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ORIGINAL ARTICLE

A meta-research study of randomized controlled trials found infrequent and delayed availability of protocols

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Abstract

Objectives: Availability of randomized controlled trial (RCT) protocols is essential for the interpretation of trial results and research transparency.

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Study Design and Setting: In this study, we determined the availability of RCT protocols approved in Switzerland, Canada, Germany, and the United Kingdom in 2012. For these RCTs, we searched PubMed, Google Scholar, Scopus, and trial registries for publicly available protocols and corresponding full-text publications of results. We determined the proportion of RCTs with (1) publicly available protocols, (2) publications citing the protocol, and (3) registries providing a link to the protocol. A multivariable logistic regression model explored factors associated with protocol availability.

Results: Three hundred twenty-six RCTs were included, of which 118 (36.2%) made their protocol publicly available; 56 (47.6% 56 of 118) provided as a peer-reviewed publication and 48 (40.7%, 48 of 118) provided as supplementary material. A total of 90.9% (100 of 110) of the protocols were cited in the main publication, and 55.9% (66 of 118) were linked in the clinical trial registry. Larger sample size (>500; odds ratio [OR] = 5.90, 95% confidence interval [CI], 2.75−13.31) and investigator sponsorship (OR = 1.99, 95% CI, 1.11−3.59) were associated with increased protocol availability. Most protocols were made available shortly before the publication of the main results.

Conclusion: RCT protocols should be made available at an early stage of the trial.

Keywords: Randomized controlled trials; Trial protocols; Trial registration; Protocol publication; Meta-research; Transparency

1. Introduction

Randomized controlled trials (RCTs) are important for clinical decision-making [1], and publicly available protocols help ensure consistency of trial processes, ethical conduct, transparency, and valid research results [2,3]. The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use Good Clinical Practice guidelines require every protocol to be reviewed and approved by an ethics committee before enrollment of the first patient [4], and making protocols publicly available has been promoted as good research practice over the last decade [5].

Previous research has investigated the importance of making protocols available to the public [6−9]. Protocol availability increases research quality on account of detailed consideration of methodological procedures [10]. Moreover, protocols contain additional information which aids with the interpretation of study results and reduces bias, by predetermining outcomes and reducing selective outcome reporting ("cherry-picking") and outcome switching [2,8,9,11−13]. Publishing and making protocols publicly available may reduce misreporting of results, improve the design of future trials, increase transparency, and promote ethical compliance [11,14−18]. These benefits are even more substantial if protocol availability precedes the reporting of trial results. Timely availability of protocols informs researchers about the original intent of the study and if this intent was maintained during conduct [19]. This is especially important since changes in outcomes and conflation between exploratory vs. confirmatory purposes (hypothesis generation and hypothesis testing) are common [19,20], lead to bias [19,21], and are known to inflate the type I error rate and contribute to the replication crisis [19]. Later versions of protocols may not reflect the original purpose of the study. Finally, timely availability of protocols provides investigators with greater confidence in their statistical inference [13,19,22,23].

Although the benefits of making protocols publicly available are well established, data quantifying their availability and the timing of their availability are limited to three studies [6,24,25]. Sender et al. [6] primarily focused on nonpharmacologic trials, Lucey et al. [24] only included RCTs that were submitted to the Lancet, and Spence et al. [25] only included RCTs whose results were only published in high-impact journals [25]. Overall, there is limited generalizability concerning these findings [6,24].

In this study, we aimed to determine the proportion of publicly available protocols, as well as the timing of their availability, from a random sample of RCTs approved by ethics committees in Switzerland, Germany, Canada, and the United Kingdom in 2012 [26]. Moreover, we determined the public source of the protocols, if they were cited by the corresponding main publication, and if they were referenced in a clinical trial registry. Finally, we investigated factors associated with increased protocol availability in a multivariable logistic regression model.

2. Methods

Our study sample was derived from a previous study (Adherence to Spirit Recommendations Study [ASPIRE]) and included a random convenience sample of RCTs approved by ethics committees in Switzerland (Basel, Bellinzona, Bern, Geneva, Lausanne, St. Gallen, and Thurgau), Canada (Hamilton), the United Kingdom (the Bristol office of the UK National Research Ethics Service responsible for 19 research ethics committees in the United Kingdom), and Germany (Freiburg) in 2012 (see supplementary material for more details) [26]. In a substudy of the ASPIRE project (DISContinued trials II [DISCO II]), we assessed the proportion of RCTs that were nonregistered, discontinued, and unpublished 10 years after ethical approval [27]. For DISCO II, we excluded RCTs if they were still ongoing, were never started (information collected from ethics committees or from investigators), or were identified as pilot or feasibility studies (see the flow diagram in supplementary

What is new?

Key findings

- One-third of RCTs provided a publicly available protocol; greater availability was associated with investigator sponsorship and larger sample size.
- Protocols were typically made available shortly before the publication of RCT results.
- Protocols of investigator-sponsored trials were made available earlier than those of industry-sponsored trials.
- Only about half of the clinical trials registry entries provided a link to the corresponding protocol.

What this adds to what was known?

- Overall poor availability of protocols in a representative sample.
- Multivariable regression model analysing factors associated with increased protocol availability.

What is the implication and what should change now?

- RCT protocols should be made available through clinical trial registries and mandatory requirements by journals.

material). Building on this sample, we assessed the proportion of study protocols that were made publicly available and at what time point over the course of the trial.

2.1. Data collection

Baseline characteristics such as trial design, sponsorship, intervention type, country, multicenter or single-center status, and planned sample size were extracted by the ASPIRE research team for each RCT from study protocols approved by research ethics boards [26].

The search for trial registration and publications of results is described in detail in the DISCO II study [27]. In brief, we searched the World Health Organization International Clinical Trials Registry Platform, ClinicalTrials.gov, the European Union Clinical Trial Registry, International Standard Randomised Controlled Trial Number registry, and the Google search engine to identify trial registration details. We searched PubMed, Google Scholar, and Scopus for publication of trial results. Both searches were conducted in duplicate and included searching for (i) full titles, (ii) short titles, (iii) study acronyms, and (iv) the study population and intervention (with or without adding the control group).

The corresponding study protocols and publications of primary results were identified through screening of trial registries, PubMed, Google Scholar, and Scopus using the same search strategy. We also reviewed trial registries to identify protocols that were linked or made available as a separate file. For all trial publications retrieved, we searched for the corresponding protocol by screening the citations and supplementary material. A protocol was defined as a document containing the essential items of the Standard Protocol Items: Recommendations for Interventional Trials guideline; however, we did not examine the completeness or quality protocols. All searches and data extractions were conducted independently and in duplicate by pairs of trained reviewers. Disagreements between investigators were resolved by discussion to achieve consensus. All searches were conducted up to February 2022.

For each RCT, we extracted the start date of the trial from the registry, which was determined as the date of first patient enrollment, the format of the available protocols (i.e., as peer-reviewed publication, supplementary material to the primary result publication, Portable Document Format available in the trial registry, or other), and the date of publication for both the protocol and publication of primary results. We assumed the availability date was equal to that of the published primary results when protocols were made available as supplementary material, expect when previously published protocols were identified. If a protocol was available as both a peer-reviewed publication and supplementary material, we coded the format as ''peer-reviewed publication.'' Finally, we documented whether available protocols were cited in the publication of primary results or found (linked) in a clinical trial registry.

2.2. Analysis

We summarized characteristics of included RCTs using the median and interquartile range (IQR) for continuous variables and numbers accompanied by percentages for categorical variables. We produced a multivariable logistic regression model (including calculation of odds ratio, 95% confidence intervals, and P values), in which the dependent variable was protocol availability, and the independent variables were sample size (<100, $100-500$, >500), sponsorship (industry vs. investigator), multicenter vs. single-center trials, and drug vs. nondrug interventions.

We determined the time point the protocol was made available during the trial by calculating the relative time ratio (RTR) as follows:

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

Table 1. Characteristics of included RCTs and protocol availability

Trial characteristics	All included RCTs	RCTs with a publicly available protocol
All ethically approved RCTs from our sample	326 (100%)	118/326 (36.2%)
Sponsorship		
Investigator -sponsored	147 (45.1%)	56/147 (38.1%)
Industry -sponsored	179 (54.9%)	62/179 (34.6%)
Study designs		
Parallel -arm	296 (90.8%)	109/296 (36.8%)
Factorial	10 (3.1%)	6/10 (60.0%)
Cluster	4 (1.2%)	3/4 (75.0%)
Others[a]	16 (4.9%)	0/16 (0%)
Drug vs. non-drug		
Drug	207 (63.5%)	77/207 (37.2%)
Non-drug	119 (36.5%)	41/119 (34.5%)
Single-center or multicenter		
Single-center	60 (18.4%)	12/60 (20.0%)
Multicenter	266 (81.6%)	106/266 (39.8%)
National	67 (25.2%)	27/67 (40.3%)
International	199 (74.8%)	79/199 (39.6%)
Number of participants		
<100	73 (22.4%)	14/73 (19.2%)
100–500	151 (46.3%)	45/151 (29.8%)
>500	102 (31.3%)	59/102 (57.8%)
Country of ethical approval		
Switzerland	165 (50.6%)	54/165 (32.7%)
United Kingdom	89 (27.3%)	35/89 (39.3%)
Germany	37 (11.3%)	9/37 (24.3%)
Canada	35 (10.7%)	20/35 (57.1%)
Registration		
Registered	306 (93.9%)	118/306 (38.6%)
Not registered	20 (6.1%)	0/20 (0%)
Results availability		
Full text publication of primary results available	256 (78.5%)	110/256 (43.0%)
Primary results available as conference abstract and poster	8 (2.5%)	0/8 (0%)
Primary results not available	62 (19.0%)	8/62 (12.9%)

Abbreviations: RCT, randomized controlled trial.
[a] Others: crossover, split body, and unsure.

The start of the trial was defined as the date of first patient enrollment, which was extracted from the registry entry. The dates of availability for protocols and publications were extracted from the journal in the case of published protocols and results (date available online) and from the clinical trial registry or website for non–peer-reviewed sources. An RTR of <0 indicates the protocol was published before the start of the trial, whereas an RTR >1 indicates the protocol was made available after the publication of the primary results. We conducted a sensitivity analysis for the RTR excluding protocols that were only available as supplementary material (see appendix). A P value of 0.05 was considered statistically significant for all analyses. We used R, version 1.4.1103, for all data management and analyses.

3. Results

We included 326 RCTs in this study (see the flow diagram in supplementary material). The median number of participants was 262 (IQR = 100–600).

Approximately half of the trials were industry initiated (179 of 326; 54.9%), the majority were multicenter studies (266 of 326; 81.6%), and most used a parallel group study design (296 of 326; 90.8%) (Table 1).

For the 326 included RCTs, we identified 118 (36.2%) publicly available protocols. Most were available as peer-reviewed publications (56 of 118; 47.5%) or as a supplementary file with the primary results (48 of 118; 40.7%) (Table 2). When available, 90.9% (100 of 110) of the protocols were referenced by the primary result publication:

Table 2. Forms of protocol availability and whether they were linked in a trial registry

Availability	*N* (%)
Total number of protocols available	118 (36.2%)
Protocol as peer-reviewed publication	56/118 (47.5%)
Protocol as a supplementary file with the primary result publication	48/118 (40.7%)
PDF on a trial registry	12/118 (10.2%)
Other type of protocol availability[b]	2/118 (1.7%)
Protocol linked[a]	
Protocol linked as PDF in a clinical trial registry	66/118 (55.9%)
Protocol linked in result publication[c]	100/110 (90.9%)
Protocols without publication	8/118 (6.8%)

Abbreviations: PDF, Portable Document Format.

Supplementary material protocols by journal: The New England Journal of Medicine = 27 of 48 (56.3%), The Lancet Oncology = 6 of 48 (12.5%), Journal of mAmerican Medical Association = 3 of 48 (6.3%), Journal of Clinical Oncology = 3 of 48 (6.3%), and other = 9 of 48 (18.8%).

[a] Protocols can be linked to both the registry and the publication of results (n = 50).

[b] 2 as PDF on Google scholar or website.

[c] 118 (total number of protocols) −8 (protocols available without publication) = 110 available publications.

55.9% (66 of 118) of available protocols were provided through a link in a clinical trial registry.

Larger sample size (n > 500) and investigator-sponsored trials were associated with increased odds of protocol availability (Table 3). Increased sample size showed evidence for a dose effect, in which each category was associated with an increased proportion of available protocols. The availability of study protocols between drug and nondrug trials was comparable between groups. Among the 118 publicly available protocols, 31 (26.3%) corresponded to trials published in Journal of American Medical Association (JAMA) and New England Journal of Medicine (NEJM) which require protocols to be included with all trial submissions (although 1 trial in JAMA did not provide a protocol). The remaining 88 (74.6%) protocols were associated with trials published in journals that do not require investigators to include a protocol with their trial submission.

Most protocols (101 of 110, 91.8%) were available after the start of the trial (i.e., after the enrollment of the first patient; RTR >0). Only 1 protocol (1 of 110, 0.9%) was made available before enrollment of the first patient (RTR <0), and 2.7% of trial protocols (3 of 110) were made available after publication of the primary results (RTR >1). Protocols were typically made available shortly before publication of the primary results of the RCT (median RTR = 0.90 [IQR = 0.43, 1.00]) but were made available earlier in investigator-sponsored trials (Fig. 1, Table 4). Results from our sensitivity analysis show that industry trials often make their protocols available later as supplementary material (see appendix).

4. Discussion

This meta-research study determined that protocols were only made publicly available for about a third of RCTs in our sample. Larger sample size and investigator sponsorship were associated with increased odds of protocol availability. Moreover, protocols were typically made available shortly before the publication of the primary results, and most industry-initiated trials only made their protocols available at the same time as publication of trial results.

Previous research corroborates our results of low protocol availability with a similar proportion found in a study of nonpharmacological RCTs (48 of 133, 36.1%) [6]. In another study examining 261 manuscripts submitted to The Lancet, 250 trials (96%) included a protocol with their submission; however, only 36% made the protocol publicly available (95 of 261, 36%) [24]. Contrary to our findings, Spence et al. determined much higher protocol availability (299 of 364, 82%) in a sample of RCTs published in the top five general medicine journals [25]. The availability of study protocols varied depending on the journal, ranging from 50% (8 of 16) in British Medical Journal (required by the journal to make protocol available since September 2014 [28]) and more than 95% in NEJM and JAMA [25]. NEJM (since September 2012 [29]) and JAMA (date unclear) require investigators to make their protocols available in order to publish the primary results in the journal. Considering that only one RCT in our sample published

Table 3. Trial characteristics associated with protocol availability in logistic regression

Characteristics[a]	Available (n = 118)	Not available (n = 208)	Univariable			Multivariable		
			OR	95% CI	*P* value	OR	95% CI	*P* value
Sample size <100	14 (11.9%)	59 (28.4%)	Reference			Reference		
100–500	45 (38.1%)	106 (51.0%)	1.79	0.93–3.63	0.093	1.83	0.91–3.83	0.09
>500	59 (50%)	43 (20.7%)	5.78	2.93–12.02	<0.001	5.90	2.75–13.31	<0.001
Multicenter (vs. single center)	106 (89.8%)	160 (76.9%)	2.65	1.38–5.44	0.005	2.01	0.92–4.62	0.087
Investigator (vs. industry) sponsorship	56 (47.5%)	91 (43.8%)	1.16	0.74–1.83	0.518	1.99	1.11–3.59	0.021
Drug (vs. non-drug) intervention	77 (65.3%)	130 (62.5%)	1.13	0.71–1.81	0.619	0.92	0.51–1.68	0.788

Abbreviations: OR, odds ratio; CI, confidence interval.

[a] Reference values: sample size <100, multi-center trials, investigator-initiated trials and drug trials.

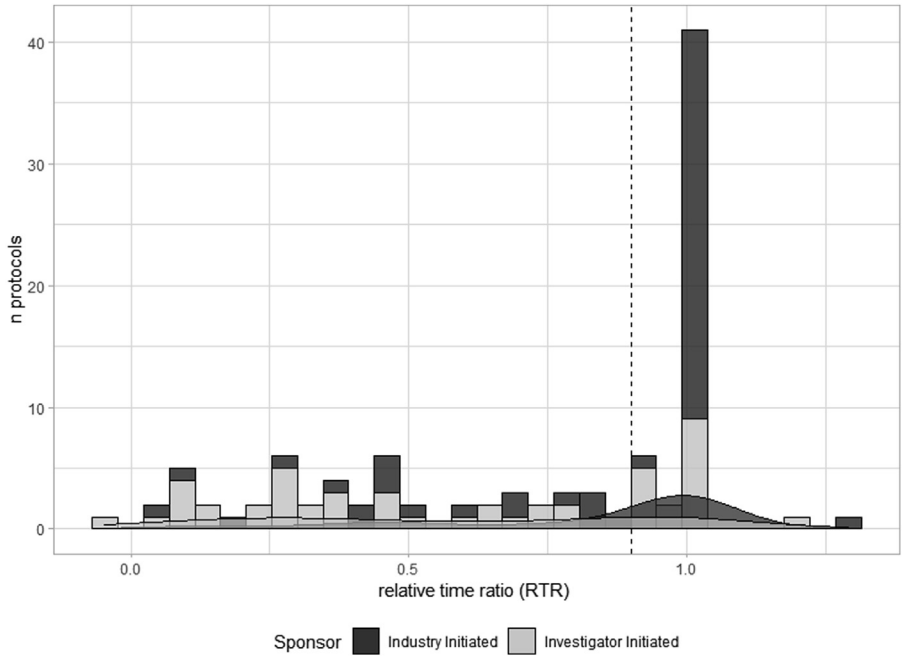

Fig. 1. Relative time ratio (RTR) of protocol availability by the sponsor. RTR = days from the start of the trial to protocol publication/days from the start of the trial to primary result publication. RTR 0 = start of trial. RTR 1 = publication of trial results. — median RTR.

in JAMA did not provide a protocol, this may highlight how stricter requirements by journals may prove as a suitable measure to improve protocol availability [5,8]. However, some journals have expressed reluctance to implementing such standards as it may pose an unnecessary burden for investigators conducting smaller trials [24]. Given that it is mandatory to submit a protocol to the ethics committees and other regulatory authorities for approval, this argument does not appear to outweigh the benefits of having protocols available for all conducted RCTs. Apart from initiatives from journals, funding agencies such as the National Institutes of Health (NIH) in the United States are promoting protocol availability through policies requiring investigators to make their protocols available in a trial registry together with the trial results [30].

Corroborating our results, Spence et al. found that protocols were typically made available toward the end of the trial [25]. Spence et al., however, only included protocols published in journals (not considering other formats), thus resulting in overall earlier protocol availability compared to our results. Our study showed earlier accessibility in investigator-sponsored trials and in RCTs with smaller sample sizes, which may be explained by the fact that academic studies benefit more from additional publications generated through protocols [31]. Although similar proportions of protocols were found as peer-reviewed publications and supplementary materials, the latter were by definition only made available with the primary results, therefore leading to overall later availability. This may also explain why trials with larger sample sizes were made available later, since many large trials are industry sponsored, are published in high-impact journals, and thus have their protocols published as a mandatory supplement in JAMA or NEJM, for instance. Although peer-reviewed feedback for protocols fosters methodological integrity and boosts public awareness and trial trustworthiness [8], the publication process

Table 4. Relative time ratio to protocol availability by categories

Characteristics	Count (%) n = 110*	Median RTR [IQR]
Sample size		
<100	11 (10.0)	0.55 [0.31, 0.89]
100–500	40 (36.4)	0.69 [0.27, 1.00]
>500	59 (53.6)	0.96 [0.57, 1.00]
Number of centers		
Single center	9 (8.2)	0.41 [0.27, 0.65]
Multicenter	101 (91.8)	0.93 [0.46, 1.00]
Sponsorship		
Investigator	51 (46.4)	0.60 [0.26, 0.94]
Industry	59 (53.6)	1.00 [0.69, 1.00]
Intervention		
Drug	74 (67.2)	1.00 [0.66, 1.00]
Non-drug	36 (32.7)	0.46 [0.26, 0.91]
Country of trial approval		
Switzerland	50 (45.5)	0.93 [0.46, 1.00]
United Kingdom	33 (30.0)	0.67 [0.29, 1.00]
Germany	8 (7.3)	1.00 [0.64, 1.00]
Canada	19 (17.3)	0.94 [0.42, 1.00]

Abbreviations: RTR, relative time ratio; IQR, interquartile range.
RTR = days from the start of the trial to protocol publication/days from the start of the trial to primary result publication.
n = 110* = Trials with available protocol and published results.
RTR <0 = protocol available before the start of the trial.
RTR >1 = protocol available after primary result publication.
RTR 0–1 = protocol available during trial.

is associated with lengthy waiting periods, making timely availability difficult. Other platforms such as registries, preprint servers and preregistration platforms, and registered reports may help facilitate earlier availability of trial protocols [19,20,32−35]. Previous research suggests that trial registries constitute optimal centralized platforms for timely protocol availability [6,8,9]. However, only 10% of the included RCTs made their protocol available through a trial registry. Generally, RCTs can take a long time to complete. Making protocols available earlier (i.e., before the investigators analyze their data) and therefore prespecifying how the data will be analyzed may improve the trustworthiness of study results. Furthermore, early sharing of study protocols allows for detailed discussions of methodological procedures, increases transparency, lowers duplication of research, and increases opportunities for collaboration between interested researchers.

To our knowledge, ours is the first study to quantify protocol availability, as well as timing, in a large and generalizable sample and to explore factors associated with higher availability. Our study has several limitations: first, the sample size was low in some categories (countries, design) which reduce our ability to explore for differences. Second, we included trials approved in 2012 to provide sufficient time for protocols to be made available. As there has been increasing pressure over time to making protocols publicly available [5], it is possible that availability has improved. We do plan a study with a sample of RCT protocols approved by ethics committees in 2016 to assess trends over time. Third, we included RCTs from four different high-income countries, and our findings may not be generalizable to trials conducted in low- and middle-income countries. Fourth, the participating ethics committees outside Switzerland constituted a convenience sample, but to the best of our knowledge, these were in no way particular compared to other ethics committees in Canada, Germany, or the United Kingdom.

In conclusion, only about one-third of RCTs in our cohort made a protocol publicly available, despite consensus in the scientific community that doing so improved transparency, accessibility, and reporting of RCTs. Protocols were typically made available shortly before the publication of the primary results; however, industry-initiated trials were much more likely to publish protocols after data analysis. Larger sample size and investigator sponsorship were associated with increased odds of protocol availability.

Increased efforts should be made to improve early trial protocol availability, for example, through clinical trial registries or mandatory requirements by journals, funders, ethics committees, or other authorities.

CRediT authorship contribution statement

Christof Manuel Schönenberger: Conceptualization, Investigation, Data curation, Writing − original draft. **Alexandra Griessbach:** Conceptualization, Formal analysis, Investigation, Data curation, Writing − original draft, Visualization. **Ala Taji Heravi:** Investigation. **Dmitry Gryaznov:** Investigation. **Viktoria L. Gloy:** Investigation. **Szimonetta Lohner:** Investigation. **Katharina Klatte:** Investigation. **Nilabh Ghosh:** Investigation. **Hopin Lee:** Investigation. **Anita Mansouri:** Investigation. **Ioana R. Marian:** Investigation. **Ramon Saccilotto:** Investigation. **Edris Nury:** Investigation. **Jason W. Busse:** Investigation. **Belinda von Niederhäusern:** Investigation. **Dominik Mertz:** Investigation. **Anette Blümle:** Investigation. **Ayodele Odutayo:** Investigation. **Sally Hopewell:** Investigation. **Benjamin Speich:** Conceptualization, Methodology, Investigation, Writing − review & editing, Supervision, Project administration. **Matthias Briel:** Conceptualization, Methodology, Investigation, Writing − review & editing, Supervision, Project administration, Funding acquisition.

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Supplementary data

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