 and 8-34 in supplementary Table A1 were calculated and summary statistics (median and ranges) were calculated for items 5-7. All analyses were performed in Stata version 15.¹⁹ A risk of bias assessment was not undertaken as this study aimed to describe best practice and not evaluate outcomes.

Patient and public involvement

This review forms part of a wider research project that was developed with input from a range of patient representatives. There were no study participants directly involved in this review but the

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original proposal and patient and public involvement (PPI) strategy were reviewed by service user representatives (with experience as clinical trial participants and PPI advisors) who provided advice specifically with regard to communication and dissemination to patient and public groups.

RESULTS

Data extraction

A total of 585 items were extracted twice across all three reviewers to check the quality of the data extraction. A total of 95 discrepancies were identified. This gave agreement of 84%. During this independent check several items were flagged for potential poor agreement. These items were 100% independently extracted by one author and verified. The items were: study duration; the AE collection method; timing of collection; how binary harm outcomes were summarised; whether continuous outcomes were dichotomised; if continuous outcomes were left as continuous how they were analysed.

Study characteristics

The search identified 184 eligible trial reports (BMJ n=3; JAMA n=38, Lancet n=62; and NEJM n=81) in which a total of 496911 participants were randomised with a median of 556 participants per trial (range 30, 205513; interquartile range (IQR) 281, 1704). The median trial follow-up was 52 weeks (range 48 hours to 10 years; IQR 24, 104 weeks) and 93% were multi-centre trials. Fifty-percent of

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studies had an active comparator and over 50% of trials received some element of industry funding

(Table 1).

Table 1: Characteristics of included studies						
Characteristic	1	N=184				
	Median	(IQR)	min, max			
Sample size	556	(281, 1704)	30, 205513			
Centres ^a	35	(12, 100)	1, 1368			
Trial duration (weeks) ^b	52	(24, 104)	0.3, 521			
	n	%				
Journal						
BMJ	3	1.6				
JAMA	81	44.0				
Lancet	38	20.7				
NEJM	62	33.7				
Funded by						
Public	70	38.3				
Industry	80	43.7				
Both	33	18.0				
Centre						
Single-centre	12	7.0				
Multi-centre	161	93.0				
Control						
Placebo	95	51.6				
Active	80	43.5				
Both	8	4.4				
Neither	1	0.5				

Abbreviations: *IQR* = *Inter-quartile range; min* = *minimum; and max* = *maximum*

°11 reports did not specify the number of centres

^b2 reports did not specify trial duration

^cOne trial compared interventional drug to behavioural change intervention

Collection and assessment methods

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Sixty-two percent (n=114) of reports made reference to some form of passive (e.g. spontaneously reported by patients) AE monitoring or collection methods. Of these only 46.5% (53/114) or 29% of total reports included specific details (prompts e.g. questions about specific events or AEs in general, questionnaires, or diaries) regarding these collection methods (Supplementary Table A3, examples 1-2).^{20, 21} The timing of collection was well documented (91%, 48 out of 53 reports) in the reports that included specific details about the prompts used to collect AEs. Although specific details on clinical examinations (e.g. vital signs and blood pressure) and laboratory tests were not widely reported (only 57% of reports (95 out of 166 reports with clinical examinations and/or laboratory results presented) included details on the timing of such assessments) it was often clear from the reported clinical and laboratory results respectively) (Table 2).

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Section	Component Data ite	m	N=1		
Collection			n	%	
	Component Data item ion How was AE/harm information collected? Passive collection Passive collection (n=114) No method of collection reported Did they undertake proactive screening? Clinical examinations Laboratory tests Timing of prompted collection specified (n=53) Timing of active collection specified (n=166) Which, if any, dictionary was used to code AE data? CTCAE MedDRA CTCAE and MedDRA DAIDS ICD-10 Researcher defined Other No dictionary reported No dictionary reported				
	Passive	collection	114	62	
	Pro	mpted collection (n=114)	53	46	
	No meti	nod of collection reported	70	38	
	Did they undertake proactive screening?				
	Clinical	examinations	153	83	
	Laborat	ory tests	146	7	
	Timing of prompted collection specified (n=	53)	48	9(
	Timing of active collection specified (n=166)	,	95	5	
			55	5	
	Which, if any, dictionary was used to code AE data	a?			
	CTCAE		18	ç	
	MedDR	Ą	43	2	
	CTCAE a	nd MedDRA	1	0	
	DAIDS		2	1	
	ICD-10		1	0	
	Researc	her defined	2	1	
	Other		3	1	
	No dicti	onary reported	114	6	
Assessment					
	Who assigned attribution to study drug?				
	Blinded	assessor	9	Z	
	Unblind	ed assessor	7	Э	
	Both		1	C	
	Not spe	cified	164	8	
	Not app	licableª	3	1	
Analysis	C				
	Was any analysis for AEs specified in the methods	section?			
	Yes		57	3	
	Was a population for AE analysis specified?				
	Yes		82	4	
	Was there a planned interim analysis with stopping	ng criteria?			
	No	<u>:</u>	138	7	
	Yes for e	efficacy	24	1	
	Yes for e	efficacy & futility	11	6	
	Yes for e	efficacy & safety	3	1	
	Yes for e	efficacy, futility & safety	2	1	
	Yes but	no other details given	6	3	

10th revision.

NOTE: Denominator specified in item column if it differs from total sample

°3 reports made no reference to AE data throughout the article

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Prespecified analysis

Thirty-one percent of reports provided information on the planned analysis for AEs in the statistical analysis section of the paper and 45% pre-specified a safety population (Supplementary Table A3, examples 3-4 and Table 2).^{22, 23} A quarter of trials reported planned interim analysis with stopping criteria (Table 2), five (2.7%) of which included specific criteria on stopping for a harmful event (Supplement Table A4²⁴⁻²⁸).

Selection of AEs and reporting practices

Two reports only made generic statements regarding AE data: *"there were no significant adverse events related to the procedure"* and *"no excess in mortality or major adverse events were found..."*. Three reports made no mention of AEs throughout the manuscript.²⁹⁻³³

Twenty-four (13%) trials only provided a summary of the number of AEs or serious AEs rather than listing the actual AEs that occurred. For example *"Six serious adverse events occurred in the acetaminophen group and 12 in the ibuprofen group."*³⁴ Of these 24 trials, 10 did provide specific details of the types of events in an appendix. This means 8% of trials either did not report AEs or only included a summary (Table 3).

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Component	Data item	N=1	.84
		n	%
What was reported in the r	nanuscript?		
	Actual AE terms	73	39
	Summaries of AE type (e.g. AE, SAE)	24	13
	Both	80	43
	Neither	7	3.
What was reported in the a	appendix?		
	Actual AE terms	76	41
	Summaries of AE type (e.g. AE, SAE)	7	3
	Both	22	12
	Neither	3	1.
	Not applicable ^a	76	41
Which population was the	AE analysis performed on?		
	All randomised	54	29
	Those that took at least a single dose	75	40
	Other	35	19
	Not specified	17	9
	Not applicable ^b	3	1
Were drop-outs/withdrawa	als reported?		
	No	33	17
	Yes by treatment arm	144	78
	Yes overall	2	1
	Not applicable ^c	5	2
Were withdr	awals due to AEs reported? (n=146)		
	No	89	61
	Yes	51	34
	Not applicable ^d	6	4
Were specific	c AEs causing withdrawals reported? (n=51)		
	No	39	76
	Yes	12	23
How were binary AE outco	mes summarised by arm?		
	Not summarised ^e	6	3
	Number of people with an event	154	83
	Number of events	11	6
	Both	12	6
	Unclear	1	0
Were frequencies of AEs re	ported by arm?		
	No	5	2
	Yes for some	13	7
	Yes for all	160	87
	Not applicable ^e	6	3
Were percentages of AEs re	eported by arm?		
-	No	18	9,
	Yes for some	25	13

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2				
З Д		Yes for all	135	73.4
5		Not applicable ^e	6	3.3
6	Were between arm differences and 9	95% CI of AEs reported?		
7		No	141	76.6
8		Yes for some	18	9.8
9		Yes for all	19	10.3
10		Not applicable ^e	6	2 2
11	Mara statistical significance tasts ha	twoon arms on AEs reported?	0	5.5
13	were statistical significance tests be	No	02	50.0
14		NO	92	50.0
15		Yes for some	31	16.9
16		Yes for all	55	29.9
17		Not applicable ^e	6	3.3
18	Were continuous AEs outcomes dich	otomised for summaries?		
19		No	10	5.4
20		Yes for some	28	15.2
22		Yes for all	108	58.7
23		Not applicable	38	20.7
24	If continuous outcomes were left as	continuous what between arm analyses w	as performe	d? (n=38)
25	Differences in measure	es of central tendency estimated with 95%		u. (ii 30)
26	Directices in measure	No	22	C0 F
27		NO	23	00.5
20		Yes for some	1	2.6
30		Yes for all	14	36.8
31	Between arm hypothe	sis tests performed		
32		No	12	31.6
33		Yes for some	2	5.3
34		Yes for all	24	63.2
35	Were any 'signal detection' approach	nes used?		
37	, , , , , , , , , , , , , , , , , , , ,	No	184	100.0
38		Yes	0	0.0
39	Were there any graphical presentation	ans of AE outcomes?	U	0.0
40	were there any graphical presentation	No.	160	00 0
41		NO	162	88.0
42		Yes	22	12.0
43	Were summaries of severity rating o	f AEs reported?		
44		No	103	56.0
46		Yes for some	41	22.3
47		Yes for all	35	19.0
48		Not applicable ^f	5	2.7
49	Were number of serious AEs reporte	d?		
50		No	44	23.9
51		Yes overall	2	1.1
53		Yes by treatment arm	132	71 7
54			132 6	22
55		latednass given? (==124)	U	5.5
56	FOR SERIOUS ALS WAS RE	iateuness given? (n=134)		
57		NO	11	57.5
58		Yes for some	18	13.4
59 60		Yes for all	38	28.4
00				

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	Yes overall	1	0.8
Were there any AEs where in	formation on duration of events was re	ported?	
	No	175	95.1
	Yes	9	4.9
Were there any AEs where in	formation on the time of occurrence of	events was reported?	
	No	132	71.7
	Yes	52	28.3
If any significance tests were	e performed on AEs was multiplicity of e	events accounted for?	
	No	81	44.0
	Yes	3	1.6
	Not applicable	100	54.4
Did the report reference the	CONSORT extension to harms		
	No	184	100.0
	Yes	0	0.0

Abbreviations: AE = Adverse Event; SAE = Serious Adverse Event; CI = Confidence Interval; and CONSORT = Consolidated Standards for Reporting Trials.

^a Make no reference to the appendix

^b 3 reports made no reference to AE data throughout the article

^c 5 reports indicate no withdrawals

^d 6 reports specify the number of withdrawals and reasons but none of the reasons are related to AEs

^e This includes 3 reports with no AE data (as per footnote ^b), 2 reports that provide generic statements regarding AE data and 1 report that only reported continuous outcomes

^f This includes 3 reports with no AE data and 2 reports that provide generic statements regarding AE data (as per footnote ^e)

^g 6 papers specifically state that no serious adverse events occurred

Eighty-nine percent of trials reported a subset of all the AEs they collected. How AEs are 'selected' for inclusion in the article was not consistent or clear, and in 3% of studies it was impossible to discern how the authors had selected the AEs they presented for inclusion. Twenty-six percent of reports selected events based on a frequency threshold e.g. events experienced by greater than x% in any group; 9% of reports used a measure of severity to select events e.g. AEs of grade 3 or higher; 23% of reports included events based on seriousness; and 8% included AEs based on relatedness to treatment (percentages are not independent as the majority of reports used several different criteria for selection). Supplementary Tables A5 and A6 provide full details of selection criteria used.

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We found that 41% of trials analysed AEs in participants that received at least one dose, 29% of trials used all randomised participants and 9% did not specify the analysis population (Table 3). Further details on analysis populations used are given in supplementary Table A7.

Nearly 80% of trials reported the number of participants who withdrew from the trial; of these 35% (51 of 146 reports) reported whether the withdrawals were due to AEs and of these 24% (12 of 51 reports) reported the actual events that caused withdrawals. Results presented and analysis performed was predominantly on 'patients with at least 1 event' with 84% of reports providing no information on the number of events occurring. An example of how to incorporate information on number of events is presented in reference ³⁵. Forty-one percent of trials reported information on the severity of AEs. Five percent of trials include a report of at least one event with duration, but presenting such data is limited in the main report. The trials that did present this information did so in a variety of ways. For example incorporating the information into the AE table with summary statistics such as the mean duration of certain events or presenting it for a subgroup of events in the footnotes of AE tables e.g. *"One event of non-serious squamous cell carcinoma (day 210, resolved on day 215; adalimumab treatment was not interrupted*)."³⁶⁻³⁸ Twenty-eight percent of reports included information on the timing of AEs (Table 3).

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Serious adverse events were typically well documented (73%) and six reports (3%) explicitly stated that no serious events had occurred. However, for forty-four reports (24%) it was not possible to discern if no serious events had occurred or whether they were simply omitted from the report. Forty-two percent (57 of 134 reports) of reports included details on whether the events had been classified as related to the intervention (Table 3).

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Analysis of AE outcomes

Binary

The majority of trials summarised binary outcomes using frequencies (94%) and percentages (87%). Despite a lack of power to undertake formal hypothesis testing, 47% reported p-values for binary outcomes. For example "There were no between-group differences in the rate of patients with at least 1 adverse event (16.7% [14 patients] in the clopidogrel group vs 21.8% [19 patients] in the placebo group; difference, -5.2% [95% Cl, -17% to 6.6%]; P = .44)." However, with a total safety population of 171 such a test would have only had 13% power to detect such a difference and was therefore substantially underpowered. The conclusion that "No significant increase in adverse events was observed" makes no reference to the 95% confidence interval presented which indicates that the findings were in fact compatible with a 17% decrease in experiencing at least on AE as well as a near 7% increase.39 ilen

Continuous

There was a pervasive practise (59%) of categorising continuous clinical and laboratory outcomes. Of the trials that did not dichotomise continuous AE data nearly 70% performed some form of statistical significance testing (Table 3). Whilst continuous outcomes do not suffer to the same degree regarding lack of power, multiple testing is still a problem, however no multiplicity corrections for continuous outcomes were performed.

Of the trials that performed statistical significance testing on AE data, only three made an adjustment for multiplicity of tests (all three on dichotomised outcomes).^{36, 40, 41} Two of which used a Bonferroni correction and adjusted for the number of pairwise comparisons between each of the

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treatment groups for each individual event rather than the total number of significance tests performed. As such both analyses would have still been effected by issues of multiple testing.

Twelve percent of reports used graphs to illustrate AE data (Table 3). The CONSORT extension highlighted the value of graphs for summarising such data, especially for conveying information on time-to-event outcomes.⁴² An example of such a plot is included in the supplement of reference ⁴³ (eFigure2).

We assessed any reference to the CONSORT harm extension and found that none of the included studies mentioned it. Of the four journals included in the review, the Lancet was the only journal that made specific reference to the harm extension in their guidelines to authors.

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DISCUSSION

The safety profile of a medicinal product is established through evidence collected from several sources including clinical trials, observational studies and spontaneous reports.⁴⁴ The advantage of clinical trial data is that these provide a controlled comparison of the rate of AEs allowing causality to be evaluated but have the disadvantage that the sample size is often not large enough to detect rare ADRs.

To ensure that a useful and comprehensive picture of the safety profile is provided to all relevant parties clear reporting of AEs from clinical trials is required. Recent research has shown the quality of reporting is substandard.⁷⁻¹⁶ The aim of this study was to review contemporary practice across four leading medical journals for AE collection, analysis and reporting practices, highlighting any areas for

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improvement and examples of good practice. We found that the collection, reporting and analysis of AE data in clinical trials is inconsistent and RCTs as a source of safety data are underutilised. Analysis of AE was often inappropriate with suboptimal practice including ignoring valuable information on repeated events and inappropriate practice of underpowered multiple hypothesis testing.

Collection and assessment methods

The CONSORT extension to harm was developed with the aim to improve reporting of safety data in RCTs.⁴² None of the included studies referenced the CONSTORT harm extension and of the items in our review that are covered in CONSORT many were not well reported.¹⁷ This suggests that the CONSORT extension is not being routinely adopted by authors to aid their reporting. Most journals now request that authors include a completed CONSORT checklist when they submit their article but we are not aware of any journal that request the CONSORT harm extension to also be submitted. Of the four journals in this review the Lancet is the only journal that makes specific reference to the harm extension in their guidelines to authors. The CONSORT statement contains a single item related to safety, item 19: 'all important harms or unintended effects in each group' should be reported.⁴² This may explain why some items listed on the CONSORT extension for harm were reported by so few trials. The mandatory submission of CONSORT harms by journals may support better reporting.

We found that the method of AE collection was poorly reported. This has important implications for the type and frequency of AEs reported with "passive collection resulting in fewer recorded AEs".^{45,} ⁴⁶ Where the method was given the timing of collection was typically also reported and we would recommend continuation of this practice. The frequency of AE collection has further important implications on the number of events reported. More frequent assessment and longer follow-up will

result in more AEs reported.¹⁷ It is important to consider these factors when making conclusions about the safety profile.

The method of attribution between drug and AE was another area where reporting practice was inadequate. However, the joint pharmaceutical/journal collaboration indicate that such attribution has 'limited value' given the 'inherent subjectivity in such attribution'.¹⁸

Prespecified analysis

We found that formal assessments of AEs regarding stopping for emerging ADRs utilising statistical rules was rare. Subjective assessments of overwhelming amounts of data could easily lead to potential signals of harm being missed. There could be benefits to incorporating more objective statistical methods alongside clinical review to assist the evaluation of AE information to help better identify drug harm relationships. Graphical displays have gone some way towards aiding interpretation.⁴⁷⁻⁵¹

Selection of AEs and reporting practices

Due to space constraints in journal reports AE information is often included in the appendix. Whilst we encourage use of appendices and supplementary material for including additional detail on AEs, we caution authors against depositing all AE data into such documents without attempting to present a summary of the AE profile in the main article. It is important that the main report strikes a

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balance between efficacy and harm therefore allowing a risk-benefit assessment to be made solely from the article.

The failure to report any information on AEs restricts interpretation and prevents a risk-benefit assessment. We identified two reports that made generic summaries of the overall safety profile and it was clear in both that there had been harmful effects. However, the authors did not include any further information. Three reports contained no information leaving readers uninformed as to any additional information these studies may provide on the safety profile. Ambiguous reporting prevents building an accurate picture of the safety profile. As such profiles are developed on accumulating evidence, it is important that each study report to the same standard and information is not wasted.

We found that the selection criteria used by authors to decide what AEs to include in the report were arbitrary and inconsistent. This will have important implications when synthesising data across studies to construct safety profiles. Authors would benefit from guidance to facilitate consistency but research in this area is lacking. Lineberry et al. recommended clinically relevant events that should always be reported (deaths, SAEs and events leading to discontinuation of intervention) and criteria that should be considered when deciding what other AEs to report e.g. interest based on the disease(s) under investigation, comorbidities of the study population, intervention mechanism, trial duration.¹⁸ Standard outcomes for a drug class would be one potential solution to avoid issues of inconsistency suggested by Cornelius et al.¹¹

CONSORT recommend that AE analyses should be performed on the intention-to-treat (ITT) population to maintain the random assignment.¹⁷ However it is clear from our review that this

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population label is not always appropriately and consistently applied. There is a tendency for studies to make modifications to the ITT population. Using the ITT or modified-ITT population is likely to underestimate the risk by inflating the denominator with participants who may have never received the study drug.⁵² Such estimates are appropriate for health economic evaluations where estimates of the cost-effectiveness will inform policy level decisions regarding how to treat the population. However, a more appropriate population for AE analysis to inform prescriber and patient decisions may be those that receive at least one dose. It is important that authors clearly define and specify a suitable safety analysis population and consider how this affects their conclusions.

Proxy outcomes can be used as a measure of the impact of AEs on patients. Examples include the number of withdrawals due to any reason, withdrawals due to AEs, the number of events an individual experiences, the severity of the AE and the duration. A high proportion of trials reported withdrawal for any reason and this is likely to be as a result of the CONSORT recommendations.⁴² The other outcomes were not frequently reported and increasing this could facilitate interpretation.¹⁷ This information would permit better evaluation of the impact of AEs and the tolerability of the intervention to inform patients' and clinicians' treatment decisions. Reporting numbers that experience at least one event only and not providing information on repeated events masks valuable information that may be important to the patient and the cost-effectiveness evaluation. For example, chronic, repeated headaches over an extended duration will have an important impact for patients compared to a single headache or headaches over a short duration but it is not possible to distinguish between these two scenarios when reported as 'at least one event'.¹⁸ Severity of events was also an important aspect that was often not differentiated. For example, there would be a different impact on patients' quality-of-life with mild compared to severe nausea, which could lead to changes in dosing regimens. Displaying such information for all AEs in tables would soon become overwhelming and make interpretation difficult. Graphical approaches

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have been suggested as a solution to aid review. Examples of such a plots can be found in reference ⁵³. Online appendices and supplementary material provide more opportunity to include this important information.

For serious adverse events information on the time of likely onset can be useful information to inform patient monitoring plans. For example, the documented risk of suicide and suicidal ideation within the first few weeks of starting anti-depressant allows patients and prescribers to remain alert and monitor closely for this period. Nearly a third of reports included such information and we would encourage authors to adopt this practice.

Analysis of AE outcomes

The majority of trials in this review included a balanced report of AEs alongside benefit. However many included generic statements regarding the safety profile such as 'the intervention was well tolerated' or 'the intervention exhibited a good safety profile' and these were frequently based on post-hoc statistical tests. Guidelines caution against such tests.¹⁸ The results of which are difficult to interpret as a lack of significance does not indicate that the intervention is safe and conversely multiple testing without adjustment will increase the number of significant differences due to chance.^{54, 55}

Graphs are an efficient method to convey and interpret large amounts of data and can make it easier to flag potential safety signals.^{50, 51, 53} Twelve percent of studies included in the review used graphs to present AE data and an example of one such report is given in the supplementary eTable of reference ⁵⁶.

 summarised in Table 4.

Table 4: Recommendations to improve adverse event analysis and reporting in clinical trial report publications

	Recommendation
Analysis	Incorporate objective statistical methods to assist the
	evaluation of adverse event information.
	Consider avoiding dichotomising continuous data.
	When count outcomes are available (such as repeated events
	within participants) use appropriate statistical methods.
C.	Clearly define exposure and specify a suitable safety analysis
	Use graphical approaches to help summarise large amounts of data.
Reporting	Report adverse event data according to the CONSORT harm
	checklist.
	Increase the uptake of mandatory submission of CONSORT
	harm by journals.
	Include a relevant summary of the adverse event profile in the
	main article. Resist depositing all adverse event data into
	appendices without summarising.
imitations of trials	

Limitations of trials

Trials are a valuable source for high quality adverse event data but compared to observational studies have smaller sample size, follow-up periods and generalisability, which restrict the ability to detect rare ADRs, ADRs with long latency and drug interactions in complex populations. The typical duration of a trial means there is often insufficient follow-up to fully characterise the safety profile as it provides limited information on long-term exposure. Stringent inclusion criteria restrict the population the intervention is assessed in and so limited information on drug-interactions is obtained.⁵

Limitations of this study

Articles included in this review were published in four of the top ranked medical journals therefore results are likely to be biased towards better findings than we would expect if we included all RCTs. Articles are only for year 2015-2016 and as such may not reflect current practice. We also acknowledge that only completing 10% independent check of extracted data would not have removed subjectivity from the data extraction but are happy that ongoing discussion between authors to clarify any queries would have kept this to a minimum. Despite these limitations, this review characterises what those leading the field are doing and provides some examples of good practice that could be adopted.

Conclusions and recommendations for future work

RCTs are a valuable source of information establishing the safety profile of medicinal products. Our review has demonstrated that data is not being fully utilised. Analysis of AE data is frequently inappropriate and RCT reports published over a recent period in high impact general medical journals often provide insufficient and inconsistent information to allow a comprehensive summary of the safety profile to be established.

This research has identified two areas that would benefit from future research. i) Improving the consistency of reporting important AE outcomes across trials to facilitate comparison and synthesis. This is in line with work from the COMET Initiative group (http://www.comet-initiative.org/). The development of CORE safety outcomes by drug class could be considered.⁷ ii) Evaluation of methods to analyse AEs in RCTs.

COMPETING INTERESTS

None declared.

FUNDING

This research was supported by the NIHR grant number DRF-2017-10-131.

DATA SHARING STATEMENT

No additional data are available.

AUTHOR STATEMENT

RP conceived the idea for this review, conducted the search, carried out data extraction and analysis, and wrote the manuscript. VC conceived the idea for the review, performed data extraction, critical revision of the manuscript and supervised the project. LH performed data extraction and critical revision of the manuscript. OS performed critical revision of the manuscript.

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Table A1: Data	items extracte	a from pu	Directions	Instruction	s S DS
		1	Study number	uses) t
Starday data ila		2	Journal	n 20 seig s rel	5 5 5
Study details		3	Funding source: public, private, both or unspecified.	Studies avil explicately of	be assumed to be funded by industry only if this is ated.
Study		4	Control: placebo, active or both	Selections	ebo if no active treatment is given, else active. Both elected for trials with multiple arms where there is group receiving no active treatment and one group n active treatment.
characteristics		5	Number of centres	(Allata	
		6	Number randomised	min	
		7	Study duration (length of trial follow-up)	ing,	
Methods	Details of how AE outcomes were defined (coding, attribution) and were collected (mode of	8	Describe the collection method: passive surveillance, patient prompted, clinical examinations (e.g. vital signs or urine samples), and laboratory tests. (Select all that apply)	Passive: Is study with was passive Promoted questions questionna	authors state that AEs were collected throughout the no further information we will assume that collection e. Prompted methods include, but are not limited to about both specific events and AEs in generatives, or diaries.
li cuious		9	Stated the timing of collection.	on imil	
		10	Mention dictionary for coding of events: Researcher defined, MedDRA, CTCAE, WHO-ART, COSTART, ICD-10, other or not applicable	June 1 ar tech	
	timing)	11	Describe who undertook the assessment of attribution to study drug: blinded assessor, unblinded assessor or not specified	nok	<u>د</u>
Planned analysis	Details of any	12	Describe analysis for AE outcomes in the statistical methods.	Reference harm even analysed.	nust be made to harmful events e.g. AEs or a specifi t, this cannot be simply how binary events will b
	analysing AE	13	Define a 'safety' population for analysis.	е с	5
	outcomes	14	Specify a planned interim analysis with stopping criteria: based on efficacy, based on safety, based on both efficacy and safety, yes but no other details given, no planned interim analysis or unclear	Criteria for the DMC	stopping must be set out, it is not enough to say the eviewed the data.
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3 4 5 6		Details of what was reported and where	15	What was reported in the main paper: summaries of type of AEs (e.g. AE, SAE, AR, ADR), actual AE terms, both, neither or not applicable?	Not applicable is relevant when for example authors explicitly state there are no events or there is only one event so summaries are inappropriate.
/ 8 9 10 11 12 13			16	What was reported in the appendix: summaries of type of AEs (e.g. AE, SAE, AR, ADR), actual AE terms, both, neither or not applicable?	Not applied ble is relevant when for example authors explicitly state that there are no events or there is only one event so summaries are inappropriate. We will only search the appendix/supplementary material for AE dotation the main article makes reference to it.
14 15			17	Who was the AE analysis performed on: all randomised, participants who took at least a single dose, other or not specified?	t and d
16 17 18 19			18	How were number of drop-outs/withdrawals reported: By treatment arm, overall, not reported or not applicable?	Not book to be a constructed by the construction of the constructi
20 21 22	Results		19	Were drop-outs/withdrawals due to AEs reported: Yes, no or not applicable?	Not applicable if drop-outs/withdrawals are not reported or if it is reparted that there are no drop-outs/withdrawals.
23 24 25			20	Were specific AEs causing withdrawals reported: Yes, no or not applicable?	Not applicable if drop-outs/withdrawals due to AEs are not reported of if it is reported that there are no drop- outs/Bithdrawals due to AEs.
26 27 28 29			21	What was the selection criteria for the AEs reported?	Free text esponse where possibilities can include for example: most dependent, above a severity threshold, SAEs. Include defails of what's in the main journal article and what is in the appendix separately.
30 31 32 33 34	0 1 2 3 4 5 6	Details of how AEs were summarised		What summary information was given. Number of people, number of	Only celect 'number of events' if presented for each individual events of events. Not applicable is only relevant when report that there are no
35 36		- binary	22	events, both, unclear, not summarised or not applicable?	AES. G
37 38		outcomes	23	What analysis was performed: frequencies, percentages, differences and 95% confidence intervals, significance tests, other? (Select all that apply)	Bibli
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Details of how AEs were summarised	24	Were continuous outcomes dichotomised: Yes for all, yes for some, no or not applicable?	This Encloydes meas contiguous and then blood pressure etc.	sures that will have been captured as dichotomised for example blood levels,
and presented - continuous outcomes	25	If continuous outcomes were analysed as continuous what analysis was performed: differences in measures of central tendency, significance tests, other? (Select all that apply)	/arch 20 Enseig uses rel	
Details of	26	Were signal detection methods used?	19. [nem ated	
now AES were	27	Were any graphical summaries of AEs presented?	bown to t	
summarised	28	Were severity ratings given: Yes for all, yes for some, no or not applicable?	ווסמכ Supe ext a	
and presented	29	Were numbers of serious events presented: Yes by treatment arm, yes overall, no or not applicable?	If dealing reported enough to constitute	as part of the efficacy outcome it is not reporting serious events.
	30	Were serious events coded as treatment related: Yes for all, yes for some, no or not applicable?	http://bm ES) . hining, A	
	31	Provided information on the duration of events?	This reference to the leng	th of the actual AE i.e. how long did it last.
	32	Provided information on the timing of events?	This Beferento the time	e of onset of the AE.
	33	Accounted for multiplicity of statistical tests?	nj.co , an	
	34	Referenced CONSORT extension for harms?	om/o	
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Table A2: Rationale for items extracted

Item	Rationale
How AE data was	Variation in the collection and definition of events could explain differences in
collected (mode of	the incidence of observed events. ^{13, 14} For example specifically asking
collection, timing) and	participants about an event of interest in one treatment group whilst relying on
defined (coding,	patient report in another is likely to lead to a disparity in incidence of events
attribution) during the	unlikely to be related to the medicinal product.
study.	
Assessment practices of	Attribution of causality by an unblinded assessor allows for subjectivity and
severity of the event or	bias (even if subconscious) to enter into their decision which can have
relatedness to the	important implications on the risk-benefit assessment.
medicinal product.	
Planned AE analysis (final	For example, the intention-to-treat population is likely to underestimate the
and interim monitoring	AE risk by inflating the denominator. Therefore, this needs to be considered
plans and analysis	when making conclusions about a drug's safety profile.
populations).	
How events were	Due to the space constraints in journal articles it is not always feasible to
selected for inclusion in	report all AEs experienced by participants. Therefore, articles often only
the journal article.	report a subset of AEs and how these are selected for inclusion has important
	implications for the safety evaluation. Arbitrary selection criteria can lead to
	inconsistencies in what is presented across trials for the same disease and/or
	drug. This prevents an accurate overview of the AEs experienced and
	invalidates any potential systematic review of events.
How and what summary	For example, the number of events and duration of events provides insight
event information was	into the impact of AEs, with repeated or longer events potentially having far
presented in the journal	wider clinical implications than a single, shorter event for both patients and
article.	prescribers.
How AEs were analysed.	There are many challenges to be considered when analysing AEs in clinical
	trials. For example, inappropriate statistical testing can lead to misleading
	conclusions e.g. failure to find a statistically significant result leading authors
	to conclude that the medicinal product is safe or chance imbalance could lead
	the authors to erroneously stopping a trial too early. ³⁻⁶

Table A3: Examples	of reporting	practice in	reviewed	articles
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Example	Study	Example practice	Example
no.		• •	•
1	Litonjua et al. ²⁰	Description of AE collection method	"Study staff met with pregnant women monthly to administer a brief health questionnaire, assess medication use, and monitor for complications (via the questionnaire and medical record review) After delivery, children were monitored by telephone every 3 months and in-person annually for 3 years, during which time infants' health, respiratory symptoms, and medications were assessed"
2	Miller et al. ²¹	Description of AE collection method	"Safety evaluations included physical examinations, assessment of vital signs, clinical laboratory tests, and reporting of adverse events at each study visit"
3	Libman et al. ²²	Description of planned AE analysis	"The proportions of participants experiencing any adverse event, any related adverse event, any gastrointestinal event, any event other than a gastrointestinal event, at least 1 severe hypoglycaemic event, and at least 1 diabetic ketoacidosis event in each treatment group were compared using the Fisher exact test. The number of adverse events, new adverse events, serious adverse events, and non-serious adverse events were compared between groups using a Wilcoxon rank sumtest."
4	Gross et al. ²³	Description of planned AE analysis	"Safety analyses and secondary efficacy analyses used binomial regression, analysis of covariance, or the marginal Cox proportional hazards model as appropriate"

Table A4	: Stopping	criteria	for	safety
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Study	Main article text	Appendix text
Myles et al. ²⁴	"O'Brien–Fleming stopping boundaries were used to assess efficacy, and <u>a less stringent boundary was</u> <u>used to assess harm</u> ."	
Billings et al. ²⁵	"The data and safety monitoring board (DSMB) reviewed patient recruitment practices, safety reporting, and data quality after 30 patients completed the study; performed an interim analysis after 277 patients had completed the study to assess <u>safety of the intervention</u> ; and performed a second interim analysis after 546 patients had completed the study to assess the safety, efficacy, and futility of the intervention. The DSMB made recommendations based on qualitative assessments of the safety, efficacy, and futility of the intervention"	 "Suspend enrolment in any study arm due to safety concerns based on study intervention. Safety concerns include: Increase in in-hospital all-cause mortality in subjects randomized to A or B such that the DSMB deems the increase is excessive compared to A or B. Increased treatment toxicity in either treatment group deemed excessive. Toxicity is defined as moderate or severe myalgias. Increased severity of adverse events deemed "Probably Related" or "Possibly Related" to study intervention in either treatment group. Itemized adverse event reports separated by treatment will be provided. Increased AKI incidence in either treatment group (secondary endpoints) deemed excessive."
Beardsley et al. ²⁶	"An independent data and safety monitoring committee oversaw trial safety and analyzed unblinded data after every 50 deaths, according to its charter"	"The Haybittle-Peto boundary, requiring p<0.001 at interim analysis to consider stopping for efficacy, will be used as guidance. <u>A level of significance of 1% will</u> <u>be used as a quide for stopping the trial early because</u> <u>of a detected harm of dexamethasone</u> . In addition, the DMEC will receive conditional power curves to assess whether it remains realistic that the trial will demonstrate superiority of dexamethasone conditional on the data accrued up to the point of the interim analysis. Importantly, the DMEC recommendations will not be based purely on statistical tables but will also use clinical judgment."
Kor et al. ²⁷	"In addition to statistical criteria for significance, the study included a priori "go-no-go" definitions for recommending continuation to phase 3 study Briefly, continuation to phase 3 would occur with a positive primary outcome finding along with an acceptable safety profile. An acceptable safety profile was defined as a serious adverse event profile for aspirin that was not statistically worse than placebo (95% CI for the relative risk of any serious adverse event covers the null value of relative risk = 1.0). The "no-go decision" was defined as early termination by the data and safety monitoring board for safety or unfavorable risk/benefit ratio. An indeterminate case in which there was a non-statistically significant effect but this effect was in a clinically meaningful direction was also defined."	Initiate Phase III Study: Demonstrated efficacy signal in addition to adequate safety profile Criteria: Early termination for benefit at interim analysis or p<0.08885 at final analysis (alpha=0.10 for study). <u>Serious adverse event profile of ASA not statistically</u> <u>worse than placebo (95% confidence interval for the</u> <u>relative risk of any SAE covers the null value of</u> <u>RR=1.0).</u> Further Development Potentially Required: Weak efficacy signal Criteria: Primary endpoint did not achieve a priori level of significance but there were at least a general consistency of secondary endpoints indicating propensity for efficacy with a larger sample size and/or more specific primary endpoint. Abandon Treatment Platform: Harm (in efficacy or safety endpoints) Criteria: Study terminated early per recommendation <u>by DSMB for safety and/or</u> <u>risk/benefit ratio concerns</u> (i.e., stop for futility, harm, unacceptable risk profile, etc.)

Nichol e al. ²⁸	et	We used a group sequential statistical approach to do two equally spaced pre-planned interim analyses (at 33% and 67% of total recruitment) to assess accumulated safety data (differential proportions of deep venous thrombosis and total mortality). This <u>approach was chosen to provide for early stopping for</u> <u>probable harm</u> or strong evidence of benefit. We applied the Haybittle-Peto criterion (17k1>3) for early	
		applied the Haybittle-Peto criterion $(Zk \ge 3)$ for early stopping at these analyses.	

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2 3	Table A5: Selection criteria used to select AFs presented in the main journal report			
4	Selection criteria	n	%	-
5	All AEs presented	20	10.87	-
7	AEs in greater than x% in any group	10	5.43	
8	AEs in greater than x% in treatment group	4	2.17	
9	AEs in greater than x% in all patients	1	0.54	
10	Most common (no criteria specified)	9	4.89	
11	Predefined AEs	26	14.13	
12	SAEs	15	8.15	
14	AEs leading to study drug discontinuation/interruption	3	1.63	т
15	Treatment related AEs	5	2 72	rot
16	Grade 3>= events	9	4 89	ecte
17	AEs in greater than x% in any group & predefined/special interest AEs	4	2 17	a pe
10 19	AEs in greater than x% in any group & frequency between groups differed by more than y% &	-	2.17	o V
20	predefined/special interest AEs	1	0.54	^o p
21	AEs in greater than x% in all patients & predefined/special interest AEs	3	1.63	/rig
22	AEs in greater than x% in treatment group & AEs of special interest	2	1.09	hť, i
23	AEs in greater than x% in any group & all SAEs	2	1.09	ncl
24 25	AEs in greater than x% in all patients & all SAEs	1	0.54	udi
26	AEs in greater than x% in any group & SAEs related to treatment	1	0.54	ng 1
27	Most common (no criteria specified) & predefined/special interest AEs	3	1.63	ior i
28	Most common (no criteria specified) & all SAEs	4	2.17	use En
29	Most common (no criteria specified) & all SAEs & AEs leading to study drug discontinuation/interruption	1	0.54	s re
30 31	Most common (no criteria specified) & treatment related SAEs	1	0.54	gne
32	AEs where frequency between groups differed by more than y% & all SAEs	1	0.54	ed t
33	AEs of special interest	6	3.26	onto
34	Grade >=3 AEs in greater than x% of patients	1	0.54	хt а
35	Grade >=3 AEs in greater than x% in intervention & y% in control	1	0.54	and
36 27	Most common (no criteria specified) grade 3>= AEs	1	0.54	dat
38	Most common SAEs (no criteria specified)	1	0.54	a A n B
39	SAEs & AE of special interest	-	0.54	inii
40	Treatment related AEs in greater than x% of patients	1	0.54	ŋġ, .
41	Treatment related AEs in greater than x% in any group	1	0.54	₽ t
42	AEs in greater than x% in treatment group & SAEs	1	0.54	rair
43 44	AEs in greater than x% in treatment group & SAEs & predefined AEs	2	1 09	ning
45	AEs in greater than x% in any group & significantly different & SAEs	1	0.54	j, ar
46	AEs in greater than x% in any group & treatment related AEs/SAEs	2	1 09	s pt
47	AEs in greater than x% in treatment group & treatment related AEs & SAEs	1	0.54	imi
48	AEs in greater than x% in treatment group & treatment related AEs in greater than v% in all patients	1	0.54	lar
49 50	AFs in greater than x% in any group & Grade 3>= events	1	0.54	fec
51	AFs in greater than x% in all patients & Grade 3>= events	1	0.54	hno
52	AFs in greater than x% in all patients & Grade $2>=$ treatment related AFs	1	0.54	log
53	AFs in greater than x% in any group & Grade $3 \ge $ events in greater than x% in any group	1	0.54	ies.
54	As in greater than y % in any group & SAEs in treatment group	T	0.54	-
55 56	AFs in greater than x% in any group & AFs of special interest & most common (no criteria specified) AFs	T	0.54	
57	leading to treatment discontinuation/interruption & predefined AEs	1	0 5 4	
58	AEs in greater than x% in any group. AEs of special interest in greater than v% in treatment group &	Ŧ	0.54	
59	treatment related deaths	1	0.54	
60				

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As in greater than y^{0} in treatment group 8 sAs in greater than y^{0} in any group		
Also and SAlso accurring more often in treatment group & SAlso in greater than your any group	1	0.54
Also and SALS occurring more often in treatment group & occurred more often in treatment group than control &	1	0.54
predefined/special interest AEs		
Also in greater than y' in any group & frequency between groups differed by more than y'' SAEs in	1	0.54
greater than z% in any group & all grade >=3 AEs	1	0.54
AEs in greater than x% patients & more than y% difference between treatment groups & AEs leading to	T	0.54
treatment discontinuation/interruption & most common SAEs (no criteria specified) & death	1	0.54
Predefined AEs, AEs leading to hospitalisation/death/study drug discontinuation/interruption & SUSARS	2	1.09
Some form of overall summary	6	3.26
Not specified how selected	6	3.26
Not summarised in main paper	11	5.98
		3
		(
		c.
Selection criteria	n	
--	---	
All AEs	1	
SAEs	1	
All AEs & SAEs	4	
AEs in greater than x% in any group		
AEs in greater than x% in treatment group		
AEs in greater than x% in all patients		
AEs in greater than x% in any group & all SAEs		
AEs in greater than x% in treatment group & all SAEs		
AEs in greater than x% in all patients & all SAEs		
AEs in greater than x% in treatment group & all SAEs		
AEs in greater than x% in treatment group & greater than in control group & all SAEs		
SAEs in greater than x% in any group		
AEs in greater than x% in any group & SAEs in greater than y% in any group		
AEs in greater than x% in any group & AEs of special interest		
Treatment related AEs		
Treatment related AEs in greater than x% in any group		
Grade 3>= events		
Predefined AEs		
AEs of special interest		
AEs leading to study drug discontinuation/interruption		
AEs leading to study drug discontinuation & SAEs		
Grade 3>= events leading to study drug discontinuation & grade 3>= laboratory results		
Treatment related AEs & AEs leading to study drug discontinuation		
AEs in greater than x% in all patients leading to treatment discontinuations, SAEs in greater than x% in any group, serious predefined (special interest AEs and clinically significant laboratory results		
group, serious predenined, special interest AES and clinically significant laboratory results		
AEs in greater than x% in any group, treatment related AEs in greater than x% in any group, treatment		
Clinical Jahoratory data		
Predefined AEs. AEs leading to hospitalisation/death/study drug discontinuation/interruption & SUSARS		
Deaths		
Some form of overall summary		
Not specified how selected		
Not summarised in the annendix		

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Table A7: Population used for AE analysis

	n	%
Those that took at least a single dose	75	40.7
All randomised	54	29.3
Randomised and not withdrawn/ineligible	19	10.3
Not specified	17	9.24
Not applicable	3	1.63
Took a single dose and underwent AE/toxicity assessment	3	1.63
Active treatment groups	2	1.09
Completed treatment and assessed for primary outcome	2	1.09
Other	2	1.09
Patients who treatment was at least attempted on	1	0.54
Intention-to-treat population	1	0.54
Randomised and assessed for primary outcome	1	0.54
Randomised and attended at least on follow-up visit	1	0.54
Randomised and remained in follow-up	1	0.54
Randomised and underwent AE/toxicity assessment	1	0.54
Randomised, eligible and received at least a single dose	1	0.54

Reporting checklist for systematic review and meta-analysis.

Based on the PRISMA guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the PRISMA reporting guidelines, and cite them as:

Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement

		Reporting Item	Page Number
	#1	Identify the report as a systematic review,	1
		meta-analysis, or both.	
Structured	#2	Provide a structured summary including, as	2
summary		applicable: background; objectives; data	
		sources; study eligibility criteria,	
		participants, and interventions; study	
		appraisal and synthesis methods; results;	
		limitations; conclusions and implications of	
		key findings; systematic review registration	
		number	
Rationale	#3	Describe the rationale for the review in the	5-6
		context of what is already known.	
Objectives	#4	Provide an explicit statement of questions	6
		being addressed with reference to	
		participants, interventions, comparisons,	
		outcomes, and study design (PICOS).	
	Foi	r peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml	

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	Protocol and registration	#5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address) and, if available, provide registration information including the registration number.	n/a - review protocol was not published
0 1 2 3 4 5 6	rEEligibility criteria	#6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rational	6-7
7 8 9 0 1 2 3 4	Information sources	#7	Describe all information sources in the search (e.g., databases with dates of coverage, contact with study authors to identify additional studies) and date last searched.	6 6 view of uses
5 5 7 8 9 0 1	Search	#8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	n/a - we manually searched the electronic contents table of the journals for reports of original RCTs
2 3 5 5 7 3 9	Study selection	#9	State the process for selecting studies (i.e., for screening, for determining eligibility, for inclusion in the systematic review, and, if applicable, for inclusion in the meta-analysis).	7 a 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1
) <u>)</u> 3 4 5 5 7	Data collection process	#10	Describe the method of data extraction from reports (e.g., piloted forms, independently by two reviewers) and any processes for obtaining and confirming data from investigators.	g, and similar technolog
2 9 1 2 3 4 5 5 7 8 9	Data items	#11	List and define all variables for which data were sought (e.g., PICOS, funding sources), and any assumptions and simplifications made.	7 , j
0		For	peer review only - http://bmjopen.bmj.com/site/about/guic	delines.xhtml

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1 2 3 4 5 6 7 8 9	Risk of bias in individual studies	#12	Describe methods used for assessing risk of bias in individual studies (including specification of whether this was done at the study or outcome level, or both), and how this information is to be used in any data synthesis.	n/a – the review was to identify current practice, we did not look at and synthesize the actual results of individual studies and as such this assessment was	MJ Open: first published as
10				hot relevant	10.1
12 13 14	Summary measures	#13	State the principal summary measures (e.g., risk ratio, difference in means).	8	136/bmjoj
15 16 17 18 19 20 21	Planned methods of analyis	#14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I2) for each meta-analysis.	8 8 8	convictor including
22 23 24 25 26 27 28	Risk of bias across studies	#15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	n/a – please see item #12	1 March 2019. Dow Enseignement
29 30 31 32 33 34 35	Additional analyses	#16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	n/a – no such analysis was performed	Inloaded from http: Superieur (ABES)
36 37 38 39 40 41 42	Study selection	#17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	n/a – manual search resulted in only eligible articles being downloaded	//bmjopen.bmj.com
43 44 45 46 47 48 49	Study characteristics	#18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citation.	9 9	V on June 11, 2025 ;
50 51 52 53 54	Risk of bias within studies	#19	Present data on risk of bias of each study and, if available, any outcome-level assessment (see Item 12).	n/a – please see item #12	at Agence Bibli
55 56 57 58 59 60	Results of individual studies	#20 For	For all outcomes considered (benefits and harms), present, for each study: (a) simple summary data for each intervention group peer review only - http://bmjopen.bmj.com/site/about/guid	n/a – only simple descriptive statistics are presented to describe current practice elines.xhtml	ographique de l

		BMJ Open	Page 4
		and (b) effect estimates and confidence intervals, ideally with a forest plot.	
Synthesis of results	#21	Present the main results of the review. If meta-analyses are done, include for each, confidence intervals and measures of consistency.	9-13
Risk of bias across studies	#22	Present results of any assessment of risk of bias across studies (see Item 15).	n/a – please see item #12
Additional analysis	#23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	n/a – please see item #16
Summary of Evidence	#24	Summarize the main findings, including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., health care providers, users, and policy makers	13-21
Limitations	#25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias).	26/27
Conclusions	#26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	27
Funding	#27	Describe sources of funding or other support (e.g., supply of data) for the systematic review; role of funders for the systematic review.	28
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	For	peer review only - http://bmjopen.bmj.com/site/about/guidel	ines.xhtml