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Adverse event reporting and trial registration in venous leg ulcer trials published since the 2001 CONSORT statement revision: A systematic review

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ABSTRACT

Aim: To be in accord with the Consolidated Standards of Reporting Trials (CONSORT) Statement, all important adverse events in randomised controlled trials (RCTs) should be reported, as well as trial registration. Neither concern has been investigated in venous leg ulcer trials. We therefore aimed to quantify and explore compliance with adverse event reporting and trials registration in RCTs that reported interventions for treating venous leg ulceration.

Materials and methods: We searched the Cochrane Controlled Trials Register, Medline, Embase, and CINAHL for studies reported between 2001 and 2017. Included studies must have been described as randomised controlled trials evaluating any intervention in a VLU population. Data was then extracted by one author into a standard form and checked by a second author.

Results: We screened 3100 titles and identified 204 trials involving pharmaceuticals (82), medicated and non-medicated devices (102), organisational (5) or other interventions (15) published in 76 journals. Eighty-four trials reported adverse events (41.2%), while 18 reported no events occurred (8.8%) and 78 did not report adverse events (38.2%). Types of adverse events reported included all-cause (20.1%), ulcer-related only (38.2%), treatment-related only (11.3%) and serious adverse events only (1.0%). Only 38 trials were registered (18.6%). Trial registration was associated with reporting of any adverse events (Odds Ratio 3.0, 95%CI 1.1–7.9), as was the trial being a pharmaceutical trial (Odds Ratio 2.9, 95%CI 1.5–5.7) or a multicentre trial (Odds Ratio 4.2, 95%CI 2.2–8.1).

Conclusion: Adverse event reporting in VLU trials is variable with about one third of trials not reporting on adverse events at all. Trials registration is a the modifiable factor associated with better reporting of adverse events. Journal editors could explore how they can promote trials registration to enhance better reporting of harms in VLU trials.

Randomised controlled trials (RCTs) are the most reliable method for evaluating the effects of treatments [1]. Typically trials are powered to determine the efficacy or effectiveness of an intervention as a primary outcome with adverse events usually captured as a secondary outcome. Adverse event rates within trials are important inputs into understanding the potential risks of a treatment alongside its potential benefits. An adverse event is commonly defined in RCTs as any untoward medical occurence that may present with a treatment, although is not necessarily related to the treatment [2]. The revised Consolidated Standards of Reporting Trials (CONSORT) Statement required reporting of all important adverse events [3], although these were not defined. An extension on reporting of harms was published in 2004, as the single item mentioned in the 2001 revision was not thought to "do full justice to the importance of harms-related issues" [4]. Nevertheless adverse event reporting in trial publications remains suboptimal [5], even in highly regulated areas such as oncology [6].

The CONSORT Statement also requires reporting of trial registration. Public domain trial registers have been open to accept RCTs since 2000 when both *ClinicalTrials*.gov and Current Controlled Trials (then called the International Standardised RCT Number) became available on the internet. The International Committee of Medical Journal Editors (ICMJE) announced they would no longer publish RCTs after 1 July 2005 that had not been prospectively listed on such registers [7]. The ICMJE now recommends that all medical journal editors require registration of trials. The aim of such statements is to ensure that the evidence base is complete and accessible so that syntheses can

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summarise the benefits and the harms of a treatment. Compliance with trial registration remains, however, incomplete [8].

Venous leg ulcers (VLU) are a relapsing and remitting wound of the lower leg, associated with chronic venous insufficiency. The standard treatment is compression to improve venous return, along with wound products to manage the wound bed [9]. Many of the compression systems and wound products will have been evaluated in RCTs, albeit without the regulatory stringencies imposed on pharmaceutical evaluations. However, clinicians and patients will be underinformed about the risk/benefit calculus unless there is complete capture of adverse events in VLU trials. There is minimal guidance on how adverse events should be reported in venous leg ulcer (VLU) trials [10], although wound care products are not without risk. For instance, patients with VLU are more susceptible to allergic contact dermatitis than controls, and the allergens can be dressing and bandaging materials as well as the ingredients of skin lotions and topical medications [11]. If adverse events are not reported in VLU trials, then the evidence base for the safety of products is incomplete. An evaluation of all the outcomes reported in 102 VLU RCTs published between 1998 and 2013 found only two reports used the term adverse events as an outcome, although other outcomes that would be adverse events were also reported e.g. pain [12]. An update of that review reported 61% of 144 trials reported on adverse events [13].

There has been no comprehensive assessment of compliance with reporting on adverse events or trial registration requirements in VLU trials. The objectives of this review of VLU trials were to [1] identify the number of VLU trials that have reported adverse events since the CONSORT Statement first included an item on reporting of harms in trials, to [2] determine the number of VLU trials by source of publication that have been registered on a public domain clinical trials register; and [3] explore factors that were associated with reporting adverse events.

1. Methods

We searched the Cochrane Controlled Trials Register, Medline, Embase, and CINAHL for RCTs of any intervention for treating VLU published in English between 2001 and October 2017. Search terms were venous ulcer, varicose ulcer, gravitational ulcer, ulcus cruris and truncations of the same. Trials that included a mix of wounds or ulcer aetiologies were excluded unless the report separated results by wound type. Both authors independently reviewed the citations identified from the electronic and other searches. The searches were imported into Covidence (www.covidence.org) for screening and full-text review. Papers meeting the inclusion criteria were obtained for full-text review and where there was any uncertainty, we obtained the paper. Full-text papers were independently reviewed by both authors and reasons for exclusion recorded. Any disagreements were resolved by discussion.

Data was extracted by the summer scholar (Author 2) using a standardised Excel form and checked by the principal investigator (Author 1). Extracted data included journal name, year, country, number of study centres, trial registration, source of funding, trial design elements (sequence generation and allocation concealment), type of intervention, type of adverse event reporting (see Box.1), and use of formal taxonomy for classifying adverse events. We used the Cochrane risk of bias criteria to assess whether a trial had recorded sufficient information about sequence generation and allocation concealment [14]. We used Web of Science to identify five-year Journal Impact Factor (JIF); if the five-year JIF was not available, we used the most recent one-year JIF. We determined whether journals supported the ICMJE recommendations for trial registration by reviewing the web-based list of journals that have sought to be listed as following their Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals (http://www.icmje.org/journals-following-the-icmje-recommendations/) or the Surgical Journal Editors Group consensus statement [15]. Journals that want to be included on the ICMJE list of publications that follow ICMJE guidance are told that the listing implies the journal's enforcement of ICMJE's trial registration policy. (http://www.icmje.org/icmje-recommendations.pdf, accessed 27 February 2018). The date of listing was obtained from that web-list or publication of consensus statements.

We conducted all analyses in SPSS v25. We tested for normality where the data was continuous and reported medians with interquartile range (IQR) when the data was non-parametric. We used the Chi-squared test to examine univariate associations between trial characteristics and adverse event reporting for categorical variables or the appropriate test for continuous data depending on whether the data was normally or non-normally distributed. We assessed the variables for correlation and in the absence of correlations greater than 0.7, we included variables in the model where the p-value for the univariate test was less than or equal to 10%. We used backwards stepwise elimination for the multiple logistic regression models, with variables retained where the p value was less than or equal to 10%.

2. Results

2.1. Description of trials

We found 6300 references and screened 3001 titles and abstracts after duplicates were removed (Fig. 1). We identified 208 trials from 206 reports, but we could only obtain 202 reports of 204 trials despite repeated attempts to obtain the outstanding reports. Overall, 19,264 participants were randomised in the 204 trials with a median of 67 participants per trial (IQR 40–117). The largest trial randomised 457 participants [16], while the smallest trial randomised 10 participants [17]. One hundred and twenty-nine trials (63.2%) were conducted in Europe, 22 trials (10.8%) in North America, 17 trials (8.3%) in South America, 15 trials (7.4%) in Australasia, and the remaining 10.4% of trials in the Middle East (5) or South and East Asia (5), across regions (7), or the region could not be identified (4). Ninety-eight trials (48.0%) were multicentre trials (Table 1) and the median number of study sites was 2 (IQR 1 to 10). We could not identify the number of centres in 32 trials (15.7%), but 74 trials were single centre trials (36.3%).

Most trials involved either a drug (82, 40.2%) or a non-medicated device (73, 35.8%) as the experimental intervention. Medicated devices accounted for 29 trials (14.2%) and organisational interventions for 5 trials (2.4%). The remaining 15 trials (7.4%) involved exercise interventions (7), larval therapy (3), surgery (3) or skin grafting (2). The funding source was industry in 75 trials (36.8%), public good research funding in 37 trials (18.1%), mixed industry and public good funding in 8 trials (3.9%) and no external funding in 12 trials (5.9%). Seventy-two trials (35.3%) did not report their funding source.

2.2. Adverse event reporting

Forty-one trials (20.1%) reported all-cause adverse events, 18 trials (8.8%) reported VLU-associated adverse events, while 23 trials (11.3%) only reported treatment-related adverse events and two trials (1.0%) only reported serious adverse events. Seventy-eight trials (38.2%) did not report adverse events, while it was unclear what types of adverse events were being reported in another further 24 trials (11.8%) and 18 trials (8.8%) reported no adverse events occurred, without specifying what types of adverse event might have been reported. Seven trials (2.9%) reported using a formal definition of adverse events, while only three trials (1.0%) reported using a formal taxonomy for classifying the adverse events (the Medical Dictionary for Regulatory Activities and the International Classification of Diseases).

2.3. Journal reporting and trial registration

The 204 trials were published in 76 journals (eTable) at a mean rate

Box 1
Explanation of terms

Term	Explanation
Adverse event	Any unfavourable sign, symptom or occurence that eventuates during a treatment, but may not be related to the treatment.
Serious adverse event	Any untoward medical event that results in death, hospitalisation, persistant or significant disability, birth defect, or other important medical concern.
All-cause adverse events	Outcome where all adverse events reported
Serious adverse events	Outcome where serious adverse events are reported
Condition-specific adverse events	Outcome where only adverse events associated with the condition are reported
Treatment-related adverse events	Outcome where only adverse events assigned a causal relationship with the treatment are reported (not to be confused with treatment-emergent adverse events, which are simply events that have a temporal relationship with the treatment).

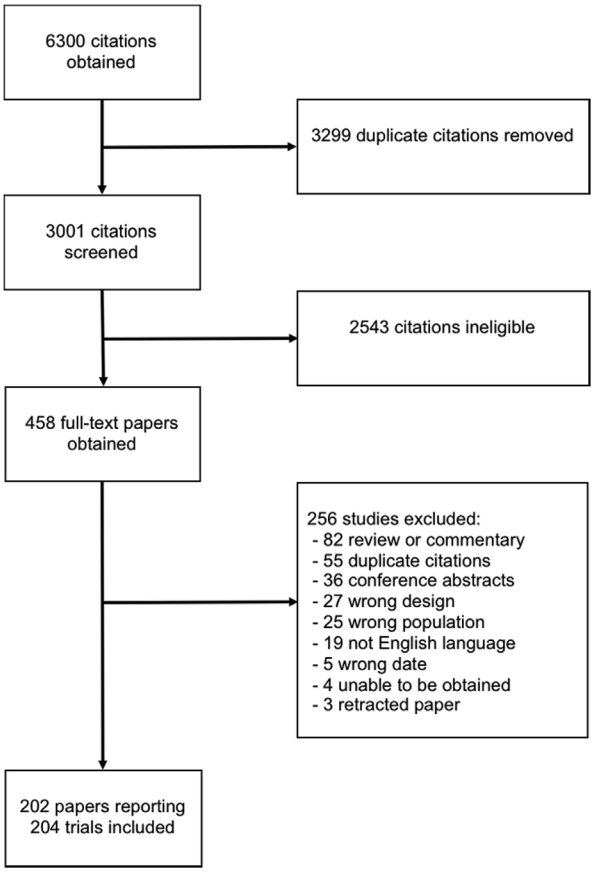

Fig. 1. PRISMA diagram showing studies included at each stage of the search strategy.

of 12 trials (SD 3.6) per year; one published report was retracted, but we have included the unpublished thesis [18]. Twenty-four journals published more than one trial and accounted for 152 reports (74.5%). At the time of the search was conducted, 17 journals (22.4%) were listed as supporting the ICMJE recommendations on trials registration. Seven of the 24 journals that published more than one trial were listed as supporting the ICMJE requirements for trial registration (etable), while five more have sought listing since the search for this review was conducted. Thirty-eight trials (18.6%) were registered. One trial was registered prior to the 2004 ICMJE announcement and 37 since that announcement. Registration has been increasing since 2007, but less than 50% of the trials published in any single year have been registered (Fig. 2).

Table 1
Characteristics of included trials.

Feature	Registered	Not Registered	Total
	N (%)	N (%)	N (%)
Type of Adverse Events reported			
All-cause events	14 (36.8)	27 (16.3)	41 (20.1)
Condition-specific events only	3 (7.9)	15 (9.0)	18 (8.8)
Treatment-related events only	7 (18.4)	16 (9.6)	23 (11.3)
Serious Adverse Events only	–	2 (1.2)	2 (1.0)
Reported no events occurred	2 (5.3)	16 (9.6)	18 (8.8)
Unclear	5 (13.2)	19 (11.4)	24 (11.8)
Did not report events	7 (18.4)	71 (42.8)	78 (38.2)
Fig. 2 Type of trial			
Parallel-group	38 (100.0)	162 (97.6)	200 (98.0)
Cross-over	3	1 (0.6)	1 (0.5)
Within-participant		3 (1.8)	3 (1.5)
Design features reported			
Sequence generation	34 (89.5)	71 (42.8)	105 (51.5)
Allocation concealment	26 (68.4)	48 (28.9)	74 (36.3)
Number of centres			
Multicentre	28 (73.7)	70 (42.2)	98 (48.0)
Single centre	10 (26.3)	64 (38.6)	74 (36.3)
Not reported	–	32 (19.3)	32 (15.7)
Intervention			
Drug	11 (28.9)	71 9 (42.8)	82 (40.2)
Medicated device	5 (13.2)	24 (14.5)	29 (14.2)
Non-medicated device	16 (42.1)	57 (34.3)	73 (35.8)
Organisational	1 (2.6)	4 (2.4)	5 (2.5)
Other	5 (13.2)	10 (6.0)	15 (7.4)
Funding source			
Industry	14 (36.8)	61 (36.7)	75 (36.8)
Public	14 (36.8)	23 (13.9)	37 (18.1)
Mixed	4 (10.5)	4 (2.4)	8 (3.9)
None	–	12 (7.2)	12 (5.9)
Not reported	6 (15.8)	66 (39.8)	72 (35.3)
Trials Register			
ClinicalTrials.gov	15 (7.4)	–	15 (7.4)
Current Controlled Trials	9 (4.4)	–	9 (4.4)
ANZCTR	10 (4.9)	–	10 (4.9)
Other	4 (2.0)	–	4 (2.0)
Not registered	–	166 (81.4)	166 (81.4)

2.4. Trial registration and quality assessments

Trial registration was associated with improved reporting of important markers for trial quality, namely sequence generation and allocation concealment. Thirty-five registered trials (92.1%) adequately reported random sequence generation sufficient that a risk of bias assessment could be determined compared to 71 unregistered trials (42.8%). Thirty-four registered trials were judged as low risk of bias and one registered trial was judged as high risk of bias, while the remaining three registered trials were judged as having an unclear risk of bias on sequence generation. Seventy-one unregistered trials (42.8%) reported sufficient information to be judged as low risk of bias, while the remaining 95 unregistered trials were judged as having an unclear

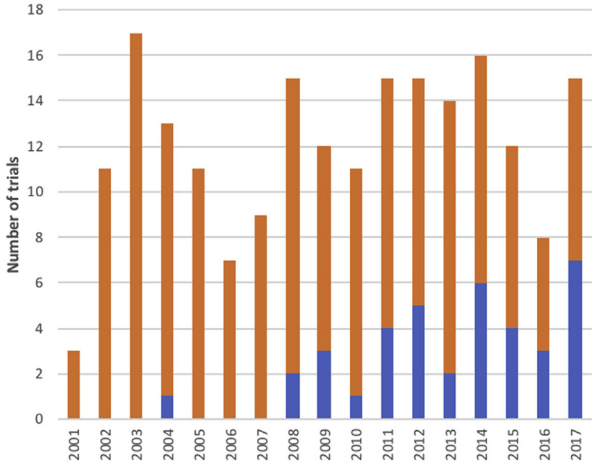

Fig. 2. Number of trials by year of first publication and whether trials reported being registered (blue) or not (orange). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

risk of bias. Registered trials were about two times more likely to have sufficient information for a risk of bias assessment on sequence generation (RR 2.2, 95%CI 1.8 to 2.6, $p < 0.0001$).

Twenty-seven registered trials (71.0%) adequately reported allocation concealment sufficient that a risk of bias assessment could be determined compared to 49 unregistered trials (29.5%). Twenty-six registered trials were judged as low of risk of bias and one registered trial was judged as high risk of bias, while the remaining 11 registered trials were judged as having an unclear risk of bias. Forty-nine unregistered trials (29.5%) reported sufficient information for a risk of bias assessment, with 48 unregistered trials judged as having low of risk of bias and one unregistered trial judged as high risk of bias, while the remaining 117 unregistered trials were judged as having an unclear risk of bias. Registered trials were almost two and a half times more likely to have sufficient information reported such that a risk of bias assessment could be made on allocation concealment (RR 2.4, 95%CI 1.8 to 3.3, $p < 0.0001$).

2.5. Trial characteristics associated with adverse event reporting

Drug trials and drug or medicated device trials were highly correlated ($r = 0.750$) and hence only the binary variable for drug or other trials was retained in the initial regression model. Funding source and ICMJE listing were not significantly different between those trials that reported all-cause or any adverse events and those that did not and therefore were not included in the initial regression model. Five-year journal impact factor and sample size were not normally distributed and a non-parametric test was applied to these univariate analyses (Mann Whitney *U* test). Both variables were eliminated from the regression models for both all-cause or any adverse event reporting (Table 2).

Being a drug trial, multicentred trial and trial registration were the best predictors of all-adverse event reporting (predictive accuracy = 81.9%), explaining 22.2% of the variability in the dependent variable. The model was stronger in predicting which trials did not report all-cause adverse events (98.2%) than predicting which trials did report all-cause adverse events (17.1%). Being a drug trial, multicentred trial, and trial registration were also the best predictors of any type of adverse event reporting (predictive accuracy = 67.6%), explaining 22.1% of the variability in the dependent outcome. The model was stronger in predicting which trials reported any adverse events (85.6%) than which trials did not report any adverse events (39.2%).

3. Discussion

Advising patients on treatment options requires an understanding of the risks and benefits of the treatments, a calculus that cannot be complete unless all harms are reported in clinical trials. We found five in every 10 trials either did not report adverse events or reported they did not occur. In trials that did report adverse events, the types of events reported were highly variable; the trials reported all-cause adverse events or VLU-only associated adverse events or only treatment-related adverse events or only serious adverse events. Factors associated with adverse event reporting were whether the trial was multicentred, a drug intervention, or whether the trial was registered.

This review is the first to focus on adverse event reporting in venous leg ulcer trials. A recent update of a previous systematic review examing VLU outcomes reported in trials published between 1998 and 2018 found 61% of trials had reported adverse events, although they offered no further analysis [13]. That review found 144 trials and the smaller sample may explain the slightly higher number of trials reporting adverse events. By comparison, our review included 204 reports and about half the trials reported on adverse events, although only seven trials offered a definition of adverse events in the methods section of the papers and fewer still identified a taxonomy for categorising the adverse events. The CONSORT Statement extension on reporting harms recommends that the absolute risk of adverse events be reported by arm, event type and seriousness [4], which would normally require both a definition of event as well as a taxonomy for summarising the events into clinically meaningful aggregates. A possible explanation for not collecting or reporting on adverse events in VLU trials is that 60% of the trials were not drug trials and it some may believe that adverse events are unlikely to occur when devices, bandages, and dressings are being evaluated. However, both medicated and non-medicated device trials reported all-cause adverse events, while some drug trials either did not report adverse events (24) or reported no adverse events occurred (10). It is thus clear that there is no consensus on whether adverse events should be reported in VLU trials, let alone how adverse events should be reported in trials.

This review is the first investigation that shows the extent to which VLU RCTs and journals publishing such research have failed to comply with the calls for registration of trials. The rates of trial registration have been increasing over the last decade, but in any one year fewer than 50% of VLU trials have reported trial registration in the publication, despite the pressure for mandatory prospective registration by leading editorial groups.[7] [15] This is the only factor associated with adverse event reporting that can be modified by journal editors. Trials that were registered were also more than twice as likely to have had sufficient information for readers to assess important elements of internal validity (sequence generation and allocation concealment). We have previously argued that journals need to support trial registration to ensure that readers have sufficient information to make judgments about trials' quality [19]. However, most of the 76 journals publishing VLU trials were not listed on the ICMJE website as supporting trial registration, including seven of the ten journals that have published five or more trials.

The first simple improvement journal editors could take to provide for better trial reporting of adverse events would be to endorse trial registration and list the journal on the ICMJE website as supporting the same. However, passive measures alone, such as endorsement may be insufficient [19], and wound journal editors need to act collaboratively to promote trial registration for VLU trials and ensure compliance with the same. Other measures to improve adverse event reporting will be more complicated. Upstream, regulatory agencies could provide stronger guidance to researchers about what adverse events should be reported and how the data should be summarised. The forthcoming core outcomes report for VLU trials will hopefully also include discussion of adverse event reporting [20].

Finally, while the 2010 update of the CONSORT Statement and its

Table 2
Univariate and multivariate associations between trial characteristics and reporting all-cause or any adverse events.

	Univariate analysis						Multivariate analysis			
	Reported all-cause AE			Reported any AE			Reported all-cause AE		Reported any AE	
	Yes	No	P value	Yes	No	P value	Odds Ratio	P value	Odds Ratio	P value
	N (%)	N (%)		N (%)	N (%)		(95%CI)		(95%CI)	
Intervention										
Drug	25 (61.0)	57 (35.0)	0.002	58 (46.4)	24 (30.4)	0.023	4.2	0.0001	2.9	0.002
Other	16 (39.0)	111 (65.0)		67 (53.6)	55 (69.6)		(1.9-9.3)		(1.5-5.7)	
Multicentre										
Yes	30 (73.2)	68 (41.7)	0.0001	76 (60.8)	22 (27.8)	0.0001	4.0	0.001	4.2	0.0001
No	11 (26.8)	95 (58.3)		49 (39.2)	57 (72.2)		(1.7-9.1)		(2.2-8.1)	
Trial registered										
Yes	14 (34.1)	24 (14.7)	0.004	31 (24.8)	7 (8.9)	0.004	2.7	0.027	3.0	0.022
No	27 (65.9)	139 (85.3)		94 (75.2)	72 (91.1)		(1.1-6.7)		(1.1-7.9)	
Sample size[a]	92	60	0.001	82	52	0.002	1.0	0.152	1.0	0.233
	(55-210)	(39-104)		(42–126)	(34-88)		(0.9-1.0)		(0.9-1.0)	
5-Year JIF[a]	2.7	1.9	0.013	2.4	1.7	0.002	1.0	0.545	1.0	0.694
	(1.7-3.5)	(1.4-3.4)		(1.7-3.4)	(1.1-2.5)		(0.9-1.1)		(0.8-1.2)	
Funding Source										
Industry	21 (61.8)	54 (55.1)	0.499	58 (61.1)	17 (45.9)	0.116	–		–	
Not	13 (38.2)	44 (44.9)		37 (38.9)	20 (54.1)					
ICMJE Listed										
Yes	2 (4.9)	13 (8.0)	0.497	7 (5.6)	8 (10.1)	0.228	–		–	
No	33 (95.1)	150 (92.0)		118 (94.4)	71 (89.9)					

[a] Median (interquartile range).

attendant checklist included a reference to the 2004 extension on reporting of harms [4,21] the checklist still only makes reference to important harms rather than all harms. It is not at all clear what is meant by “important harms” and such ambiguity allows authors too much leeway in reporting or not reporting harms. Any future revision of the CONSORT Statement should consider recommending requiring all harms be reported rather than “important harms”.

3.1. Limitations

This review is subject to two main limitations. First, we only included English language reports and although it is best practice to not have language restrictions, language restrictions may not have an impact on conclusions they were once thought to have [22]. Second, we did not search trials registers to determine trial registration but relied on inclusion in the published report as required by the CONSORT Statement. It is, therefore, possible that journal policies and word limits may have had an impact on the content reported, a factor we could not account for in our analysis.

4. Conclusions

The approach to reporting adverse events in VLU trials is variable, with more than one third of the trials not reporting on adverse events at all. Multicentred trials, drug trials and registered trials are more likely to report adverse events. However, inadequate numbers of VLU trials are registered and journal editors should consider how they might assist the drive to ensure the registration of all RCTs.

Contributions

Author 1: Conceived the idea for the study, wrote the review protocol, screened titles, abstracts, and full-text articles for inclusion in the review, checked extracted data, reviewed and updated analyses, revised and finalised the completed paper.

Author 2: Screened titles, abstracts, and full-text articles, built the data collection form, extracted data, conducted initial descriptive analyses, and drafted the methods and results sections of the paper.

Declaration of competing interest

Author 1 has led two trials included in this review. We have no other conflicts to declare.

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Author 2 received a University of Auckland Summer Studentship in order to undertake the data collection for this review.

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