

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

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Accepted 5 June 2025; Published online xxx

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

Funding: This project was supported by the Swiss Federal Office of Public Health (<https://www.bag.admin.ch/bag/en/home.html>) (MB). C.M.S. was funded by the Janggen Pöhn Foundation (<https://www.janggen-poehn.ch>) and the Swiss National Science Foundation (MD-PhD grant Number: 323,530_221860) (<https://www.snf.ch/en>). S.L. was supported by a research grant from the National Research, Development and Innovation Office of Hungary (NKFIH_FK_143633) (<https://nkfi.gov.hu/about-the-office>) and the Hungarian Academy of Sciences (MTA) within the framework of the Lendület Programme (<https://mta.hu/english>). The funder played no role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Registration: This review was prospectively registered on Open Science Framework.

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

¹ Shared last authorship.

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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. © 2025 The Author(s). Published by Elsevier Inc. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>).

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](https://www.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 (<i>n</i> = 347)	RCTs with publicly available protocol (<i>n</i> = 228)	RCTs without publicly available protocol (<i>n</i> = 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 (<i>n</i> = 181)	Nonindustry sponsored RCTs (<i>n</i> = 166)	Total RCTs (<i>n</i> = 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](https://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 (<i>n</i> = 228)	Protocol not available (<i>n</i> = 119)	OR	95% CI	<i>P</i> 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](https://clinicaltrials.gov). This policy change may explain, at least in part, the increase in publicly available protocols of

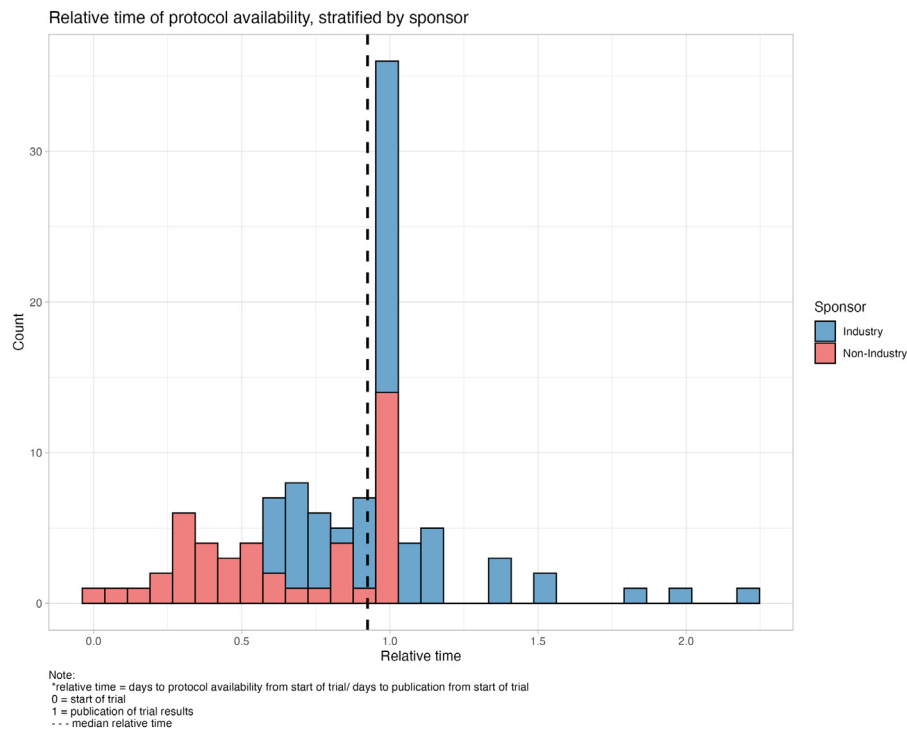


Figure. Relative time ratio of protocol availability. Relative time = days to protocol availability from start of the trial/days to publication from the start of the trial. 0, start of the trial and 1, publication of trial results. —, median relative time.

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](https://clinicaltrials.gov) [35]. Although it became more common to share trial protocols on [ClinicalTrials.gov](https://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 Schöenberger: 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 Hope-well:** 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.

Acknowledgments

The authors thank all participating research ethics committees from Germany (Freiburg), Switzerland (Basel, Bel-linzona, Bern, Geneva, Lausanne, St. Gallen, Frauenfeld, and Zurich), Canada (Hamilton), and the United Kingdom (National Health Service Health Research Authority) for their support and cooperation.

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.

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