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ORIGINAL RESEARCH

Public availability of randomized clinical trial protocols: a repeated meta-research study

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Abstract

Objectives: Making protocols of randomized clinical trials (RCTs) publicly available is important for the trustworthiness and quality of medical research. In a previous study assessing 326 RCTs with ethical approval in 2012, only 36% had a publicly available protocol. We aimed to generate current evidence on the availability of RCT protocols and to evaluate changes over time.

Study Design and Setting: Using a representative sample of RCTs approved in 2016 in Switzerland, Canada, Germany, and the United Kingdom, we investigated the number of available protocols by searching PubMed, Google Scholar, trial registries, and Google. Up to June 2024, we systematically searched for (i) protocols available as peer-reviewed publications, (ii) protocols attached to trial registries, and (iii) protocols shared with result publications of RCTs. We used multivariable logistic regression to examine the association of protocol availability with trial characteristics such as sample size, drug vs nondrug interventions, multicenter vs single-center status, and RCT approval in 2016 vs 2012.

Results: Of the 347 included RCTs, 228 (66%) had an available protocol. Forty-three percent (150/347) of the protocols were available as files on trial registries, 26% (91/347) as supplementary material to result publication, and 23% (81/347) as peer-reviewed publications. Protocol availability improved over time in industry trials (83.4% in 2016 vs 34.6% in 2012). Protocol availability for nonindustry trials remained low (46.4% 2016 vs 38.1% 2012). Multicenter trials (206/256; 77.7% vs single-center trials 22/82; 26.8%) and larger sample size

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Ethics statement: Ethical approval was not required for this meta-research study.

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(>500 participants 68/77; 88.3%, 100-500 participants 131/191; 68.6%, <100 participants 29/79; 36.7%) showed higher protocol availability.

Conclusion: The availability of protocols increased in RCTs approved in 2016 compared to RCTs from 2012. This was mainly driven by industry sponsored trials. Efforts to further improve protocol availability should be continued, especially in nonindustry sponsored RCTs.

Keywords: Randomized controlled trial; Meta-research; Protocol; Trial protocol; Transparency

1. Introduction

Randomized clinical trials (RCTs) are the gold standard for causal inference and testing interventions in medical research. Each RCT needs an ethically approved protocol in which the objectives, design, methodology, and statistics of the trial are clearly prespecified [1]. However, many RCTs have methodological weaknesses, resulting in a substantial problem of misconduct and waste of resources in medical research [2]. Making RCT protocols publicly available is an accepted cornerstone to improve scientific transparency and counteract research waste [3]. Available protocols may improve research conduct on the following levels:

First, since results publications of RCTs often contain limited information, the corresponding protocols deliver important information on the methodology and conduct of the trial. This enables critical appraisal and interpretation of the results [4]. Protocols are a crucial requisite to perform a comprehensive risk of bias assessment, assure the internal validity of RCTs, and lay the foundation for solid evidence synthesis [5,6].

Second, available RCT protocols can prevent selective reporting of outcomes (also referred as ''outcome switching'' or ''cherry picking''), as well as retrospective changes in sample size justification or statistical analysis [7–9]. Selective reporting causes misleading results and biased estimates of single RCTs as well as of meta-analyses. Previous studies showed additional benefits of protocols compared to the information available on trial registries [10,11].

Third, trial protocols play a role in the applicability of trial results into clinical practice, for instance, by detailed reporting of the inclusion criteria and the tested intervention, information frequently missing in the result publication [12,13].

Finally, making the trial protocol publicly available also brings advantages for the trialists. They can refer to the protocol, which improves credibility and provides a basis for defending results to editors and reviewers [14].

Making trial protocols available is accepted as good research practice and part of the Consolidated Standards of Reporting Trials statement [15]. Several high impact journals require the publication (*NEJM* [16], *JAMA* [17], *The BMJ* [18], and *PLOS medicine* [19]) or submission (*The Lancet* [20,21] and *Annals of Internal Medicine* [22]) of protocols to publish result articles. Nevertheless, the protocol availability in our prior research was low [23]. Previously, we performed a study including a random sample of 326 RCTs approved in Switzerland, Germany, Canada, and the United Kingdom in 2012. We found that around one-third of all RCTs had an available protocol. Now, we perform an update of this study, using a similar sample of RCTs, approved in 2016, to investigate whether the proportion, the source, or the timing of publication of available protocols has changed in comparison to RCTs approved in 2012.

2. Methods

We report this study in accordance to the current Strengthening the Reporting of Observational studies in Epidemiology reporting guideline [24]. We closely followed the methods from our previous study to assess if the protocol availability has improved [25]. Detailed methods are available in our prospectively published protocol [26].

For this meta-research study, we used a sample of RCTs approved by ethics committees in Switzerland (all 7 ethics committees from Switzerland), Canada (the Hamilton Integrated Research Ethics Board), the United Kingdom (the Bristol office of the UK National Research Ethics Service), and Germany (University of Freiburg Medical Center Ethical Committee) in 2016 (Appendix section 1 for details). This sample was collected for two previous projects in which we assessed (i) the reporting quality of ethically approved RCT protocols (ie, the *Adherence to Spirit Recommendations Study* [ASPIRE]) before and after the publication of the Standard Protocol Items: Recommendations for Interventional Trials [27] statement in 2013 [28,29]; and (ii) evaluated what happened to these RCTs in terms of registration, premature discontinuation, and nonavailability of study results (paper in press). For this study, we excluded RCTs if they were still ongoing, were never started (information collected from ethics committees or from investigators), or were pilot or feasibility studies.

2.1. Search and data collection

Baseline characteristics for each RCT (trial design, sponsorship, drug vs nondrug trials, country, multicenter or single-center status, and planned sample size) were

What is new?

Key findings

- Two-thirds of randomized clinical trials (RCTs) approved in 2016 provided a publicly available protocol, which constitutes a substantial improvement compared to one-third of RCTs approved in 2012.
- This increase is mainly driven by the improved protocol availability in industry-sponsored trials making protocols available via trial registries.
- Industry sponsorship, larger sample size, and multicenter status were associated with increased protocol availability for RCTs.

What this adds to what is known

- First comparison of protocol availability over time with comparable methodology.

What is the implication and what should change now?

- Funders, regulators, and publishers could have a major role in enforcing regulations to improve protocol availability particularly in nonindustry sponsored trials.

extracted by the ASPIRE study team from RCT protocols approved by ethic committees in 2016 [28]. We defined "drug trials" as any RCTs assessing pharmaceuticals, including biologics and vaccinations.

For each RCT, we searched in duplicate for trial registrations and result publications. For trial registrations, we searched the World Health Organization International Clinical Trial Registry Platform database, ClinicalTrials.gov, the European Union Clinical Trial Registry, the International Standard Randomised Controlled Trial Number registry, and Google. For trial results, PubMed, Google Scholar, and Scopus were searched. At all sources we used the following strategies to conduct the search: (i) searching for full titles; (ii) short titles; (iii) study acronyms; and (iv) searching for the study population and intervention (with or without specifying the control group or name of the investigator if available).

In the next step, we searched in duplicate for the corresponding protocol for each RCT (last search June 2024). In brief, we searched PubMed, Google Scholar, and Google for RCT protocol publications. Furthermore, we checked all identified registry entries for attached protocols and examined if protocols were provided as supplementary material for all identified RCT result publications. We defined a protocol as a document that was labeled a protocol in a peer-reviewed article, in a file linked to a trial registry, or in the documentation of ethics committees. We excluded posters, abstracts, or short reports labeled as protocols.

We collected data regarding the start of the trial (start of recruitment), the type and source of available protocol (peer-reviewed, via registry, supplementary material), the date when the protocol was first publicly available, and the date of result publication. Moreover, we checked if available protocols were cited/linked in the result publication or indexed in the trial registry. All data collection was performed independently and in duplicate using REDCap (Vanderbilt University) [30,31]. Discrepancies were resolved by discussion and if needed, by a third reviewer.

2.2. Analysis

We summarized the characteristics of RCTs descriptively. We used medians/IQRs for continuous variables and frequencies/percentages for categorical variables.

To assess when the protocol was made available relative to the publication of the trial results (for RCT with published results), we calculated a relative time ratio (RTR) using the following formula:

$$RTR = \frac{\text{number of days from start of trial to protocol publication}}{\text{number of days from the start of trial to result publication}}$$

An RTR of <0 indicates that the protocol was published before the start of the trial, whereas an RTR >1 indicates that the protocol was made available after the publication of the results.

We used a multivariable regression model to investigate factors influencing the protocol availability (dependent variable). Independent variables were sample size (<100 [reference], 100-500, >500), sponsorship (industry vs non-industry [reference]), multicenter vs single-center trials (reference), and drug vs nondrug (reference) trials. The model output is presented as odds ratio (OR) with 95% CIs. This analysis was performed with trials approved in 2016 and with a pooled data set of trials approved in 2012 and in 2016. The models are specified in Appendix section 2.

For all analyses, we used R, (version 4.0.4; February 15, 2021) [32]. All used packages are referenced in the Appendix section 3.

3. Results

We included a total of 347 RCTs, approved in 2016 (see flow chart in the Appendix section 4). About half of the included RCTs were industry-sponsored trials (181/347; 52.2%), two-thirds investigated drugs (212/347; 61.1%), and the majority were multicenter trials (265/347; 76.4%) (Table 1). Most of the included RCTs had between 100

Table 1. Characteristics of included RCTs approved in 2016 and availability of protocols

RCT characteristics	All included RCTs (n = 347)	RCTs with publicly available protocol (n = 228)	RCTs without publicly available protocol (n = 119)
Sponsorship			
Industry	181 (52.2%)	151/181 (83.4%)	30/181 (16.6%)
Nonindustry	166 (47.8%)	77/166 (46.4%)	89/166 (53.6%)
Trial design			
Parallel	322 (92.8%)	217/322 (67.4%)	105/322 (32.6%)
Other[a]	25 (7.2%)	11/25 (44.0%)	14/25 (56.0%)
Drug vs nondrug intervention			
Drug	212 (61.1%)	163/212 (76.8%)	49/212 (23.2%)
Nondrug	135 (38.9%)	65/135 (48.1%)	70/135 (51.9%)
Single center vs multicenter			
Single center	82 (23.6%)	22/82 (26.8%)	60/82 (73.2%)
Multicenter	265 (76.4%)	206/265 (77.7%)	59/265 (22.3%)
RCT results publication available			
Yes	249 (71.8%)	189/249 (76.2%)	60/249 (24.1%)
No	99 (28.5%)	39/99 (39.4%)	59/99 (59.6%)
Number of participants			
<100	79 (22.8%)	29/79 (36.7%)	50/79 (63.3%)
100-500	191 (55.0%)	131/191 (68.6%)	60/191 (31.4%)
>500	77 (22.2%)	68/77 (88.3%)	9/77 (11.7%)
Country of ethical approval			
Canada	29 (8.4%)	22/29 (75.9%)	7/29 (24.1%)
Germany	33 (9.5%)	24/33 (72.7%)	9/33 (27.3%)
Switzerland	188 (54.2%)	109/188 (58.0%)	79/188 (42.0%)
The United Kingdom	97 (28.0%)	73/97 (75.3%)	24/97 (24.7%)

RCTs, randomized controlled trials.
[a] Crossover (n = 13), factorial (n = 5), cluster (n = 4), split body (n = 4).

and 500 participants (191/347; 55.0%). Out of 347 RCTs, 228 (65.7%) had a publicly available protocol (Table 1; Appendix section 5).

Most protocols were made available via a trial registry (150/347; 34.2%), followed by supplementary files with the RCT results publication (91/347; 26.2%) and protocols published as peer-reviewed publications (81/347; 23.3%). Industry-sponsored trials had a higher protocol availability (151/181; 83.4%) compared to nonindustry-sponsored trials (77/166; 46.4%). This was mainly driven by protocols published via trial registries (135/181; 74.6% industry-sponsored trials vs 15/166; 9.0% nonindustry-sponsored trials), whereas the nonindustry-sponsored trials had more peer-reviewed published protocols (31/181; 17.1%

Table 2. Type of available protocols stratified by sponsor for trials approved in 2016

Protocol availability	Industry sponsored RCTs (n = 181)	Nonindustry sponsored RCTs (n = 166)	Total RCTs (n = 347)
No protocol identified	30 (16.6%)	89 (53.6%)	119 (34.3%)
Protocol identified as	151 (83.4%)	77 (46.4%)	228 (65.7%)
File on a clinical trial registry	135 (74.6%)	15 (9.0%)	150[a] (43.2%)
Supplementary file to the result publication	61 (33.7%)	30 (18.1%)	91 (26.2%)
Peer-reviewed publication	31 (17.1%)	50 (30.1%)	81 (23.3%)
File on the trial website	5 (2.8%)	4 (2.4%)	9 (2.6%)
PDF file on Google Scholar	0	2 (1.2%)	2 (0.6%)
Other[b]	0	4 (1.2%)	4 (1.2%)

RCTs, randomized controlled trials.
[a] Source: ClinicalTrials.gov (n = 146), the International Standard Randomised Controlled Trial Number registry (n = 2), German Clinical Trials Register (Deutsches Register Klinischer Studien) (n = 1), Australian New Zealand Clinical Trials Registry (n = 1).
[b] Other: PDF on Google (n = 1), study protocol of the pilot RCT (n = 1), preprint (n = 1).

Table 3. Characteristics associated with protocol availability (multivariable logistic regression) in RCTs approved in 2016

Characteristics	Protocol available (n = 228)	Protocol not available (n = 119)	OR	95% CI	P value
Sample size <100	29 (12.7%)	50 (42.0%)	Reference		
Sample size 100-500	131 (57.5%)	60 (50.4%)	2.36	1.25-4.43	0.008
Sample size >500	68 (29.8%)	9 (7.6%)	6.00	2.39-15.06	<0.001
Multicenter (vs single center)	206 (90.4%)	59 (49.6%)	3.17	1.61-6.24	0.001
Nonindustry (vs industry)	77 (33.8%)	89 (74.8%)	0.37	0.20-0.68	0.002
Drug (vs nondrug)	163 (71.55)	49 (41.2%)	1.45	0.81-2.60	0.216

RCT, randomized controlled trial, OR, odds ratio.

industry-sponsored trials vs 50/166; 30.1% nonindustry-sponsored trials; Table 2). The protocol availability was higher for RCTs approved in 2016 compared to our previous sample from 2012, where 118 out of 327 (36.2%) had a publicly available protocol (see Appendix section 6) [26]. This increase was caused by a higher proportion of protocols in trial registries (2012: 13/326; 4.0% vs 2016: 150/347; 43.2%) and peer-reviewed protocol publications (2012: 56/326; 17.2% vs 2016: 81/347; 23.3%; Appendix section 7).

Available protocols from the 2016 sample were more often linked to the trial registry (196/228 [86.0%] vs 66/118 [55.9%]) but less often linked to the trial result publication (140/228 [61.4%] vs 100/118 [84.7%]) (Appendix section 8). Our multivariable logistic regression analysis of the 2016 RCT sample showed that medium (100-500 participants) and larger (>500 participants) sample sizes as well as multicenter status and industry sponsorship were associated with increased odds of protocol availability (Table 3). In contrast, in the 2012 RCT sample, nonindustry-sponsored trials showed higher odds of having an available protocol (Appendix section 9). In a regression model with pooled data from trials approved in 2012 and 2016, medium (100-500 participants; OR: 2.12; 95% CI 1.32-3.43; P = .001) and larger (>500 participants; OR: 6.12; 95% CI 3.45-11.07; P < .001) sample size, and multicenter trials (vs single-center trial; OR: 2.66; 95% CI 1.59-4.52; P < .001) showed significantly higher odds of having an available protocol (Appendix section 10, 11, 12).

Figure shows the relative time point of protocol availability. About half of all protocols (74/140; 52.9) were made available before the publication of the results and about one-third (48/140; 34.3%) were made available together with the RCT result publication (RTR = 1). On average, nonindustry-sponsored trials made the protocols available earlier than industry-sponsored trials. Some protocols of industry-sponsored RCTs (18/140; 12.9%) were made available after the publication of the main results. No protocol was published before the start of recruitment. We conducted a sensitivity analysis for the RTR, excluding protocols only available as supplementary material to RCT result publication (Appendix section 13).

4. Discussion

Our study showed that about two-thirds of RCTs approved in 2016 had a publicly available protocol, representing a substantial increase compared to the 36% observed in RCTs approved in 2012 [25]. The increased number of available protocols is mainly driven by available protocols of industry-sponsored trials (2012: 37% vs 2016: 83%). In contrast, the number of available protocols in nonindustry-sponsored trials increased only marginally (2012: 38% vs 2016: 46%).

Publishing protocols via trial registries have replaced peer-reviewed protocol publications and protocols published as a supplement with the trial results as the preferred way to make protocols available. This has been mainly driven by industry-sponsored trials, making 75% of trial protocols available on a trial registry for RCTs approved in 2016 compared to 6% for RCTs approved in 2012. For nonindustry trials, peer-reviewed publications remained the most common source for sharing trial protocols (approximately 30% for RCTs approved in 2012 and 2016). Compared to industry, academic trialists might be more interested in generating additional publications. However, making protocols available via the trial registries offers multiple advantages. It is free of charge, enables uploading original ethical-approved protocol documents with time stamp (also for possible amendments), and does not incur common delays and extra efforts associated with peer-reviewed publication. Compared to protocols published together with the trial results, protocols published in registries can be shared at the beginning of the trial, which is important to counteract research waste and selective reporting effectively.

Since January 2017, the US government requires all trials investigating drugs or devices which are or are intended to be approved, licensed, or cleared by the US Food and Drug Administration to have a publicly available protocol [33]. These trials, precisely defined as "applicable clinical trials" [34], must upload a protocol within 12 months after completion of data collection for the primary outcome to ClinicalTrials.gov. This policy change may explain, at least in part, the increase in publicly available protocols of

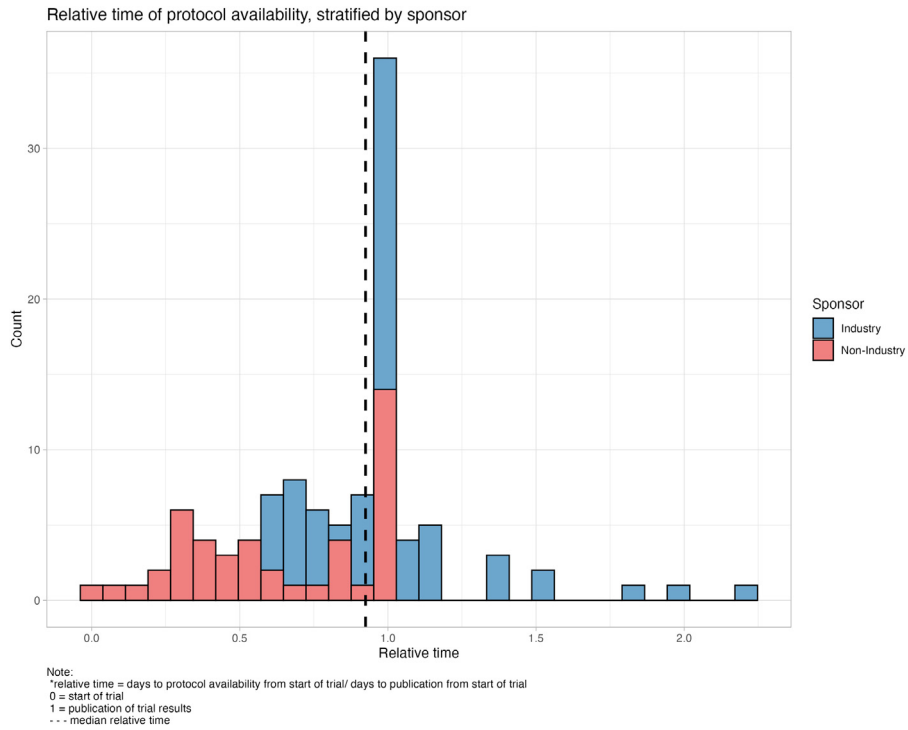

Figure. Relative time ratio of protocol availability. Relative time = days to protocol availability from start of the trial/days to publication from the start of the trial. 0, start of the trial and 1, publication of trial results. —, median relative time.

industry-sponsored trials approved in 2016 because many of them fell under this obligation. As nonindustry sponsors rarely conduct drug approval studies, this policy change might not have had the same impact on nonindustry trials.

To further increase the protocol availability in nonindustry-funded trials, similar regulations from other stakeholders (eg, protocol publication as prerequisite for funding and publication, similar to trial registration) might be needed [2]. For instance, since 2017, the National Institute of Health (NIH), the world's biggest funding agency, has required that all NIH-funded RCTs publish the protocol via ClinicalTrials.gov [35]. Although it became more common to share trial protocols on ClinicalTrials.gov, we think the potential of other registries is still largely unused. A first step was taken by the European Medicines Agency, which, since 2023, has required that all trials make their protocols available via the new Clinical Trials Information System registry [36].

Evidence from other studies on this topic is limited. A recent study reported lower protocol availability (24.8%, 146/589), but they excluded protocols available via registries [37]. Spence et al found high protocol availability (82%, 299/354) among RCTs published in high impact journals in 2016 [38]. Similar findings were produced by Campbell et al, also focusing on RCTs published in high impact journals in 2018 [11]. These findings are in-line with our data and can be explained by the policies of these journals. In studies assessing protocol availability not restricted to high impact journal, the protocol availability was low ranging from 15% to 36% [11,23,39–42]. All these studies were conducted before 2020, making them comparable to the findings observed in our RCT sample approved in 2012.

This is the first study investigating the availability of trial protocols at two time points in a representative sample. We obtained our RCT sample directly from ethic committees and did not rely on published trials, which was the approach of the aforementioned studies. Our study has the following limitations: First, our sample of RCTs received ethical approval in 2016. Hence, it is possible that protocol availability rates might have further changed when assessing a more recent sample. However, using a sample from 2016 enabled us to evaluate all potential sources of protocol availability, including those published as appendices alongside main trial results, and to determine at what time point protocols are made available. Second, within this study, we did not assess the quality of available protocols. Incomplete protocols or protocols with blacked out key parts undermine the role of publicly available protocols in transparent research [43,44]. Third, we included trials from four high-income countries. This may limit the generalizability of our findings.

In conclusion, we observed improved availability of RCT protocols over the last years, particularly among industry-sponsored trials. However, further efforts are needed to enhance the protocol availability for nonindustry RCTs. Funding bodies, ethics committees, and governmental authorities could be instrumental in facilitating this process.

CRediT authorship contribution statement

Christof Manuel Schönenberger: Writing − original draft, Visualization, Project administration, Methodology, Formal analysis, Data curation, Conceptualization. **Malena Chiaborelli:** Writing − review & editing, Data curation. **Ala Taji Heravi:** Data curation. **Lukas Kübler:** Data curation. **Pooja Gandhi:** Conceptualization. **Zsuzsanna Kontár:** Data curation. **Julia Hüllstrung:** Writing − review & editing, Data curation. **Mona Elalfy:** Data curation. **Jan Glasstetter:** Writing − review & editing, Data curation. **Dmitry Gryaznov:** Data curation. **Belinda von Niederhäusern:** Data curation. **Anette Blümle:** Writing − review & editing, Data curation. **Jason W. Busse:** Data curation. **Szimonetta Lohner:** Writing − review & editing, Data curation. **Sally Hopewell:** Data curation. **Alexandra Griessbach:** Data curation, Conceptualization. **Matthias Briel:** Writing − review & editing, Supervision, Resources, Funding acquisition, Conceptualization. **Benjamin Speich:** Writing − review & editing, Supervision, Methodology, Conceptualization.

Declaration of competing interest

C.M.S. received a travel grant from Gilead Science for another project not related to this work. B.S. and M.B. received unrestricted grants from Moderna (2021/22) for the conduct of the COVERALL-2 and COVERALL-3 study (unrelated to this project). B.S. has received honoraria from Moderna and Roche for presenting study results not related to this work. There are no competing interests for any other author.

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Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.jclinepi.2025.111865.

Data availability

The data that has been used is confidential.

References

[1] ICH E6 (R2) Good clinical practice - scientific guideline. Available at: https://www.ema.europa.eu/en/ich-e6-r2-good-clinical-practice-scientific-guideline. Accessed December 15, 2016.

[2] Ioannidis JPA, Greenland S, Hlatky MA, Khoury MJ, Macleod MR, Moher D, et al. Increasing value and reducing waste in research design, conduct, and analysis. Lancet 2014;383(9912):166−75. https://doi.org/10.1016/S0140-6736(13)62227-8.

[3] Chan A-W, Hróbjartsson A. Promoting public access to clinical trial protocols: challenges and recommendations. Trials 2018;19(1):116. https://doi.org/10.1186/s13063-018-2510-1.

[4] Chan A-W, Song F, Vickers A, Jefferson T, Dickersin K, Gøtzsche PC, et al. Increasing value and reducing waste: addressing inaccessible research. Lancet 2014;383(9913):257−66. https://doi.org/10.1016/S0140-6736(13)62296-5.

[5] Jørgensen L, Paludan-Müller AS, Laursen DRT, Savović J, Boutron I, Sterne JAC, et al. Evaluation of the Cochrane tool for assessing risk of bias in randomized clinical trials: overview of published comments and analysis of user practice in Cochrane and non-Cochrane reviews. Syst Rev 2016;5(1):80. https://doi.org/10.1186/s13643-016-0259-8.

[6] Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ 2019;366:l4898. https://doi.org/10.1136/bmj.l4898.

[7] Chan AW, Pello A, Kitchen J, Axentiev A, Virtanen JI, Liu A, et al. Association of trial registration with reporting of primary outcomes in protocols and publications. JAMA 2017;318(17):1709−11. https://doi.org/10.1001/jama.2017.13001.

[8] Chan A-W, Hróbjartsson A, Jørgensen KJ, Gøtzsche PC, Altman DG. Discrepancies in sample size calculations and data analyses reported in randomised trials: comparison of publications with protocols. BMJ 2008;337:a2299. https://doi.org/10.1136/bmj.a2299.

[9] van den Bogert CA, Souverein PC, Brekelmans CTM, Janssen SWJ, Koëter GH, Leufkens HGM, et al. Primary endpoint discrepancies were found in one in ten clinical drug trials. Results of an inception cohort study. J Clin Epidemiol 2017;89:199−208. https://doi.org/10.1016/j.jclinepi.2017.05.012.

[10] Perlmutter AS, Tran VT, Dechartres A, Ravaud P. Statistical controversies in clinical research: comparison of primary outcomes in protocols, public clinical-trial registries and publications: the example of oncology trials. Ann Oncol 2017;28(4):688−95. https://doi.org/10.1093/annonc/mdw682.

[11] Campbell D, McDonald C, Cro S, Jairath V, Kahan BC. Access to unpublished protocols and statistical analysis plans of randomised trials. Trials 2022;23(1):674. https://doi.org/10.1186/s13063-022-06641-x.

[12] Blümle A, Meerpohl JJ, Rücker G, Antes G, Schumacher M, von Elm E. Reporting of eligibility criteria of randomised trials: cohort study comparing trial protocols with subsequent articles. BMJ 2011;342:d1828. https://doi.org/10.1136/bmj.d1828.

[13] Hoffmann TC, Erueti C, Glasziou PP. Poor description of non-pharmacological interventions: analysis of consecutive sample of randomised trials. BMJ 2013;347:f3755. https://doi.org/10.1136/bmj.f3755.

[14] Peat G, Riley RD, Croft P, Morley KI, Kyzas PA, Moons KG, et al. Improving the transparency of prognosis research: the role of reporting, data sharing, registration, and protocols. PloS Med 2014;11(7):e1001671. https://doi.org/10.1371/journal.pmed.1001671.

[15] Schulz KF, Altman DG, Moher D. CONSORT 2010 statement: updated guidelines for reporting parallel group randomized trials. Ann Intern Med 2010;152(11):726−32. https://doi.org/10.7326/0003-4819-152-11-201006010-00232.

[16] Medicine NEJo. Submission guidlines. Available at: https://www.nejm.org/author-center/new-manuscripts Accessed May 2025.

[17] Association JoAM. Instructions for authors. Available at: https://jamanetwork.com/journals/jama/pages/instructions-for-authors. Accessed May 8, 2025.

[18] BMJ submission guidlines. Available at: https://www.bmj.com/about-bmj/resources-authors/article-types. Accessed May 8, 2025.

[19] Medicine P. Submission guidlines. Available at: https://journals.plos.org/plosmedicine/s/submission-guidelines.Accessed2Jan2018. Accessed May 8, 2025.

[20] Lancet infomration for authors. Available at: https://www.thelancet.com/pb-assets/Lancet/authors/tl-info-for-authors-1740074875577.pdf. Accessed May 8, 2025.
[21] McNamee D, James A, Kleinert S. Protocol review at the Lancet. Lancet 2008;372(9634):189−90. https://doi.org/10.1016/S0140-6736(08)61053-3.
[22] Medicine AoI. Author information. Available at: https://www.acpjournals.org/journal/aim/authors. Accessed May 8, 2025.
[23] Sender D, Clark J, Hoffmann TC. Analysis of articles directly related to randomized trials finds poor protocol availability and inconsistent linking of articles. J Clin Epidemiol 2020;124:69−74. https://doi.org/10.1016/j.jclinepi.2020.04.017.
[24] von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Ann Intern Med 2007;147(8):573−7. https://doi.org/10.7326/0003-4819-147-8-200710160-00010.
[25] Schönenberger CM, Griessbach A, Taji Heravi A, Gryaznov D, Gloy VL, Lohner S, et al. A meta-research study of randomized controlled trials found infrequent and delayed availability of protocols. J Clin Epidemiol 2022;149:45−52. https://doi.org/10.1016/j.jclinepi.2022.05.014.
[26] Schönenberger CMGA, Taji HA, Amstutz A, Speich B, Briel M, ASPIRE Research Group. The availability of randomized controlled trial protocols and the timing for their accessibility: A protocol for a meta-research study extension. Available at: https://osf.io/zvjb7/?view_only=. Accessed June 26, 2025.
[27] Chan AW, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleza-Jerić K, et al. SPIRIT 2013 statement: defining standard protocol items for clinical trials. Ann Intern Med 2013;158(3):200−7. https://doi.org/10.7326/0003-4819-158-3-201302050-00583.
[28] Gryaznov D, von Niederhäusern B, Speich B, Kasenda B, Ojeda-Ruiz E, Blümle A, et al. Reporting quality of clinical trial protocols: a repeated cross-sectional study about the Adherence to SPIrit Recommendations in Switzerland, Canada and Germany (ASPIRE-SCAGE). BMJ Open 2022;12(5):e053417. https://doi.org/10.1136/bmjopen-2021-053417.
[29] Gryaznov D, Odutayo A, von Niederhäusern B, Speich B, Kasenda B, Ojeda-Ruiz E, et al. Rationale and design of repeated cross-sectional studies to evaluate the reporting quality of trial protocols: the Adherence to SPIrit REcommendations (ASPIRE) study and associated projects. Trials 2020;21(1):896. https://doi.org/10.1186/s13063-020-04808-y.
[30] Harris PA, Taylor R, Minor BL, Elliott V, Fernandez M, O'Neal L, et al. The REDCap consortium: building an international community of software platform partners. J Biomed Inform 2019;95:103208. https://doi.org/10.1016/j.jbi.2019.103208.
[31] Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)–a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform 2009;42(2):377−81. https://doi.org/10.1016/j.jbi.2008.08.010.
[32] Team RC. R: a language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing. Available at: https://www.R-project.org/. Accessed June 26, 2025.
[33] Department HaHS. Clinical Trials Registration and Result Information Submission. Washington DC: Department of Health and Human Services; 2016. Available at: https://www.federalregister.gov/documents/2016/09/21/2016-22129/clinical-trials-registration-and-results-information-submission. Accessed June 26, 2025.
[34] Medicine NLo. Support and training materials. Available at: https://clinicaltrials.gov/submit-studies/prs-help/support-training-materials#FinalRuleWebinar. Accessed May 2, 2025.
[35] Zarin DA, Tse T, Williams RJ, Carr S. Trial reporting in ClinicalTrials.gov — the final rule. New Engl J Med 2016;375(20):1998−2004. https://doi.org/10.1056/NEJMsr1611785.
[36] Bruckner T. EMA will no longer allow pharma companies to keep clinical trial protocols secret. Available at: https://www.transparimed.org/single-post/revised-ctis-transparency-rules. Accessed June 26, 2025.
[37] Mathieu S, Bouillon-Minois JB, Renard Triché L, Coudeyre E, Ingrid C, Thomas F, et al. Protocol publication rate and comparison between article, registry and protocol in RCTs. BMC Med Res Methodol 2025;25(1):31. https://doi.org/10.1186/s12874-025-02471-y.
[38] Spence O, Hong K, Onwuchekwa Uba R, Doshi P. Availability of study protocols for randomized trials published in high-impact medical journals: a cross-sectional analysis. Clin Trials 2020;17(1):99−105. https://doi.org/10.1177/1740774519868310.
[39] Lucey M, Clark J, Glasziou P. Public availability of trial protocols. Lancet 2017;390(10113):e54−5. https://doi.org/10.1016/S0140-6736(17)33255-5.
[40] Coskinas X, Simes RJ, Martin AJ. Changes to design and analysis elements of research plans during randomised controlled trials in Australia. Med J Aust 2022;217(10):526−31. https://doi.org/10.5694/mja2.51715.
[41] Kahan BC, Ahmad T, Forbes G, Cro S. Public availability and adherence to prespecified statistical analysis approaches was low in published randomized trials. J Clin Epidemiol 2020;128:29−34. https://doi.org/10.1016/j.jclinepi.2020.07.015.
[42] Babu C, Mell L, Lee N, Zakeri K. Public access to protocols of contemporary cancer randomized clinical trials. Trials 2021;22(1):418. https://doi.org/10.1186/s13063-021-05382-7.
[43] Balaban N, Mohyuddin GR, Kashi A, Massarweh A, Markel G, Bomze D, et al. Projecting complete redaction of clinical trial protocols (RAPTURE): redacted cross sectional study. BMJ 2023;383:e077329. https://doi.org/10.1136/bmj-2023-077329.
[44] Lohner S, Gryaznov D, von Niederhäusern B, Speich B, Kasenda B, Ojeda-Ruiz E, et al. Reporting quality of trial protocols improved for non-regulated interventions but not regulated interventions: a repeated cross-sectional study. J Clin Epidemiol 2021;139:340−9. https://doi.org/10.1016/j.jclinepi.2021.05.011.