Meta-Research to Improve the Planning and Reporting of Randomized Clinical Trials

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Prof. Dr. Primo Schär, Dean

This Chapter May Have Ended, But the Story Continues

Saadi Shirazi

Table of Contents

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Plain summary

The ongoing challenge of poor research persists in the scientific community, highlighting concerns about unreliable findings, misguiding decision-making processes, and losing public trust. A key solution lies in addressing the burden of inadequate methods by making adjustments. Better planning and reporting are essential to tackle this issue effectively. Meta-research, involving interdisciplinary research on research methods, offers insights into existing challenges. In this PhD, we proposed two main meta-research projects to identify problems and suggest solutions, ultimately improving the planning, and reporting of randomized controlled trials (RCTs): i) The pattern of RECRUITment In randomized clinical trials (RECRUIT-IT) study, and ii) Subprojects of the ASPIRE (Adherence to SPIRIT Recommendations) Study on different methodological topics.

i) RECRUIT-IT study:

We conducted an empirical study using individual participant recruitment data from RCTs, gathered from convenient national, and international networks, to empirically identify common trial recruitment patterns. Our findings indicate that approximately two-thirds of RCTs had an overall linear recruitment trajectory, facilitating straightforward predictions of future recruitment. Principal investigator (PI) sites generally contributed more, longer, and faster in participant recruitment, underscoring their crucial role in ensuring successful trial conduct.

ii) Subprojects of the ASPIRE study:

Our team has built a database of 760 RCT protocols already approved by research ethics committees in Switzerland (Basel, Bellinzona, Bern, Geneva, Lausanne, St. Gallen, Thurgau, Zurich), Germany (Freiburg), Canada (Hamilton), and UK; 360 RCT protocols from 2012 and 400 from 2016. We used this database and complemented it with additional information from RCT protocols and corresponding publications to provide empirical evidence on A) non-registration, discontinuation, and non-publication of RCTs, B) the prevalence and reporting of patient reported outcomes (PROs) in RCT protocols and publications, and C) reporting of prespecified subgroup analyses in RCT protocols. The results of subproject A showed that non-registration (6%), and non-availability of results (20%) remain significant issues, with non-industry trials being more affected than industry trials. Additionally, approximately one third of all RCTs were prematurely discontinued, mainly due to poor participant recruitment. The results of subproject B showed that 70% of RCTs specified PROs as either primary or secondary outcomes, with significant variability among medical disciplines and interventions.

The reporting standard for PROs in both protocols and publications was suboptimal, with a considerable proportion failing to adhere to protocol specifications when reporting PRO results. Similarly, the results of subproject C showed that planned subgroup analyses in the majority of RCT protocols were remained persistently inadequately in addressing fundamental scientific principles such as prior research considerations, limiting the number of subgroup analyses, and applying appropriate statistical methods.

The insights from the RECRUIT-IT study provide investigators with an overview of common trial recruitment patterns on the trial-level and the site-level, facilitating prediction and monitoring of participant recruitment in RCTs. Consequently, they can intervene to improve recruitment if it is needed, reducing the risk of unsuccessful recruitment and trial discontinuation. Assuring recruitment preserves research integrity by allowing the study to progress as intended, thereby minimizing the chance of discontinuation and research waste.

Insights from ASPIRE subprojects have raised awareness and highlighted the importance of various methodological challenges in trial registration, results publication, and planning and reporting of PROs and subgroup analyses. Enhancing registration and publication practices can reduce duplication, publication bias, and enhance transparency, thus reducing research waste. Simultaneously, effective planning and adherence to PRO protocols and improving methodological quality in subgroup analysis have a crucial role in ensuring the credibility of RCT results, aiding in waste reduction, and promoting more robust and transparent clinical research.

Abbreviations and acronyms

ASPIRE	Adherence to SPIrit Recommendations
COMET	Core Outcome Measures in Effectiveness Trials
COVERALL	COrona VaccinE tRiAL pLatform
CLEAR methods center	CLinical research Empirical Assessment & Recommendations methods center
CTTI	Clinical Trials Transformation Initiative
CTUs	Clinical Trial Units
DISCO	DISCOntinued Trials
EQUATOR network	Enhancing the QUAlity and Transparency Of health Research network
FDA	Food and Drug Administration
HRQoL	Health-Related Quality of Life
ICMJE	the International Committee of Medical Journal Editors
LIGHTS	LIbrary of Guidance for HealTh Scientists
PPHS	PhD Program Health Sciences
PROs	Patient reported outcomes
RCTs	Randomized Clinical Trials
RECRUIT-IT	RECRUITment In randomized clinical Trials
REWARD	Reduce Research Waste and Reward Diligence
RECs	Research Ethics Committees
PROTEUS-Trials consortium	Patient-Reported Outcomes Tools: Engaging Users & Stakeholders Trials consortium
ROR	Research on Research
SAMS	Swiss Academy of Medical Sciences
SERI	State Secretariat for Education, Research, and Innovation
SPIRIT	Standard Protocol Items: Recommendations for International Trials
SWAT	Study Within A Trial
SCTO	Swiss Clinical Trial Organization
SNSF	Swiss National Science Foundation
STEAM	Swiss Clinical Trials Empirical Assessment & Methods
TWICS	Trials Within Cohorts

1 Introduction

1.1 The need for better planning and reporting of randomized clinical trials

The call for "less research, better research, and research done for the right reasons" by Doug Altman in 1994, remains still relevant in the context of health research [1-5], highlighting concerns about persistent issues in poor design, conduct, and reporting over the past decades [6]. An analysis by Chalmers & Glasziou estimated that approximately 85% of research resources are wasted [7]. Recent research on two quantitative intervention reviews, spanning from May 2020 to April 2021 and published by all clinical Cochrane Review Groups, revealed that over 56% of participants were involved in what could be classified as bad research. The cost of these “bad research” ranged from £726 million - £8 billion, estimating 88% of researches are wasted [5]. These issues are compounded by evidence suggesting that many of the published clinical research may be either false or of little use [8, 9]. The 2014 "Increasing Value, Reducing Waste" series in the Lancet highlighting numerous sources of waste, including poorly formulated or selected research questions, insufficient methodologies, non or selective reporting of results, and poor quality of reporting [6, 10-13]. In response to this imperative need for improvement in clinical research practices, the principal authors of the series launched the Reduce Research Waste and Reward Diligence (REWARD) campaign (https://www.thelancet.com/campaigns/efficiency/statement). Despite some progress, challenges are remaining due to limited awareness, different stakeholders` motivations, and slow improvements in research practice [1-3].

A strong methodology is the foundation of good research, providing a structured framework for successful conduct [14, 15]. It encompasses the systematic design, implementation, and analysis of research methods to ensure the validity, reliability, and reproducibility of study findings. An essential aspect of reducing waste in research lies in addressing the burden attributed to inadequate methods, which could be reduced through simple and inexpensive adjustments [14]. The design, methods, and dissemination of randomized clinical trials (RCTs) is an essential part in order to ensure the validity and reliability of clinical research evidence resulting in reducing waste [1, 7, 16]. It helps to guard against questionable research practices like trial discontinuation, HARKing, cherry-picking, and P-hacking [17-21]. Transparent and comprehensive reporting further enhances internal validity, minimizes bias, ensures publication availability, promotes transparency, and facilitates critical evaluation, contributing to the integrity and credibility of clinical research for evidence-based medicine [7, 12, 16, 22].

To address these challenges effectively, it is important to undertake an empirical investigation of our research processes. By doing so, we can identify and quantify existing problems, and

facilitating the development of suitable solutions. “Meta-Research” or “Research on Research” (RoR) typically consists of interdisciplinary studies, which are conducted on research itself [23, 24]. Meta-research examines various research aspects like methods, reporting, reproducibility, and analysis, offering evidence to inform evidence-based decisions, thereby enhancing research relevance, validity, efficiency, and transparency [23, 24]. The White Paper on Clinical Research, mandated by the State Secretariat for Education, Research, and Innovation (SERI) and recently published by a working group convened by the Swiss Academy of Medical Sciences (SAMS), underscores the importance of conducting meta-research to improve clinical research in Switzerland [25].

In this PhD thesis, we aimed to improve the planning and reporting of RCTs by conducting meta-research on different aspects of trial methodology.

1.2 Recruitment challenges in randomized clinical trials

About 25% of RCTs enrolling patients (as opposed to enrolling healthy volunteers) are prematurely discontinued, and the main reason for discontinuation is poor recruitment of participants [26, 27]. Poor recruitment of RCT participants can lead to underpowered trials, risking premature stopping of effective interventions, prolonging trial durations, increasing costs, raising ethical concerns, and, eventually, promoting research waste [26-28]. Reasons for recruitment failure in clinical trials can be numerous. Several qualitative studies identified patient-related, funding-related, trial team-related, and trial design-related reasons for recruitment failure [29, 30], with most of them being preventable with better recruitment planning [31].

To enhance the accuracy of forecasting and tracking participant recruitment in RCTs, evidence-based guidance and tools are needed. To our knowledge, there is only one study providing empirical evidence on patterns of patient recruitment. Approximately two decades ago, Haidich and Ioannidis proposed that participant enrollment in the first two months was strongly correlated with further participant enrollment. However, their empirical findings were based on a limited sample of individual patient recruitment data from 77 RCTs conducted by the AIDS Clinical Trials Group in the US between 1986 and 1996 [32, 33]. Therefore, obtaining empirical evidence on common recruitment patterns of RCTs and to describe recruitment patterns is crucial for addressing essential questions in this context.

1.3 Ensuring comprehensive and transparent planning and reporting for different aspects of clinical trial methodology

1.3.1 The role of registration and publication

Over the years, concerns have persisted within the scientific community regarding reporting biases, where negative results from clinical trials are less likely to be published than positive ones [34]. It is essential to make all RCT results, including those from discontinued trials, available to minimize resource waste and to ensure that evidence is not lost, but made available for meta-analyses. To address this issue and to enhance transparency, proposals were made for comprehensive clinical trial registries, leading to the establishment of platforms such as ClinicalTrials.gov in 1997 [35].

Despite the implementation of laws and guidelines by esteemed bodies like the International Committee of Medical Journal Editors (ICMJE) [36, 37], the World Medical Association's Declaration of Helsinki [37], and the final rule of Food and Drug Administration Amendments Act of 2007 [38], or locally the Switzerland's legislation [39], all of which mandate prospective registration (i.e. registration before enrolling the first participant), and publication of trial results, the rate of non-registration, discontinuation, and non-publication is an ongoing issue [27, 40].

A meta-research study indicated that 6% of RCTs approved in 2012 remained unregistered, 10% were registered retrospectively, 20% were prematurely discontinued, primarily due to poor recruitment, with 60% of those trials remaining unpublished [27]. Moreover, premature discontinuation was associated with a reduced likelihood of publication. This pattern was also observed for Swiss RCTs approved between 2016 and 2020, despite the implementation of laws mandating registration, underscoring the importance of examining the current status of registration and results publication [40].

1.3.2 Use of patient-reported outcomes in clinical trials

Patient-reported outcomes (PROs) refer to direct reports from patients about their health without interpretation by clinicians [41]. PROs include a wide range of patient-reported elements: 1) disease symptoms or treatment side effects, such as pain, fatigue, or anxiety; 2) functional outcomes like physical, sexual, social, emotional, or cognitive functioning; and 3) multidimensional such as health-related quality of life (HRQoL) or health utility [42]. PROs play an essential role in capturing patients' experiences, enhancing the understanding of their health status, and contributing to evidence-based clinical research and decision-making [43]. The importance of PROs has been recognized by major regulatory authorities, international policy makers, and patients [41, 44, 45].

Well-planned and well-reported PROs can enhance the credibility of results for patient-centered care and informed decision-making. Insufficient data gathering for some outcomes during the trial may arise when characteristics of PROs are not reported adequately in the protocol [46]. Therefore, crucial information is not available for decision-making, increasing the risk of cherry-picking and selective reporting [18].

Previous meta-research has revealed that PROs, including HRQoL, were often insufficiently planned as outcomes in clinical trial protocols. Even when included in the planning, the results on PROs were frequently left unreported in publications [47]. Moreover, the reporting quality of PROs seem to be highly variable, prompting the development of reporting guidelines for PROs in trial protocols and result publications to enhance consistency and standardization practices [48-51]. Several meta-research studies have focused on specific diseases, like cancer, or specific types of PROs, particularly HRQoL [52-59]. However, empirical data on the planning of PROs in RCT protocols and their reporting in corresponding result publications across medical specialties have so far been lacking.

1.3.3 The significance of reporting quality in subgroup analysis

Subgroup analyses are common in RCTs and meta-analyses [60-62]. These analyses aim to understand whether the effects of an intervention vary across different subgroups of participants, such as age groups or sexes. Subgroup analysis is vital for precision medicine or stratified medicine as it allows researchers to identify specific patient characteristics or subpopulations that respond differently to interventions [63, 64]. By recognizing variations, clinical decisions have the potential to be more precise, optimize benefits, prevent harm, and advancing the goals of personalized medicine.

However, in the past results from subgroup analyses have often been found to be misleading [65-68]. Researchers, clinicians, and policy makers should approach these claims with a critical mindset, considering the statistical, methodological, and clinical implications of such findings. Pre-specification, and a detailed planning are essential to enhance the reliability of subgroup findings in RCTs and meta-analyses [68-70]. Therefore, empirical evidence on the quality of planning subgroup analysis is needed.

1.4 Main objectives

1.4.1 Overall objective

The objective of this thesis is to improve the planning and reporting of RCTs by conducting meta-research on participant recruitment patterns, non-registration, discontinuation, and non-publication of RCTs, and the planning and reporting of PROs and subgroup analysis.

1.4.2 Specific objectives

- To inform the planning and monitoring of participant recruitment in RCTs through empirical investigation of individual participant recruitment data and the identification of common patterns of recruitment trajectories.
- To longitudinally compare the rates of non-registration, discontinuation, and non-publication of RCTs approved in 2016 with those approved in 2012 and in 2001-2003.
- To examine the prevalence and reporting quality of PROs in protocols and corresponding publications of RCTs approved in 2012 & 2016.
- To longitudinally examine the prevalence, characteristics, and reporting quality of subgroup analyses in RCT protocols (early 2000s, 2012 and 2016).

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2 Contribution by PhD student

I had the privilege of conducting my Ph.D. studies with Prof. Briel at the CLinical research Empirical Assessment & Recommendations (CLEAR) methods center, Department of Clinical Research, where I had previously completed my master's degree. Collaborating with an esteemed supervisor and dedicated peers, helped me grow not only as a researcher, but also as a person.

During my Ph.D. journey, I worked in two main meta-research projects aimed at identifying problems and suggesting solutions to improve the planning and reporting of RCTs:

i) The RECRUITment patterns In randomized clinical Trials (RECRUIT-IT) project

In the context of an extensive international project, " RECRUIT-IT " aimed at optimizing the planning and estimation of participant recruitment during trial conduct. my contributions consisted of different main roles throughout the study. From contributing to the study design and analysis plan to managing the massive data gathering of 300 RCTs with almost 200,000 recruited individuals, performing data cleaning and data management, conducting comprehensive analyses in R, and effectively coordinating the project.

ii) The ASPIRE (Adherence to SPIRIT Recommendations) project

The Adherence to SPIRIT Recommendations (ASPIRE) project was aimed to assess the comprehensiveness of reporting of RCT protocols in a repeated cross-sectional study to investigate the reporting quality of RCT protocols longitudinally [1]. For the ASPIRE project, our team has built a database of 760 RCT protocols already approved by research ethics committees (RECs) in Switzerland (Basel, Bellinzona, Bern, Geneva, Lausanne, St. Gallen, Thurgau, Zurich), Germany (Freiburg), Canada (Hamilton), and UK – 360 RCT protocols from 2012 and 400 from 2016.

I then actively contributed to a subproject of ASPIRE, study of DISCOntinued trials (DISCO III study) investigating whether recent efforts have improved prospective trial registration, trial completion and results publication. I used the ASPIRE database and initiated the search to determine registration information for each RCT protocol approved in 2016 and to identify the corresponding results publication. Given the scope of our work, a large team of collaborators was essential. I personally organized the data extraction phase and conducted training sessions for all the data extractors, ensuring a consistent and standardized approach, which included calibration exercises with both national and international colleagues. I also substantially contributed to the data extraction myself. For the data analysis and the drafting

of the manuscript I received supported from my colleague, Dr. Benjamin Speich, with whom I share first authorship for the DISCO III study.

Using the publications identified from the approved protocols in years 2012 and 2016, I coordinated the data extraction to gather information about PROs and the use of routinely collected data in RCT publications. In this project, I took on the first data extraction for all identified publications during the double-extraction process. I also was in charge of the data analysis. Unfortunately, after comparing the use of routinely collected data in protocols and publications, we encountered discrepancies that raised concerns about the reliability of the data extraction from protocols. Consequently, we made the decision to stop this subproject. The manuscript focusing on PROs has been prepared and submitted to PloS Med.

Moreover, I participated in several additional research projects not directly related to my PhD such as a scoping review of platform trials, the Corona Vaccine Platform Trial (COVERALL), an individual patient data meta-analysis on remdesivir in patients hospitalized with COVID-19, a project on the reproducibility and scientific integrity of big data research, and other subprojects of ASPIRE. Some of these projects have already been published, while others are pending publication and will soon be released, with my co-authorship (Section 5-further publications).

During my Ph.D., I have also been actively involved in various extracurricular activities. I had the opportunity to present my work at different national and international conferences. I managed the social media presence at the Division of Clinical Epidemiology, initiated and organized "Meet to Read" sessions with the PhD Program Health Sciences (PPHS), served as the student representative for implementing the GRACE-PhD survey at the Department of Clinical Research, contributed to teaching activities of the Division, and provided mentorship to undergraduate students. Additionally, I successfully secured admission to the competitive "ZOOM@Novartis" mentoring program, a collaborative initiative between the University of Basel and Novartis AG to examine career opportunities in industry for young women researcher.

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3 First author publications

Manuscript I: RECRUITment patterns In randomized clinical Trials (RECRUIT-IT)- a meta research study

Status: Submission planned to BMJ

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Abstract

Objective: To empirically identify different patterns of participant recruitment in randomized clinical trials (RCTs) on trial level and on trial site level to better understand and predict participant recruitment.

Design: Retrospective empirical analysis of individual participant recruitment data from 300 RCTs.

Setting: Convenience sample of RCTs from different medical fields and countries.

Data sources: The AIDS Clinical Trials Group, Swiss Group for Clinical Cancer Research, German Chronic Lymphocytic Leukemia Group, German Society of Surgery Study Center, Virtual International Stroke Trials Archive, clinical trials units in Bern, Basel, Nottingham, and Derby, individual trial investigators, and industry trial platforms.

Results: Of 300 included RCTs, 247 were completed as planned (82%), 26 stopped early due to poor recruitment (9%), and 27 stopped due to other reasons (9%). The median number of recruited participants was 344 (interquartile range [IQR], 153-737) and the median duration of recruitment was 20 months (IQR, 13-33). Most common medical fields were infectious diseases (29%, 88/300) and oncology (16%, 50/300). We identified four different overall recruitment patterns: The most frequent pattern was linear (191/300, 63%), followed by accelerating (46/300, 15%), decelerating (36/300, 12%), and with recruitment slowdowns/plateau phases (27/300, 9%). Recruitment acceleration after recruitment of 20-30% of the target sample size was rare. When examining recruitment on trial site level, we found again all four main patterns with linear being the most frequent (40/ 85 trial sites, 47%). In a subset of 49 multicenter RCTs with information about PI sites and non-PI sites we found that PI-sites are, on average, open twice as long, recruit four times more participants, and recruit twice as fast (participants per month) compared to non-PI sites. We did not identify specific trial characteristics to be associated with a linear recruitment pattern.

Conclusion: Two thirds of included RCTs followed a linear recruitment pattern, facilitating straightforward predictions once participant recruitment is underway. PI sites performed, on average, much better than non-PI sites in recruiting participants, underscoring their pivotal role in successful trial conduct and demanding caution when extrapolating recruitment performance from PI to non-PI sites.

Summary boxes

Section 1: What is already known on this topic?

- 90% of randomized clinical trials (RCTs) experience delays in participant recruitment and poor recruitment is the most frequent reason for premature trial discontinuation.
- Overoptimistic recruitment assumptions at the start and during trial conduct are common.

Section 2: What this study adds?

- The most common recruitment pattern is linear, facilitating the prediction of future recruitment during trial conduct.
- Acceleration of participant recruitment during trial conduct is rare.
- Principal investigator sites recruit more, longer, and faster; when planning a trial, investigators need to be cautious when extrapolating recruitment performance of these sites to others.

Introduction

Up to 90% of randomized clinical trials (RCTs) experience delays in participant recruitment, and about 20% of RCTs are prematurely discontinued due to poor recruitment leaving important research questions unanswered [1-3]. In addition, recruitment failure in RCTs wastes precious research resources and may compromise the public's and patients' trust and willingness to participate in clinical studies [4-6].

Overoptimistic recruitment assumptions at the start and during trial conduct are common among trial investigators and an important reason for recruitment failure [7]. A better understanding of recruitment patterns in RCTs and learnings from empirical recruitment data may help to more realistically estimate participant recruitment and to enable timely corrective actions when needed. However, empirical evidence on recruitment patterns in RCTs is scarce [8-10]. A rapid review indicated higher recruitment rates in treatment trials than in prevention trials [10]. Another study by Haidich & Ioannidis examined individual participant recruitment data of 77 RCTs from the AIDS Clinical Trials Group conducted between 1986 and 1996 and found that participant enrollment in the first two months was highly correlated with further enrollment in these trials [8, 9]. More recent meta-research on recruitment patterns across different trial settings and medical fields is lacking.

We conducted an international collaborative project on RECRUITment In Trials (RECRUIT-IT) for which we gathered individual participant recruitment data of 300 RCTs from different medical fields, countries, and settings to (i) descriptively examine recruitment patterns for the overall trial (completed and discontinued RCTs), (ii) investigate recruitment patterns at trial site level including a comparison between principal investigator (PI) sites and non-PI sites, (iii) investigate potential associations between trial characteristics and an overall linear recruitment pattern, and (iv) examine changes in recruitment progression at pivotal time points.

Methods

This is a retrospective empirical analysis of individual participant recruitment data from a convenience sample of 300 RCTs. A study protocol has previously been published [11]. We report our study according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement [12] (Appendix 1).

Study sample

We included RCTs evaluating any healthcare intervention that were completed or discontinued for any reason, randomized individual patients, had a parallel group design, and had PIs willing

to share individual patient recruitment data. We excluded RCTs focusing on pharmacokinetics, sub-studies of a larger trial, and pilot trials. As a convenience sample we approached different institutions and individual researchers through established contacts. Included RCTs were provided by the i) AIDS Clinical Trials Group (ACTG), ii) Swiss Group for Clinical Cancer Research (SAKK), iii) German Chronic Lymphocytic Leukemia Group, iv) Study Center of the German society of surgery (SDGC), v) Virtual International Stroke Trials Archive -stroke rehabilitation trial repository (VISTA), vi) Clinical Trials Unit Bern, vii) Department of Clinical Research in Basel, viii) Clinical Trials Unit Derby, ix) Clinical Trials Unit Nottingham, x) individual PIs from Switzerland and United Kingdom, and xi) industry trial platforms via the clinicalstudydatarequest.com website. Two sources, VISTA and part of industry trials, did not directly share their recruitment data; rather, we accessed and conducted all analyses within their respective platforms and exported the summary results.

Data collection

From each RCT, we collected individual recruitment data along with information on the site where each participant was recruited, including whether the site belonged to the PI or not (if available). In addition, we gathered trial characteristics, such as patient population, medical field, target sample size, anticipated recruitment time (if available), number of trial sites, involved countries, primary endpoint, trial completion status (including reasons for discontinuation, if applicable), sponsorship, use of well-established trial networks, and funding sources. Details on RCT characteristics were provided from the data source or extracted from trial protocols, trial registries, or journal publications by ATH, AG, and BK.

Data 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 across three pre-defined groups: completed trials, trials stopped due to poor recruitment, trials stopped due to other reason than poor recruitment.

We classified recruitment patterns using a visual consensus-driven approach. First, we created a recruitment trajectory for each RCT by plotting the achieved recruitment proportion of the trial's target sample size over time in months. Then, four investigators experienced in trial methodology research and participant recruitment (ST, EM, AA, MB) rated each recruitment trajectory independently following rules and definitions which enabled eventual classification of individual trajectories to recruitment patterns (Appendices 2 and 3). Disagreements of ratings were discussed in the group of raters until unanimous consensus was reached or, if necessary, a 3:1 majority was established.

To investigate recruitment patterns of individual trial sites within RCTs, we focused on trials with a minimum enrollment of 300 patients and between 3 and 60 recruiting sites. Smaller trials and trials with more than 60 sites would not have allowed us to create interpretable recruitment trajectories on site level for the visual rating. This resulted in 85 RCTs with site trajectories (see example in Appendix 4). We then selected the trial sites with the largest number of recruited participants and rated these trajectories as described above.

We conducted a comparative analysis of participant recruitment at PI sites versus non-PI sites with respect to percentage of recruited participants, duration of participant recruitment at a site, speed of recruitment (number of participants recruited per month), and start of participant recruitment at a site, focusing on a sub-sample of 49 RCTs where the PI site was known.

We conducted complete case multivariable regression to explore potential associations of an overall linear recruitment pattern with the following independent variables: (1) Trial network (industry, academic network, no obvious network); (2) medical field (cardiovascular, infectious disease, neurology, oncology, other); (3) time of participant recruitment (before vs after the year 2000); (4) national vs international trial; and (5) target sample size (continuous variable).

With respect to changes in recruitment progression at pivotal time points, the four raters (ST, EM, AA, MB) documented changes in individual recruitment trajectories in terms of when these occurred (i.e., at what percentage of the target sample size recruited the change occurred); disagreements were resolved through discussion and consensus. We specifically examined (i) how often and when (% of target sample size) a first pattern change occurred, (ii) how often these pattern changes were in-line with an increased recruitment (steeper slope) or a decreased recruitment (flatter slope), (iii) how often and when (% of target sample size) recruitment slowed down towards the end of the trial (“recruitment fatigue”), and (iv) the proportion of RCTs classified as “very slow start” but still achieving 90% or more of the target sample size. All statistical analyses were conducted using R version 4.2.2.

Results

Characteristics of included trials

Overall, we included 300 RCTs with participant recruitment data from 199’514 individuals (Figure 1). Of the 300 RCTs, 247 (82%) were completed, 26 (8%) were stopped early due to poor recruitment, and 27 (10%) were stopped due to other reasons. A total of 217 RCTs (72%) were multi-center and provided site information, for 66 multi-center RCTs (22%) we had no site-level data, and 17 RCTs (6%) were single center. For 49 of the 217 multicenter RCTs with site-level data, we knew the PI-site.

Recruitment periods of included RCTs were between 1986 and 2022 (Table 1); most trials were investigator-sponsored RCTs from established trial networks in the fields of infectious diseases and oncology. The median number of recruited participants was 405 (IQR, 214-768) and the median trial duration was 18 months (IQR, 12-31 months) in completed RCTs, 104 recruited participants (IQR, 36-286) and median trial duration of 43 months (IQR, 25-55 months) in RCTs stopped due to poor recruitment, and 114 recruited participants (IQR, 66-409) and median trial duration of 20 months (IQR, 14-28 months) in RCTs stopped due to other reasons.

Recruitment patterns on trial level

In our analysis, we identified various shapes of recruitment trajectories and classified these into four main patterns (Table 2): i) linear, ii) accelerating, iii) decelerating, and iv) plateau at any stage of recruitment. We provided detailed descriptions for all patterns in Appendix 3. A mainly linear recruitment pattern was most common in completed RCTs (167/247, 68%) and in RCTs stopped early for other reasons than poor recruitment (15/26, 57%), while in trials stopped due to poor recruitment a decelerating pattern was most prevalent (13/27, 50%). We found an overall accelerating recruitment pattern in 46 RCTs (15%) and a plateau at any stage of the recruitment process in 27 RCTs (9.0%). In none of the RCTs stopped due to poor recruitment we saw an acceleration pattern.

We found a borderline significant association of a linear recruitment pattern with RCTs from the cardiovascular field, but otherwise no evidence for an association with trial characteristics such as industry-sponsorship, presence of an established trial network, target sample size, or international setting (Appendix 5).

Critical time points for assessment of recruitment progress

The assessment of recruitment progress in RCTs has revealed pivotal time points for investigators to be aware of. In 30% of completed RCTs (74/247) the recruitment slowed down towards the end of the recruitment period when reaching about 80% of the planned target sample size (IQR: 52-94%). In 50% of trials stopped due to poor recruitment (13/26), recruitment slowed down when a median of 35% of the target sample size was reached (IQR: 30-45%). In completed RCTs without an overall linear pattern (n=80), the shape of the recruitment trajectory changed in 51 (63%) of such RCTs when about 25% of the target sample size was reached (IQR: 14-31%); in 15 of 51 RCTs (29%) the recruitment slope increased, while in the majority of 36 RCTs (71%) the recruitment slope decreased. Only 5 out of 14 trials (35%) with very slow recruitment at the beginning eventually reached 90% of their target sample size.

Recruitment patterns on trial site level

We found all four main recruitment patterns on trial site level too (Table 3). The linear recruitment pattern was again the most frequent pattern (47%); an accelerating pattern was seen in 10% of sites, a decelerating pattern in 21% and a plateau pattern in 21%. Multicenter RCTs included in the site assessment were, on average, larger but otherwise characteristics were similar to the other multicenter RCTs not included in the assessment (Appendix 6).

Recruitment at PI sites versus non-PI sites

The median proportion of participants recruited at PI sites was 4.3 times (IQR: 2.5 – 10.7 times) higher than at non-PI sites. The median time a PI site was recruiting participants was 2.0 times (IQR: 1.4 – 2.4 times) longer than the time at non-PI sites. In addition, recruitment speed, i.e. the median number of recruited participants per month per site, was 2.0 times (IQR: 1.0 – 2.8 times) higher at PI sites compared to non-PI sites. Finally, in 71% of RCTs (35/49), the first participant was recruited at a PI site. Multicenter RCTs with available PI site information were all investigator-sponsored and mainly consisted of surgical and cardiovascular trials, but otherwise trial characteristics were similar to multicenter RCTs without this information (Appendix 7).

Discussion

This empirical analysis of recruitment patterns based on individual participant recruitment data of 300 RCTs suggested that two thirds of RCTs followed a linear pattern. An overall accelerating pattern (15%), decelerating pattern (12%), and patterns with recruitment plateaus (9%) were less frequent. When about 20% of the target sample size was recruited, the recruitment trajectory changed in about half of the RCTs; in three out of four changing RCTs the recruitment slowed down, while it sped up in a quarter. In one third of RCTs recruitment slowed down when about 80% of the target sample size was recruited. On trial site level, we found half of assessed sites to follow a linear pattern, and 20% each following a decelerating and some plateau pattern. On average, PI sites were open twice as long, recruited four times more participants, and recruited participants twice as fast compared to non-PI sites. We did not identify any trial characteristics that were clearly associated with a linear recruitment pattern.

Strengths and limitations

Strengths of our study include the large and in various aspects diverse sample of RCTs with individual participant recruitment data that allowed us to identify different recruitment patterns

on the trial level as well as on the trial site level. We published a study protocol [11] and had four raters experienced in trial conduct and meta-research who assessed all plotted recruitment trajectories following an iteratively developed manual (Appendix 2 and 3).

Our study has several limitations. Firstly, we used a convenience sample of RCTs conducted between 1986 and 2023, which may not be representative of all trials conducted in this period. However, the proportion of RCTs stopped early due to poor recruitment of 10% and an IQR of planned sample size of 200 to 700 participants in our sample is in-line with previous meta-research based on representative RCT samples from different countries [1, 2]. Secondly, for 213 RCTs (71%) we did not have information on the planned recruitment duration preventing any analyses about recruitment delays and potential associations with recruitment patterns. Some trials may have extended their recruitment periods beyond the initial plan, potentially affecting recruitment patterns, particularly if additional funding was secured. Thirdly, we did not always have access to original trial protocols, so for information on important trial characteristics such as the planned target sample size we also relied on trial registries, results publications, and communications with PIs. Lastly, we lacked any background information on RCTs that could explain unusual shapes in recruitment trajectories such as plateaus or jumps in recruitment, thereby limiting our understanding of specific events in the recruitment process.

Comparison with other studies

Haidich and Ioannidis conducted a similar study to ours, but their sample was limited to 77 RCTs from the AIDS Clinical Trials network conducted in the 1980s and 1990s [8, 9], while our sample was more diverse and incorporated recent data. Haidich and Ioannidis found a high correlation between participant recruitment in the first two months with further participant recruitment; we replicated their finding for RCTs conducted in the AIDS Clinical Trial network, for RCTs within another academic trial network, and for RCTs without a trial network (Appendix 8). However, we found it challenging to draw inferences for research practice from correlation coefficients and decided, therefore, to use a visual assessment approach to identify trial recruitment patterns.

Implications for research practice

Two thirds of included RCTs followed an overall linear recruitment pattern with a mostly constant slope facilitating simple recruitment predictions during trial conduct once 20-30% of the target sample size have already been recruited. At around 25% of recruitment of the target sample size, the slope of the trajectory changed in about 60% of non-linear RCTs and a change towards slower recruitment was almost three times more frequent than a change to faster recruitment. This means that if participant recruitment in an RCT starts out with a flatter recruitment slope than planned, this pattern is likely to persist or recruitment might even slow

down more rather than accelerate. Trialists need to closely monitor participant recruitment and take action soon, ideally within 20-30% of target recruitment, in case of slower recruitment than planned. However, effective strategies for accelerating recruitment are scarce and improvements are typically rather modest [13] [14-16]. Thorough recruitment planning is crucial [7]. This study provides empirical evidence that trial investigators need to be extremely cautious when extrapolating recruitment estimates from PI sites to non-PI sites. Recruitment fatigue when reaching 80% of target sample size is common and should be considered when estimating planned recruitment duration.

Conclusions

Two thirds of included RCTs followed a linear recruitment pattern, facilitating straightforward predictions once participant recruitment is underway. PI sites performed, on average, much better than non-PI sites in recruiting participants demanding caution from investigators when extrapolating recruitment performance from PI to non-PI sites. Early recognition of the recruitment pattern can prompt trialists to implement measures to improve recruitment.

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Figure1- Flow diagram

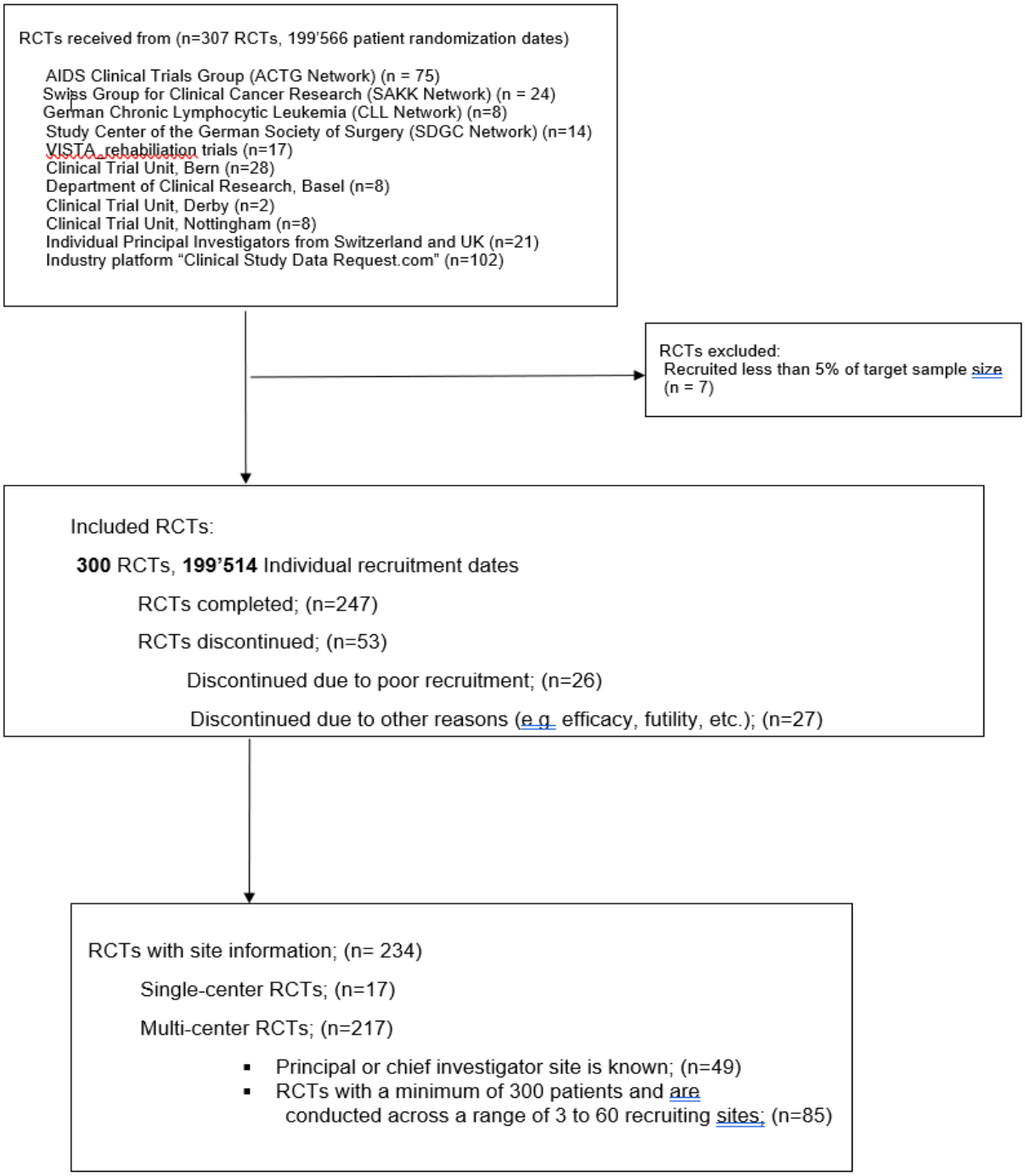
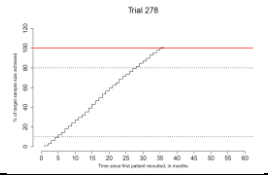
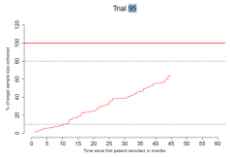
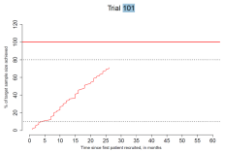
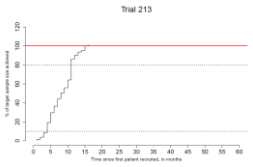
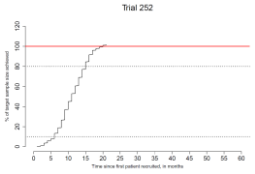
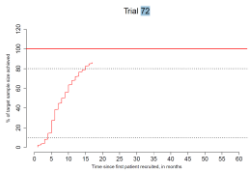
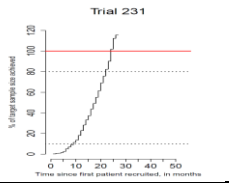
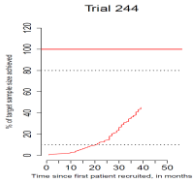
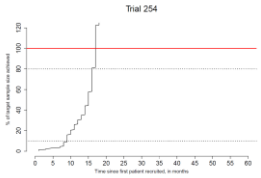
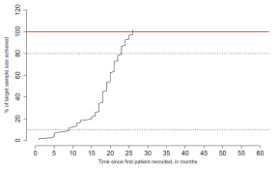
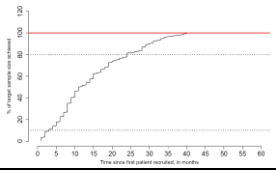
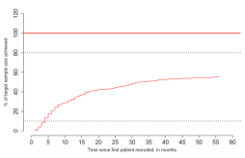
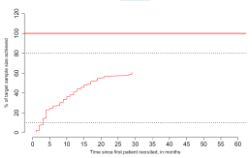
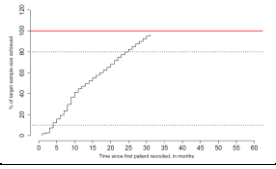


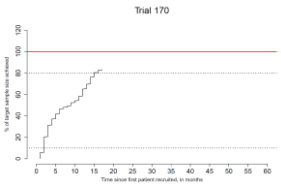
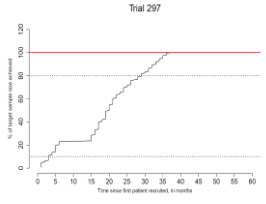
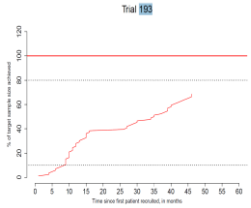
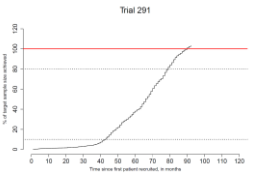
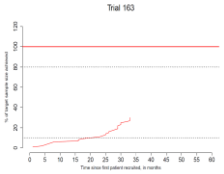
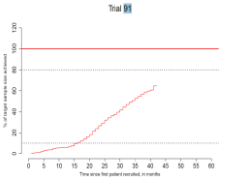
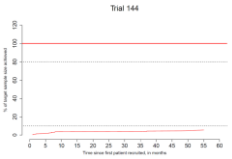
Table 1-Characteristics of 300 included RCTs

RCT characteristics	Completed (n=247)	Stopped, due to poor recruitment (n=26)	Stopped, due to other reasons (n=27)
Recruitment period range	1986-2022	1991-2017	1987-2017
Medical field n (%)			
Infectious Diseases	61 (25%)	10 (38%)	17 (63%)
Oncology	39 (16%)	6 (23%)	5 (18%)
Surgery	16 (6%)	2 (8%)	1 (4%)
Respiratory	18 (7%)	-	-
Cardiovascular	25 (10%)	1 (4%)	1 (4%)
Neurology	27 (11%)	3 (11%)	-
Psychiatry	14 (5%)	-	-
Endocrionology	17 (6%)	-	1 (4%)
Other	30 (14%)	4 (16%)	2 (7%)
Planned target Sample Size median (IQR)	360 (200-718)	198 (100-668)	230 (158-566)
Achieved Sample Size median (IQR)	405 (214-768)	104 (36-286)	114 (66-409)
Recruitment duration, months median (IQR)	18 (12-31)	43 (25-55)	20 (14-28)
Using administrative infrastructure of a network n (%)			
Investigator-sponsored RCTs with no-established trial network	59 (24%)	9 (35%)	2 (7%)
Investigator-sponsored RCTs with well-established trial network	90 (36%)	16 (62%)	23 (86%)
Industry-sponsored RCTs	98 (40%)	1 (3%)	2 (7%)

Abbreviations: RCT=randomized clinical trial; IQR=interquartile range.

Table 2- Recruitment patterns on trial level

Recruitment pattern		Completed RCTs (n=247)	RCTs stopped due to poor recruitment (n=27)	RCTs stopped due to other reasons* (n=26)
Linear	Linear throughout	106 (44%) 	9 (35%) 	13 (50%) 
	Linear with vertical element	7(3.3%) 	-	-
	Classic	54 (22%) 	-	2 (7.7%) 
Accelerating	Accelerating throughout	21 (8.6%) 	-	2 (7.7%) 
	Late acceleration	15 (5.7%) 	-	-
	Angle to more steep	8 (3.3%) 	-	-
Decelerating	Decelerating throughout	9 (3.7%) 	13 (50%) 	5 (18%) 
	Angle to less steep	9 (3.7%) 	-	-

Beginning / middle / overall plateau	Mid trial slow down	7 (2.9%) 	-	-
	Plateau in the middle	6 (2.5%) 	-	2 (7.7%) 
	Very slow start	5 (2.0%) 	2 (7.5%) 	3 (11%) 
	Overall Plateau	-	2(7.5%) 	-
Total linear		167 (68%)	9 (35%)	15 (57%)
Total accelerating		44 (18%)	-	2 (7.7%)
Total decelerating		18 (7.3%)	13 (50%)	5 (18%)
Total Beginning/ middle/overall plateau		18 (7.3%)	4 (15%)	5 (18%)

Abbreviation: RCT, randomized clinical trial

*Other reasons for stopping early included benefit, harm, futility, external evidence, unclear.

Table 3- Recruitment patterns on site level in multi-center RCTs*

Recruitment pattern		The most recruiting center of Multi-center RCTs (n=85)	Total
Linear	Linear throughout	29 (34.1%)	40 (47%)
	Classic	11 (12.9%)	
Accelerating	Accelerating throughout	4 (4.7%)	9 (10%)
	Angle to more steep	5 (5.9%)	
Decelerating	Decelerating throughout	7 (8.3%)	18 (21%)
	Angle to less steep	11 (12.9%)	
Beginning/middle plateau	Plateau in the end	4 (4.7%)	18 (21%)
	Plateau in the middle	9 (10.6%)	
	Slowdown in the middle	5 (5.9%)	

Abbreviations: RCT=randomized clinical trial.
* RCTs with a minimum of 300 patients and between 3 and 60 recruiting sites.

Table 4-Recruitment in PI sites vs. non-PI sites in multicenter RCTs, (n=49)

	PI sites	non-PI sites	Ratio
Total recruited participants, median (IQR)	90 (41-229)	17 (9.0-35.0)	4.3 (2.45 – 10.7)
Proportions of recruited target sample size, median (IQR)	0.25 (0.1-0.53)	0.05 (0.02-0.09)	4.3 (2.45 – 10.7)
Recruitment site open, months median (IQR)	29 (17-44)	13.0 (10.5-23)	1.95 (1.35 – 2.43)
Recruitment slope (mean of recruited participants per month per site), median (IQR)	3.0 (2.0-8.5)	1.5 (1.0-2.5)	2.0 (1.0 – 2.8)
Recruitment of first trial participant, n (%)	35/49 (71%)	14/49 (29%)	-

Abbreviations: PI site= principal investigator site; RCT=randomized clinical trial.

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Authors' contributions

BK, AA, GM, ATH, and MB designed the study. AA, EM, ST, and MB visually rated recruitment trajectories and classified recruitment patterns. ATH, AG, BK abstracted characteristics for included trials. ATH analyzed the data and wrote the first draft of the manuscript. AMS, ABH, JI, AB, ST, PP, Marian B, AF, BK, and EM were responsible for coordinating and managing transfer of individual participant recruitment data. All authors critically revised the manuscript and approved the final version.

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Competing interests

The authors have declared no conflicts of interest.

Ethics approval and consent to participate

The research ethics committee North-West and Central Switzerland (EKNZ) appraised this project (EKNZ-2017-0005) concluding that the project fulfills all standards for ethical research conduct and that it does not require ethical approval as per the Swiss Federal Act on Research Involving Humans, Article 2.

Data sharing

No additional data available.

Transparency statement

The lead author, Prof. Matthias Briel, affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as originally planned (and, if relevant, registered) have been explained

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Manuscript II: Non-registration, discontinuation, and non-publication of randomized trials in Switzerland, the UK, Germany, and Canada: An updated meta-research study

Status: Submission imminent

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Abstract

Objective: Previous studies found that approximately one third of randomised clinical trials (RCTs) were discontinued prematurely and that the most common reason for stopping early was poor recruitment of participants. To minimise research waste, it is crucial that all RCTs are registered and make their results available. Hence, we aimed (i) to assess the fate of RCTs approved by ethics committees in 2016 in terms of non-registration, discontinuation, and non-publication, and (ii) to examine RCT characteristics associated with discontinuation due to poor recruitment and non-publication of RCT results.

Study design and setting: We had access to 346 RCT protocols that were approved in 2016 by research ethics committees in the UK, Switzerland, Germany, and Canada. Key trial characteristics were extracted from approved trial protocols. We systematically searched for trial registrations and trial results publications. All searches were conducted in duplicate (last search January 2024; final update planned for June 2024). In case the status of an RCT was unclear we contacted the corresponding ethics committee or the principal investigator. We reported the proportion of non-registered RCTs, discontinued RCTs (including reason for early discontinuation), and non-published RCTs (considering peer-reviewed publications and results in trial registries). Multivariable logistic regression was conducted to explore RCT characteristics for non-publication and premature discontinued due to poor recruitment.

Results: Of the 346 included RCTs, 22 (6%) were non-registered (industry sponsor RCTs: 3% [5/182] vs. non-industry RCTs 10% [17/164]). Thirty percent (103/346) of RCTs were discontinued, most often due to poor recruitment (40%; 41/103). Seventy-seven percent of RCTs (267/346) made their results available. Results from industry trials were more often available compared to non-industry trials (90% vs 63%). This difference was driven by the fact that only 14% (23/164) of non-industry RCTs reported results in trial registries, compared to 82% (33/182) of industry trials. In multivariable regression industry trials were less frequently discontinued due to poor recruitment than non-industry RCTs (adjusted odds ratio: 0.41; 95% confidence interval: 0.18-0.94).

Conclusion: Non-registration, premature discontinuation due to poor recruitment, and non-publication of RCT results remain major challenges, especially for non-industry trials. To tackle these challenges, measures such as legal obligations should be considered and empirically evaluated.

Background

Well conducted randomised clinical trials (RCT) are of key importance to evaluate the effectiveness and safety of medical interventions [1, 2]. However, the evidence from RCTs can also be flawed when not all conducted RCTs are published [3]. To avoid publication bias, clinical trial registries have been introduced and it became mandatory to prospectively register (i.e. before the enrolment of the first participant) RCTs in a clinical trial registry [4]. Another challenge is that a large proportion of RCTs are prematurely discontinued because of recruitment problems leading to considerable research waste [5]. These discontinued RCTs have an even higher risk of non-publication even though also results from discontinued studies would provide crucial evidence for decision making (i.e. for meta-analyses) [6].

A meta-research study conducted by our study group included RCT protocols that were approved by research ethic committees (RECs) in Switzerland, Germany and Canada between 2000 and 2003, found that 25% of RCTs were discontinued (primarily due to poor recruitment), and that in total only 59% made their results available [6]. Repeating this meta research study (including also RECs from the UK) with protocols approved in 2012 we found that while still 30% of RCTs were discontinued, the rate of sharing results increased to 87% [7]. Furthermore, we showed that 6% of RCTs remained non-registered, that the proportion of non-industry trials sharing results on trial registries was low (16%) and that lower reporting quality in trial protocols was associated with non-publication of trial results [7]. Within this updated meta-research study assessing RCT protocols approved in 2016 we aimed to assess if (i) all RCTs were registered, (ii) trial completion rates have improved, (iii) the availability of study results increased further, and (iv) if more non-industry trials shared results in trial registries. Furthermore, combining the data from RCT protocols from 2012 and 2016 we aimed to investigate trial characteristics associated with non-publication of trial results, and trial discontinuation due to poor recruitment.

Methods

Study sample

This meta-research study is a pre-specified project conducted in the frame of the Adherence to SPIrit REcommendations (ASPIRE) study [8], assessing the reporting quality of ethically approved study protocols before and after the publication of the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) statement [9, 10]. For the ASPIRE project we acquired access to RCT protocols that were approved by RECs in 2012 and 2016 in

Switzerland (all 7 Swiss ethic committees [11]), the UK (Bristol office of the UK National Research Ethics Service responsible for 19 RECs in the UK), Canada (Hamilton), and Germany (Freiburg). For this study we closely followed the methods as used previously [6, 7] for comparability reasons. Eligible RCTs were defined as prospective studies assigning participants randomly to different interventions to study effects on health outcomes. We excluded RCTs which were never started (i.e. did not recruit any patient), trials that were at time of follow-up still ongoing, duplicate RCTs, and studies labelled as pilot, feasibility or phase 1 trials.

Data collection

Within the ASPIRE study key characteristics were extracted from approved trial protocols (i.e. type of sponsor, population, intervention, control, primary outcome, planned sample size, trial registration number) and the adherence to the SPIRIT reporting guideline was assessed (results published separately [12, 13]). Using this information from trial protocols, we systematically searched in duplicate if RCTs were registered and published approximately 8 years after receiving ethical approval (last search conducted in January 2024). For registration we checked if the registration numbers provided in the protocol were correct and if no registration number was provided, we searched for trial registration in the World Health Organization International Clinical Trial Registry Platform (ICTRP) database, the US National Library of Medicine (ClinicalTrials.gov), the European Union Clinical Trial Registry (EUCTR), the International Standard Randomised Controlled Trial Number (ISRCTN) registry and finally used the Google search engine if no registration was identified. RCTs were classified as non-registered if we could not find a registration with this search strategy. For trial publication we searched PubMed, Google Scholar and Scopus for potential full text publications. We searched for registrations and publications using the following strategy: (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).

We extracted the date of trial registration, date of first participant enrolment, trial status (i.e., completed, premature discontinuation together with reason, or unclear), availability of trial results in registry (results directly published in registry), and the planned and finally achieved sample size. RCTs reporting their status as ongoing were classified as unclear in case trial registries have not been updated in the last two years (only for trials with an estimated completion date before January 2024). RCTs were classified as discontinued if they were specifically labelled as such by investigators or in case they recruited less than 90% of the planned sample size pre-specified in the approved study protocol. We contacted ethical

committees and trial investigators to clarify unclear trial status, unclear reason for discontinuation or if we could not identify any trial results.

Analysis

Rate of trial registration, completion of trial, and availability of study results were reported together with 95% confidence intervals (CI). For availability of trial results, we considered sharing trial results on trial registries or through a peer reviewed publication as valid options and report them also separately. Amongst registered trials we assessed the proportion of retrospectively registered trials (i.e. in case the first patient was recruited before the trial was registered on any trial registry). All results were analysed stratified by type of sponsor (industry vs. non-industry) and country of ethical approval. We compared the results descriptively to the results from RCT protocols approved in the early 2000s [6] and 2012 [7].

Univariable and multivariable logistic regressions were conducted to assess if certain factors (i.e. better adherence to reporting guidelines in the protocol; larger target sample size; use of an active comparator versus placebo; multicenter versus single-center trial; reporting of any recruitment projection versus not reporting; industry- versus investigator-sponsored trials) were associated with (i) making trial results available, and (ii) premature trial discontinuation due to poor recruitment. To increase the power of the regression analyses, we repeated all regression analyses including also the data from our study on trial protocols approved in 2012 (year of approval was added as a factor in the regression model) [7]. All analyses were conducted in Stata (version 16.1) and a p-value below 0.05 was considered as threshold for significance (2 sided).

Results

Of the total 400 potentially eligible protocols that we were granted access from research ethics committees, 346 were eligible for analyses (Figure 1). The included RCTs had a median planned sample size of 220 (interquartile range [IQR] 102-450) and reported a median of 76% (IQR: 68-81%) of SPIRIT items adequately (Table 1). The majority of trials used a parallel arm design (93.1%; 322/346), were multicentric (76.0%; 263/346), and tested drugs (60.4%; 209/346). Approximately half of the RCTs were industry sponsored (52.6%; 182/346). Further information on baseline characteristics is presented in Table 1, Table S1 (stratification by country of ethical approval) and Table S2 (baseline characteristics of trial protocols receiving ethical approval in 2000-2003 [6] and in 2012 [7]).

Of the 346 RCTs, 943.6% (324/346) were registered (Table 2). Non-registration and retrospective registration (i.e. registration after the recruitment of the first patient) was more

common amongst non-industry sponsored trials (10.4%; 17/164 not registered; 14.6%; 24/164 retrospectively registered) compared to industry sponsored trials (2.8%; 5/182 not registered; 5.0%; 9/182 retrospective registered). Approximately 9 years after receiving ethical approval, results were available (considering peer-reviewed publications and results in trial registries) of 77.2% (267/346) of RCTs. Compared to non-industry sponsored RCTs, industry trials made results more often available as a peer reviewed publication (73.1%; 133/182 industry sponsored RCT *vs* 62.8%; 103/164 non-industry sponsored RCT) and especially within trial registries (81.9%; 149/182 industry sponsored RCT *vs* 14.0%; 23/164 non-industry sponsored RCT). Results were less often made available in trial registries of RCTs that received ethical approval in Switzerland (38.6%; 71/184) compared to other countries (Table S3). Of the 110 RCTs that were not published in a peer-reviewed journal, 89 (80.9%) were registered and 31 (28.2%) made the results available in the registry (61.2%; 30/49 industry sponsored RCT *vs* 1.6%; 1/61 non-industry sponsored RCT; Table 2). Compared to older trial protocols approved in 2012 the rate of nonregistered and retrospective registered studies remained unchanged (approximately 6% non-registered and 10% retrospectively registered), with relative low rates of prospective registered RCTs among non-industry trials (75%; Table S4). Availability of trial results strongly increased from the protocols approved in the early 2000`s (59.3%) to 2012 (87.1%); but no further improvement was seen for RCTs approved in 2016 (77.2%). Sharing trial results in trial registries was rarely done for non-industry RCTs approved in 2012 (15.7%) and 2016 (14.0%: Table S4).

Approximately 30% of RCTs were prematurely discontinued (103/346/ Table 1). The most common reason for early discontinuation was poor recruitment (40.8%; 42/103), followed by futility (11.7%; 12/103), and organisational and strategic reasons (11.7%; 12/103; Table 3). Compared to completed RCTs, prematurely discontinued trials were more likely to remain unpublished considering any source (Odds ratio [OR] 3.36; 95% CI 1.78-6.35) and when assessing peer-reviewed publications (OR 4.05; 95% CI 2.33-7.04) and results in trial registries separately (OR 2.10; 95% CI 1.27-3.48; Table S5). The rate of discontinued trials remained stable over the last two decades (approximately 30%) and the most common reason was always poor recruitment (approximately 40% of prematurely discontinued trials; Table S4).

Multivariable analyses confirmed that industry sponsored trials had lower odds for non-publication (OR 0.25; 95% CI 0.13-0.51; p<0.001) and being discontinued due to poor recruitment (OR 0.41; 95% CI 0.18-0.94; p=0.036; Table 4). RCT protocol with higher adherence to the SPIRIT reporting guidelines had lower odds of non-publishing trial results (OR 0.77; 95% CI 0.61-0.96; p=0.019). For the other assessed characteristics, no association was found. Adding the data from RCTs receiving ethical approval in 2012, confirmed that

better reported protocols (according to SPIRIT reporting guidelines) was associated with fewer non-available trial results (OR 0.72; 95% CI 0.61-0.85; p<0.001; Table S6). Factors associated with higher rates of non-available study results were single centre studies (OR 1.99; 95% CI 1.19-3.31; p=0.009) and RCTs receiving ethical approval in 2016 (OR 2.68; 95% CI 1.65-4.36; p<0.001). No factors, besides industry sponsored RCTs, were found to be associated with lower odds of discontinuation due to poor recruitment (Table S6).

Discussion

Our studies showed that trial registration rates, proportion of completed trials, and the rate of making trial results available are still far away from 100% and from being compliant with current laws. In more detail, prospective trial registration (i.e. before enrolling the first participant) is mandatory since 2005 according to the International Committee of Medical Journal Editors (ICMJE) [14]. Our updated meta-research study showed that for RCTs approved in 2016 - more than ten years later - still one out of four non-industry trials do not fulfil this requirement. In contrast, among industry sponsored RCTs, only 8% of trials were not correctly registered (i.e. 3% not registered, 5% retrospectively registered). These numbers are in line with what we know from RCTs approved in 2012 [7]. A study published in 2023, found that amongst Swiss trials receiving ethical approval between 2016 to 2020, 9% were not registered. This number is even slightly higher compared to our observed nonregistration rate in Switzerland (7%) and does not indicate any improvement over time [15]. Hence, action should be taken to increase registration rates (e.g. implementing laws; controlling and enforcing laws by ethical committees and publishing journals).

Furthermore, our study indicated that trial registries can be an important to make trial results accessible. Amongst the RCTs that did not publish results in a peer-reviewed article, 28% at least reported results within a trial registry (61% industry RCTs; 2% non-industry RCTs). Therefore, it is crucial to consider trial registries when conducting systematic reviews and meta-analyses [16, 17]. As shown in RCTs approved in 2012 [7], we can confirm that investigators from non-industry sponsored trials rarely share results through trial registries (i.e. only 23/174; 14%). In Switzerland it will soon become mandatory to make trial results available in a trial registry within one year after trial completion [18]. Similar laws exist already in the European Union for trials assessing medical products (i.e. drugs, vaccines, biological products) [19]. Further evaluations will be required to assess if these requirements can be enforced or if more pragmatic solutions also considering academic researchers can be implied. For example, it should be discussed if publishing results via a trial registry is required in case the results is already transparently reported in a peer-reviewed publication (assuming

that all endpoints are adequately reported). As trial registries allow to link peer-reviewed publications, one could argue that administrative burdensome processes could be avoided while transparent reporting of is ensured with such a procedure.

A further major challenge which did not improve over time is that approximately one third of all RCTs is still prematurely discontinued, mainly due to poor recruitment of participants. Our repeated data collection showed that there is no improvement over time and that trial discontinuation is still strongly associated with non-publication of trial results. New trial designs such as platform trials or Trials within Cohort studies (TwiCs) seem to allow for more efficient participant recruitment [20, 21] (*Amstutz et al., JCE; under revision*). Another possibility is that pilot trials are stronger promoted before conducting definitive trials (e.g. by researchers and funders) [22].

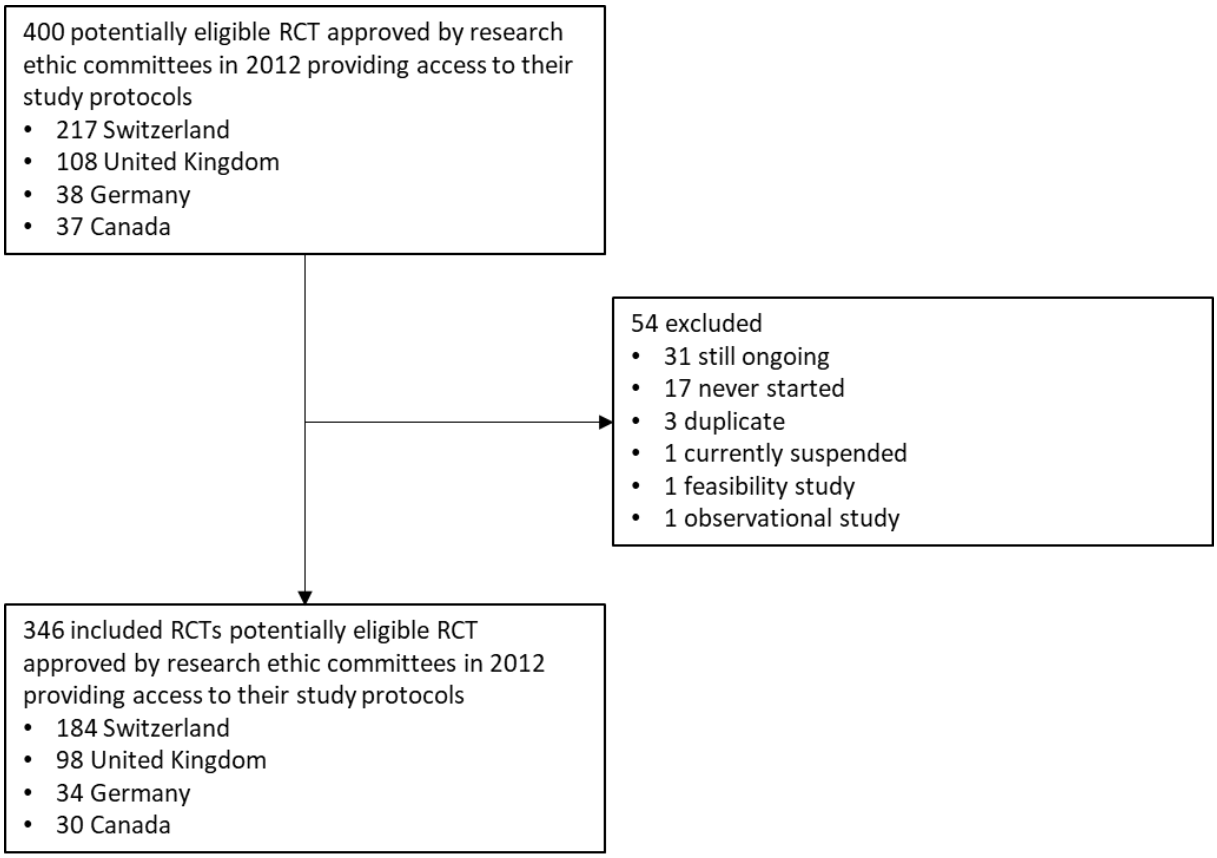
While the results availability increased strongly from RCTs approved in the early 2000`s (59%) to 2012 (87%), no increase was seen for RCTs approved in 2016 (77%). Possible reasons might be the COVID-19 pandemic which have caused recruitment delays for several studies [23] and the shorter follow-up duration of only 8 years (follow-up duration of RCTs approved in early 2000`s and 2012 was approximately 10 years).

This meta-research study has the following strengths: Having access to approved study protocols from REC in four different countries allowed us to assess unbiased rates of non-registration, discontinuation, and non-publication. Collaborating with the same ethics committees as in previous studies and following the same methods [6, 7] enabled us to make valid statements about these rates over time. Merging our data with the data from 2012 increased our power to assess factors associated with non-publication and discontinuation due to poor recruitment.

The following limitations are worth mentioning: First, the follow-up of the RCTs approved in 2016 was shorter compared to our previous studies, providing these RCTs less time to publish their results. Hence, we would not conclude that the rate of making trial results has decreased from RCTs approved in 2012 compared to 2016 despite the decrease in absolute numbers (87% vs 77%). Second, the status of some of the RCTs remained unclear despite our efforts to contact investigators and clarifying the status through contacting RECs. It is possible that some of these RCTs have never started to recruit participants and that therefore the rate of unregistered RCTs is somewhat overestimated. Third, since our sample consists of RCTs approved in 2016 in Switzerland, the UK, Germany and Canada, the rates of non-registration, discontinuation and non-publication might be different in other countries or could have changed over the last years.

In conclusion, incorrect trial registration (i.e. non-registration and retrospective registration), premature discontinuation due to poor recruitment, and non-publication of RCT results remain major challenges in clinical research. Our study has shown that industry trials perform better in these aspects and that the current focus should be how to improve these rates for non-industry trials. It has to be assessed if new laws (e.g. mandatory sharing of RCT results in trial registry) can and will be implemented by non-industry sponsored trial investigators or if further adjustments (e.g. more pragmatic solutions of making data available; providing resources from funders for administration) will be necessary.

Figure 1: Flow chart



Abbreviations: RCT=Randomised clinical trial

Table 1- Baseline table of included randomised clinical trials.

	Industry sponsored RCTs (n=182)	Non-industry sponsored RCTs (n=164)	All RCTs (n=346)
Planned sample size, median (IQR)	300 (140-560)	147 (80-332)	220 (102-450)
Proportion of adequately reported SPIRIT items in protocol, median (IQR)	0.77 (0.71-0.81)	0.75 (0.62-0.81)	0.76 (0.68-0.81)
Single centre vs. multicentre			
Single centre	6 (3.3%)	77 (47.0%)	83 (24.0%)
Multicentre	176 (96.7%)	87 (53.1%)	263 (76.0%)
Study design			
Parallel	176 (96.7%)	146 (89.0%)	322 (93.1%)
Crossover	2 (1.1%)	11 (6.7%)	13 (3.8%)
Factorial	1 (0.6%)	3 (1.8%)	4 (1.2%)
Cluster	1 (0.6%)	3 (1.8%)	4 (1.2%)
Split body	2 (1.1%)	1 (0.6%)	3 (0.9%)
Placebo controlled	108 (59.3%)	43 (26.2%)	151 (43.6%)
Recruitment-rate reported in protocol	31 (17.0%)	48 (29.3%)	79 (22.8%)
Country of ethical approval			
Switzerland	79 (43.4%)	105 (64.0%)	184 (53.2%)
United Kingdom	61 (33.5%)	37 (22.6%)	98 (28.3%)
Germany	26 (14.3%)	8 (4.9%)	34 (9.8%)
Canada	16 (8.8%)	14 (8.6%)	30 (8.7%)
Intervention			
Drug	154 (84.6%)	55 (33.5%)	209 (60.4%)
Medical devices	17 (9.3%)	27 (16.5%)	44 (12.7%)
Behavioural	2 (1.1%)	35 (21.3%)	37 (10.7%)
Surgical	2 (1.1%)	22 (13.4%)	24 (6.9%)
Other[a]	7 (3.8%)	25 (15.2%)	32 (9.2%)
Medical field			
Oncology	42 (23.1%)	15 (9.2%)	57 (16.5%)
Cardiovascular	27 (14.8%)	17 (10.4%)	44 (12.7%)
Surgical	7 (3.9%)	23 (14.0%)	30 (8.7%)
Neurology	17 (9.3%)	11 (6.7%)	28 (8.1%)
Psychiatry	0 (0.0%)	27 (16.5%)	27 (7.8%))
Other[b]	89 (48.9%)	71 (43.3%)	160 (46.2%)

[a]Process optimization in healthcare (n=9); rehabilitation (n=8); dietary supplement (n=7); diagnostic (n=3), creams and cosmetics (n=3); vaccines (n=2)
[b]Gastrointestinal (n=24); orthopaedics and rheumatology (n=23); respiratory (n=20); paediatrics (n=16); intensive care (n=15); endocrinology (n=13); haematology (n=8); infectious diseases (n=8); dentistry (n=6); dermatology (n=5); nephrology (n=5); ophthalmology (n=5); obstetrics and gynaecology (n=4); geriatrics (n=4); hepatology (n=1); public health (n=1); ear (n=1); primary care (n=1)
Abbreviations: RCT=randomised clinical trial; IQR=interquartile range

Table 2- Non-registration, discontinuation, and non-publication of randomised clinical trials receiving ethical approval in 2016

	Industry sponsored RCTs (n=182)	Non-industry sponsored RCTs (n=164)	All RCTs (n=346)
Registration status			
Registered	177 (97.3%, 93.7-99.1%)	147 (89.6%, 83.9-93.8%)	324 (93.6%, 90.5-96.0%)
Prospectively registered	168 (92.3%, 87.4-95.7%)	123 (75.0%, 67.7-81.4%)	291 (84.1%, 79.8-87.8%)
Retrospectively registered	9 (5.0%, 2.3-9.2%)	24 (14.6%, 9.6-21.0%)	33 (9.5%, 6.7-13.1%)
Not registered	5 (2.8%, 0.9-6.3%)	17 (10.4%, 6.2-16.1%)	22 (6.4%, 4.0-9.5%)
Completion status			
Completed	125 (68.7%, 61.4-75.3%)	95 (57.9%, 50.0-65.6%)	220 (63.6%, 58.3-68.7%)
Discontinued	50 (27.5%, 21.1-34.6%)	53 (32.3%, 25.2-40.1%)	103 (29.8%, 25.1-34.9%)
Unclear	7 (3.9%, 1.6-7.8%)	16 (9.8%, 5.7-15.4%)	23 (6.7%, 4.3-9.8%)
Results availability			
At any source (peer-reviewed publication or on trial registry)	163 (89.6%. 84.2-93.6%)	104 (63.4%, 55.5-70.8%)	267 (77.2%, 72.4-81.5%)
Peer reviewed publication	133 (73.1%, 66.0-79.4%)	103 (62.8%, 54.9-70.2%)	236 (68.2, 63.0-73.1%)
In trial registry	149 (81.9%, 75.5-87.2%)	23 (14.0%, 9.1-20.3%)	172 (49.7% 44.3-55.1%)
Results not available (neither as publication nor in trial registry)	19 (10.4%, 6.4-15.8%)	60 (36.6%, 29.2-44.5%)	79 (22.8%, 18.5-27.6%)
Neither registered nor published	5 (2.8%. 0.9-6.3%)	16 (9.8%, 5.7-15.4%)	21 (6.1%, 3.8-9.1%)
Not published in peer-reviewed journal but registered[a]	44 (89.8%, 77.8-96.6%)	45 (73.8%, 60.9-84.2%)	89 (80.9%, 72.3-87.8%)
Not published in peer-reviewed journal but results available in registry[a]	30 (61.2%, 46.2-74.8%)	1 (1.6%, 0.0-8.8%)	31 (28.2%, 20.0-37.6%)

[a]Only a subsample of 110 trials (49 industry sponsored; 61 non-industry sponsored) considered which were not published in a peer reviewed journal

Table 3-Reasons for trial discontinuation and sources where discontinued trials were making results available

Reasons for discontinuation	All Discontinued RCTs (n=103)	Industry-sponsored discontinued RCTs (n=50)	Non-industry sponsored discontinued RCTs (n=53)	Any results available (peer-reviewed or at trial registry)	Results available as a peer reviewed publication	Results available in clinical trial register	Results not available
Poor recruitment[a]	42 (40.8%)	16 (32.0%)	26 (49.1%)	26 (61.9%)	21 (50.0%)	12 (28.6%)	16 (38.1%)
Futility	12 (11.7%)	12 (24.0%)	0 (0.0%)	12 (100.0%)	8 (66.7%)	11 (91.7%)	0 (0.0%)
Organizational/strategic reasons	12 (11.7%)	6 (12.0%)	6 (11.3%)	6 (50.0%)	4 (33.3%)	3 (25.0%)	6 (50.0%)
Harm	6 (5.8%)	4 (8.0%)	2 (3.8%)	5 (83.3%)	3 (50%)	3 (50.0%)	1 (16.7%)
Benefit	5 (4.9%)	3 (6.0%)	2 (3.8%)	4 (80.0%)	2 (40.0%)	4 (80.0%)	1 (20.0%)
External evidence	2 (1.9%)	2 (4.0%)	0 (0.0%)	2 (100.0%)	1 (50.0%)	2 (100.0%)	0 (0.0%)
COVID-19	2 (1.9%)	2 (4.0%)	0 (0.0%)	2 (100.0%)	1 (50.0%)	1 (50.0%)	0 (0.0%)
Unclear	22 (21.4%)	5 (10.0%)	17 (32.1%)	15 (68.2%)	15 (68.2%)	6 (27.3%)	7 (31.8%)

[a] Ten studies that stated slow recruitment as reason for discontinuation mentioned in addition another reason (i.e. COVID-19 n=6; external evidence n=3; organizational/strategic reason n=1).

Table 4- Factors associated with making trial results available and discontinuation of trial due to poor recruitment

Characteristics			Univariable			Multivariable		
			OR	95% CI	*P-value*	OR	95% CI	*P-value*
Non-availability of trial results (considering peer-reviewed publication and trial registries)	**RCT results not available (n=79)**	**RCT results available (peer reviewed journal or trial registry) (n=267)**						
Proportion of adequate SPIRIT reporting, median (IQR)[a]	0.72 (0.59, 0.80)	0.76 (0.70, 0.81)	0.69	0.56-0.85	<0.001	0.77	0.61-0.96	0.019
Planned target sample size, median (IQR)[b]	120 (56, 260)	264 (120, 517)	0.86	0.77-0.96	0.006	0.93	0.87-1.00	0.061
Placebo controlled (vs not placebo controlled)	30/79 (38.0%)	121/267 (45.3%)	0.74	0.44-1.24	0.249	1.32	0.72-2.41	0.364
Single-center (vs multicenter)	38/79 (48.1%)	45/267 (16.9%)	4.57	2.65-7.89	<0.001	1.57	0.80-3.09	0.193
Reported recruitment projection	19/79 (24.1%)	60/267 (22.5%)	1.09	0.61-1.97	0.769	0.91	0.47-1.74	0.770
Industry sponsorship	19/79 (24.1%)	163/267 (61.1%)	0.20	0.11-0.36	<0.001	0.25	0.13-0.51	<0.001
Discontinued due to poor recruitment	**RCTs discontinued due to poor recruitment (n=42)**	**RCTs not discontinued due to poor recruitment (n=281)[c]**						
Proportion of adequate SPIRIT reporting, median (IQR)[a]	0.74 (0.69, 0.83)	0.77 (0.70,0.81)	0.99	0.73-1.34	0.968	1.05	0.77-1.42	0.770
Planned target sample size, median (IQR)[b]	208 (105, 316)	240 (112, 495)	0.95	0.87-1.03	0.179	0.97	0.91-1.03	0.328
Placebo controlled (vs not placebo controlled)	22/42 (52.4%)	121/281 (43.1%)	1.45	0.76-2.79	0.259	1.93	0.94-3.95	0.071
Single-center (vs multicenter)	14/42 (33.3%)	55/281 (19.6%)	2.05	1.01-4.16	0.046	1.29	0.53-3.13	0.579
Reported recruitment projection	7/42 (16.7%)	70/281 (24.9%)	0.60	0.26-1.41	0.246	0.55	0.23-1.31	0.175
Industry sponsorship	16/42 (38.1%)	159/281 (56.6%)	0.47	0.24-0.92	0.027	0.41	0.18-0.94	0.036

[a] In increments of 10%
[b] In increments of 100
[c] Studies with unclear discontinuation status excluded (n=23)
Abbreviations: OR=odds ratio; CI= confidence Interval; IQR=interquartile range; RCT=randomised clinical trial

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Competing Interests

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Manuscript III: Planning and reporting of patient-reported outcomes in randomized clinical trials: a repeated cross-sectional study

Status: Submission planned to PLoS Med

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Abstract

Introduction: Patient-reported outcomes (PROs) provide crucial information for evaluating healthcare interventions. We examined the prevalence and characteristics of PROs in randomized clinical trial (RCT) protocols across medical fields, the reporting quality of PROs, and the consistency between PROs specified in trial protocols and subsequent reporting in corresponding published trials.

Methods: We included 237 RCT protocols approved in 2012, and 252 RCT protocols approved in 2016, by ethics committees in Switzerland, Germany, and Canada. We systematically searched for corresponding peer-reviewed published trial results in PubMed, Google Scholar, and Scopus in 2022 (for protocols approved in 2012) and 2024 (for protocols approved in 2016). Pairs of reviewers independently extracted characteristics of RCT protocols, PROs specified in protocols and associated published trial results, and assessed reporting quality of trials with a PRO as their primary outcome with the Consolidated Standards of Reporting Trials – PRO extension (CONSORT-PRO).

Results: Of the 489 included trial protocols, 148 (30%) did not report use of a PRO; 98 (20%) specified a PRO as their primary outcome and 244 (50%) as a secondary outcome. The prevalence of PROs varied substantially across medical fields, ranging from 100% in rheumatology and psychiatry RCTs to less than 5% in pediatric and anesthesiology trials.

Among 342 trial protocols that pre-specified a PRO, 244 (71%) had corresponding published trials results at 8-10 years follow-up. Only 94 published trials (39%) reported all PROs as defined in their protocol, 63 (26%) failed to report any pre-specified PROs, and 87 (36%) reported more, less, or different PROs than pre-specified in their protocol. These findings were consistent between trial protocols approved in 2012 and 2016. Among 62 published trials that reported a PRO as their primary outcome, reporting quality was often inadequate with 7 of 13 items on the CONSORT-PRO met by less than half of trials.

Conclusions: Approximately 1 in 3 trial protocols do not capture PROs, and of those that do the majority specify them as secondary outcomes; however, large variability exists across medical fields. Less than half of RCT protocols with planned PROs reported them as specified in corresponding published results, suggesting potential outcome reporting bias, and PRO reporting quality was often deficient. These limitations complicate informed decision-making between patients and healthcare providers, as well as the development of evidence-based clinical practice guidelines.

Introduction

Patient-reported outcomes (PROs) are reported directly by patients and not interpreted by an observer [1]. PROs may include patient assessments of disease symptoms or treatment side effects, such as pain, fatigue, or anxiety; functional outcomes such as physical, sexual, social, emotional, or cognitive functioning; or multidimensional outcomes such as quality of life (QoL) or health utility [2]. PROs have an essential role in capturing patients' experiences and perspectives and informing evidence-based clinical practice and shared decision-making [3-5]. The importance of PROs has been recognized by regulatory authorities, international policy makers, and patients [1, 6-8].

Meta-research studies, however, have found that clinical trial protocols often fail to include PROs and, when planned, they may not be reported in associated published trials [9-11]. Further, PROs may be modified when reported, potentially reflecting outcome reporting bias [12-17]. Recognition of suboptimal reporting has led to the development of reporting guidelines for PROs in study protocols and trial publications [18-21]. Failure to specify important PRO characteristics in the protocol, for instance, may result in insufficient data gathering for these outcomes during the trial [22].

Previous meta-research studies on PROs have largely focused on a specific disease (e.g., cancer) or on a specific type of PRO (e.g., QoL) [11, 23-29]. We aimed to investigate (i) the prevalence and characteristics of PROs specified in RCT protocols approved in 2012 and 2016 across medical fields, (ii) the quality of reporting of PROs when specified as a primary outcome, and (iii) concordance between planned PROs in protocols and reported PROs in published trials.

Methods

We analyzed 549 RCT protocols from a previous study (Adherence to Spirit Recommendations Study [ASPIRE]) [30-32], that were approved by nine research ethics committees in 2012 (n=257) and 2016 (n=292), in Switzerland (Basel, Bellinzona, Bern, Geneva, Lausanne, St. Gallen, and Zurich), Canada (Hamilton), and Germany (Freiburg). All trial protocols randomly assigned patients to different interventions (or an intervention and control group) to evaluate effects on health outcomes. Methodologic details, including eligibility criteria, process of protocol selection, data extraction, and additional objectives addressed in add-on studies have previously been published [30].

Search for corresponding published trials

We systematically searched for full text publications corresponding to trial protocols in PubMed, Google Scholar, and Scopus [33]. Specifically, we searched for published trials for protocols approved in 2012 up to February 2022, and published trials for protocols approved in 2016 up to January 2024. We excluded trial protocols that were never initiated or still ongoing at the time of analysis [33].

Data collection

Using a web-based, password protected data extraction tool (https://aspire-pro.squiek.io), investigators trained in trial methodology worked in pairs of two and abstracted each study protocol and corresponding trial publication, independently and in duplicate.

From all included RCT protocols, we extracted trial characteristics such as sponsorship, intervention type, country, whether the trial was multicenter or single-center, and planned sample size [30]. We captured all reported PROs and whether they were defined as a primary or secondary outcome. We extracted information captured by PROs (e.g., physical functioning, disease-specific QoL), the instrument used to capture each PRO and evidence provided of its' validity. We extracted the same information from all identified RCT publications. In addition, for all published trials that used a PRO as their primary outcome measure, we assessed the quality of reporting with the Consolidated Standards of Reporting Trials with patient-reported outcomes (CONSORT PRO Extension) checklist [18]. Any disagreements were resolved through discussion or third-party arbitration by AA, BS, or MB.

Analyses

The characteristics of study protocols, corresponding trial publications, and PROs were summarized as frequencies and proportions for categorical variables and as medians and interquartile ranges (IQRs) for continuous variables. In the main analysis we treated composite outcomes, which included PRO and clinician-reported outcome components, e.g. the American College of Rheumatology 20/50/70 Response Criteria (ACR20/50/70), as PROs and conducted a sensitivity analysis treating such composite outcomes as non-PROs. We used R version 4.0.2 for all analyses, and comparisons were 2-tailed using a threshold for significance of $p \leq 0.05$.

Results

Of 549 approved RCT protocols (257 approved in 2012, and 292 in 2016), 60 were excluded because they were either ongoing, duplicates, or never initiated, leaving a total of 237 protocols

approved in 2012 and 252 protocols approved in 2016 for inclusion in the present study (supplementary Figure). Just over half of trials were sponsored by industry (53%, 258 of 489), and 79% (385 of 489) were multi-center trials (Table 1).

Thirty percent of protocols did not include a PRO (147 of 489) (Table 2). Of those that did, 20% were primary outcomes (17%, 40 of 237 in 2012; 23%, 58 of 252 in 2016), and 50% were secondary outcomes (51%, 122 of 237 in 2012; 48%, 122 of 252 in 2016). However, the prevalence varied substantially across medical fields, from 100% in rheumatology (22 of 22) and psychiatry (21 of 21) RCTs to less than 5% in pediatric and anesthesiology trials. Further, almost all trials of behavioral interventions (97%, 28 of 29) included a PRO. Results were consistent across different countries and the year of protocol approval.

Of the 98 study protocols that specified a PRO as their primary outcome, 39% (n=38) had not published their trial results at 8-10 years follow up (Table 2). Of the 60 protocols that had corresponding trial results published, 78% (n=47) reported PROs as specified in their protocol and 22% (n=13) modified their PRO. Of the 244 study protocols that specified a PRO as a secondary outcome, 25% (n=60) had not published their trial results at 8-10 years follow up. Of the 184 protocols that had corresponding trial results published, 25% (n=47) reported PROs as specified in their protocol and 75% (n=137) did not report some or all their PROs, or reported PROs not specified in their protocol. Results were largely consistent across medical fields and the year of protocol approval, with the exception that most psychiatry trials (55%, 5 of 9) reported modified PROs when they were a primary outcome (Table 2, Supplementary Table S1).

Most PROs captured either symptoms or disease-specific outcome measures, lacked supporting information regarding validity of the instrument used, but did provide details on how data collection was conducted (Table 3). Quality of reporting of PROs was often inadequate, with less than half of the 98 published trials that reported a PRO as a primary outcome meeting 7 of the 13 CONSORT-PRO items (Table 4). However, there was improvement between trials associated with more recently approved protocols on two items. Twenty-four percent (6 of 26) of trial results based on protocols approved in 2012 reported a supporting hypothesis for their PRO primary outcome vs. 54% (19 of 26) for trials based on protocols approved in 2016. Further, 68% (18 of 26) trial results associated with a protocol approved in 2012 reported a sample size calculation for their PRO primary outcome vs. 91% (31 of 36) of trials associated with protocols approved in 2016. Sensitivity analyses treating composite outcomes including PRO components as non-PROs revealed similar results (supplementary Tables S2-S5).

Discussion

Main findings

This meta-research study of 489 RCT protocols found that 30% did not capture PROs. Of those that did, 71% defined PROs as a secondary outcome and 29% as a primary outcome; however, the prevalence of PROs varied substantially across medical fields. Among corresponding published RCTs, only 39% reported PROs as defined in their protocols, 26% failed to report any pre-specified PROs, and 36% reported more, less, or different PROs than pre-specified in their protocol. Among published trials that reported a PRO as their primary outcome, reporting quality was often inadequate with 7 of 13 items on the CONSORT-PRO met by less than half of trials. These findings were consistent between trial protocols approved in 2012 and 2016.

Strengths and limitations

Strengths of our study include full access to a large sample of approved RCT protocols from three countries, a comprehensive search for corresponding results publications eight to ten years after trial approval, and engagement of reviewers with methodologic training who performed all data abstraction independently and in duplicate. Further, our results proved robust in sensitivity analyses with a more conservative definition of primary PROs.

Our study also has several limitations. Firstly, our study sample was limited to RCT protocols approved by research ethics committees in Switzerland, Germany, and Canada in 2012 and 2016, and may not be generalizable to other settings. Secondly, for some descriptive subgroup analyses the number of RCTs per group was limited which reduces our confidence in comparisons. Thirdly, we focused on the comparison of PROs planned in approved protocols with PROs reported in results publications and did not additionally consider PRO reporting in protocol amendments or trial registries. Fourthly, we did not assess whether research questions in RCTs were suitable for PROs or not. Fifthly, we used only two criteria (validated instrument for PRO measurement, method for PRO data collection specified) to assess the quality of PRO reporting in protocols, because our protocol sample predated the publication of the Standard Protocol Items: Recommendations for Interventional Trials-patient-reported outcome extension for writing protocols with patient-reported outcomes (SPIRIT-PRO) in 2018 [19]. Sixthly, we did not consider statistical analyses of PROs in RCTs as this was comprehensively investigated by the Setting International Standards in Analysing Patient-Reported Outcomes and Quality of Life Endpoints Data Consortium (SISAQOL) [34]. Lastly, when checking CONSORT-PRO items we adapted the original 14-item list, which we explained in the legend of Table 4, in an attempt to better reflect PRO-specific challenges [35].

Comparison with other studies

To our knowledge, this is the first study focusing on the prevalence of PROs in trial protocols and the consistency of reporting in corresponding published results across medical fields. There are, however, several studies on the planning and reporting of QoL outcomes in oncology trials. Previous meta-research on 173 protocols of cancer trials approved between 2000-2003 and corresponding results publications up to 2013 from our group found that only 20% of approved trials reported QoL outcomes, with cancer trials either not specifying QoL outcomes in their protocol (48%), not publishing trial results (21%), or failing to report pre-specified QoL outcomes in their published results (10%) [10].

Results were similar in our sample of RCT protocols approved in 2012 and 2016. Specifically, of the 84 oncology trials, 19% reported PRO results as planned in their protocol, 20% did not specify a PRO in their protocol, 13% not publishing any trial results, 26% failing to report pre-specified PROs in their published results, and 21% publishing results of more, less, or modified PROs when compared those specified in their protocol (supplementary Table S2).

A separate meta-research study examined 172 RCTs testing new drugs in metastatic non-small cell lung cancer published between 2010 and 2021 and found, similar to our study, that only 1% of trials specified QoL as a primary outcome, 23% of RCTs did not consider QoL at all, and RCTs reporting effects on QoL as a primary outcome showed modest quality of reporting with respect to CONSORT-PRO items [28]. Another analysis of QoL assessments and reporting in 106 solid cancer trials published between 2013 and 2021, found none of the trials considered QoL as primary outcome [11].

Reasons for non-reporting of pre-specified PROs in published trial results may include outcome selection bias. For example, industry-funded trials may include agreements that allow the sponsor to remove unfavorable results from draft manuscripts prior to submission[36]. Moreover, PRO data are often cumbersome to collect, and may not be considered a “serious measurement” because they are subjective [37].

Our findings suggest that, despite the publication of CONSORT-PRO guidance in 2013, the planning and reporting of PROs in trial reports remains suboptimal [11, 16, 35, 38, 39]. The Patient-Reported Outcomes Tools: Engaging Users and Stakeholders (PROTEUS) Consortium aims for more patient-centered research and promotes tools such as the SPIRIT-PRO recommendations for protocol writing, the International Society for Quality of Life Research Minimum Standards for selecting a PRO measure, the SISAQOL recommendations for PRO data analysis, the CONSORT-PRO statement, recommendations for the graphic display of PRO data, and a Clinician’s Checklist for reading and using an article about PROs

[39]. Further implementation of these tools in clinical trial research and involvement of patient partners in trial planning, conduct, and reporting may facilitate improved consideration and reporting of PROs in clinical trials. Another promising development is the increasing collection and use of PRO measures in routine clinical practice, which may also improve reporting of PROs in clinical trials [40, 41].

Conclusions

Approximately 1 in 3 trial protocols do not capture PROs, and of those that do the majority specify them as secondary outcomes; however, large variability exists across medical fields. Less than half of RCT protocols with planned PROs reported them as specified in corresponding published results, suggesting potential outcome reporting bias, and PRO reporting quality was often deficient. These limitations complicate informed decision-making between patients and healthcare providers, as well as the development of evidence-based clinical practice guidelines.

Table 1: General characteristics of clinical trial protocols planning PROs as primary or secondary outcomes

	Protocols approved in 2012 n= 237			Protocols approved in 2016 n= 252		
	PRO as a primary outcome (n= 40; 17%)	**PRO as a secondary outcome (n=122; 51%)**	**No PRO (n= 75; 32%)**	**PRO as a primary outcome (n= 58; 23%)**	**PRO as a secondary outcome (n=122; 48%)**	**No PRO (n= 72; 29%)**
Country of research ethics committee, n (%)						
Switzerland	24 (60.0%)	92 (75.4%)	49 (65.3%)	42 (72.4%)	98 (80.2%)	48 (66.7%)
Germany	10 (25.0%)	16 (13.1%)	11 (14.7%)	10 (17.2%)	15 (12.4%)	9 (12.5%)
Canada	6 (15.0%)	14 (11.5%)	15 (20.0%)	6 (10.3%)	9 (7.4%)	15 (20.8%)
Medical field, n (%)						
Surgical	7 (17.5%)	13 (10.7%)	10 (13.3%)	6 (10.3%)	13 (10.7%)	5 (6.9%)
Psychiatry	2 (5.0%)	2 (1.6%)	0	11 (19.0%)	6 (4.9%)	0
Neurology	6 (15.0%)	8 (6.6%)	5 (6.7%)	4 (6.9%)	10 (8.2%)	6 (8.3%)
Oncology	0	32 (26.2%)	10 (13.3%)	2 (3.4%)	33 (27.0%)	7 (9.7%)
Rheumatology	5 (12.5%)	5 (4.1%)	0	8 (13.8%)	3 (2.5%)	0
Gastro/intestinal	5 (12.5%)	3 (2.5%)	1 (1.3%)	7 (12.1%)	5 (4.1%)	1 (1.4%)
Other *	15 (37.5%)	59 (48.3%)	49 (65.4)	20 (34.5%)	52 (39.9%)	53 (73.7%)
Type of intervention, n (%)						
Drug	25 (62.5%)	79 (64.8%)	50 (66.7%)	29 (50.0%)	73 (59.8%)	50 (69.4%)
Behavioral	3 (7.5%)	5 (4.1%)	0	15 (25.9%)	5 (4.1%)	1 (1.4%)
Medical device	9 (22.5%)	22 (18.0%)	14 (18.7%)	4 (6.9%)	19 (15.6%)	13 (18.1%)
Surgical	1 (2.5%)	4 (3.3%)	3 (4.0%)	4 (6.9%)	8 (6.6%)	2 (2.8%)
Other †	2 (5.0%)	12 (9.8%)	8 (10.6%)	6 (10.3%)	17 (13.9%)	6 (8.3%)
Planned sample size						
Median [IQR]	264 [119, 630]	301 [100, 749]	300 [118, 600]	198 [100, 446]	260 [120, 580]	210 [102, 378]
Sponsorship, n (%)						
Investigator	15 (37.5%)	45 (36.9%)	43 (57.3%)	33 (56.9%)	52 (42.6%)	43 (59.7%)
Industry	25 (62.5%)	77 (63.1%)	32 (42.7%)	25 (43.1%)	70 (57.4%)	29 (40.3%)
Center status, n (%)						
Single center	10 (25.0%)	20 (16.4%)	11 (14.7%)	23 (39.7%)	22 (18.0%)	18 (25.0%)
Multicenter- international	26 (65.0%)	87 (71.3%)	46 (61.3%)	25 (43.1%)	88 (72.1%)	37 (51.4%)
Multicenter- national	4 (10.0%)	15 (12.3%)	18 (24.0%)	10 (17.2%)	12 (9.8%)	17 (23.6%)

Abbreviations: PRO, patient reported outcome; RCTs, randomized clinical trials

* Other category (Dermatology, Cardiology, Pediatrics, Respiratory Medicine, Anesthesiology, Endocrinology, etc.)

† Other category (Dietary Supplement, Rehabilitation, etc.)

Table 2: Planning and reporting of PROs in randomized clinical trials

	PRO pre-specified in a 2012 protocol (n=162)	PRO pre-specified in a 2016 protocol (n= 180)	Total (n=342)
PRO as a primary outcome	**n=40**	**n=58**	**n=98**
No results published, N (%)	14 (35%)	24 (41%)	38 (39%)
Published results available, N (%)	26 (65%)	34 (59%)	60 (61%)
PRO reported as specified in the protocol	19 (73%)	28 (82%)	47 (78%)
PRO reported differently than specified in the protocol	7 (27%)	6 (18%)	13 (22%)
PRO as a secondary outcome	**n=122**	**n=122**	**n=244**
No results published, N (%)	24 (20%)	36 (30%)	60 (25%)
Published results available, N (%)	98 (80%)	86 (70%)	184 (75%)
PROs reported as specified in the protocol	21 (22%)	26 (32%)	47 (25%)
Specified PROs not reported at all	36 (37%)	27 (31%)	63 (34%)
Some specified PROs not reported	17 (17%)	20 (23%)	37(20%)
Additional unspecified PROs reported	6 (6%)	4 (5%)	10 (6%)
Reported unspecified PROs & pre-specified PROs unreported	18 (18%)	9 (9%)	27 (15%)

Abbreviations: PRO, patient reported outcome; RCTs, randomized clinical trials

Table 3: Detailed characteristics of PROs reported in clinical trial protocols and in published results of trials

	2012				2016			
	RCT-Protocol		RCT-publication		RCT-Protocol		RCT-publication	
	PRO as a primary outcome (n=43)	PRO as a secondary outcome (n=344)	PRO as a primary outcome (n=26)	PRO as a secondary outcome (n=165)	PRO as a primary outcome (n=63)	PRO as a secondary outcome (n=356)	PRO as a primary outcome (n=36)	PRO as a secondary outcome (n=133)
Domain captured by specified PROs								
Symptoms	15 (35%)	84 (24%)	10 (38%)	37 (23%)	24 (38%)	79 (22%)	12 (33%)	18 (14%)
Physical functioning	3 (7%)	24 (7%)	1 (4%)	12 (7%)	4 (6%)	15 (4%)	3 (8%)	8 (6%)
Mental/emotional functioning	2 (5%)	23 (7%)	0	13 (7%)	5 (8%)	37 (10%)	1 (3%)	13 (10%)
Social functioning	1 (2%)	3 (1%)	0	0	1 (1%)	1 (1%)	0	1 (1%)
Disease-specific outcome measure	20 (47%)	82 (24%)	14 (53%)	57 (35%)	19 (30%)	78 (21%)	14 (39%)	34 (25%)
Multidimensional quality of life	1 (2%)	66 (19%)	1 (4%)	27 (16%)	0	59 (17%)	0	41 (31%)
Overall sense of well-being	0	5 (1%)	0	2 (1%)	0	3 (1%)	0	6 (4%)
Satisfaction with treatment	1 (2%)	19 (5%)	0	1 (0.5%)	2 (3%)	29 (8%)	1 (3%)	4 (3%)
Health utility	0	6 (2%)	0	1 (0.5%)	0	14 (4%)	0	1 (1%)
Other *	0	32 (10%)	0	15 (10%)	8 (12%)	41 (12%)	5 (14%)	7 (5%)
Is any hypothesis specified for PROs?	18 (43%) †	38 (11%)	6 (20%)	9 (5%)	46 (73%) ‡	57 (16%)	21 (47%)	11 (8%)
Provided evidence for validation of the instrument used to capture PROs	15(35%)†,§	139 (40%)§	15 (57%)§	60 (36%)§	25 (39%)‡,§	144 (40%)§	20 (55%)§	68 (51%)§
Reported how data was collected for PROs	28 (65%)†	227 (66%)	7** (25%)	10 (6%)	35 (55%)‡	227 (63%)	15 (44%)	21 (16%)

Abbreviations: PRO, patient reported outcome; RCT, randomized clinical trial

* Other: cannabis use, tolerance of treatment, abstinence, alcohol consumption

† 4 RCTs and 5 outcomes are missing.

‡ 2 RCTs and 2 outcomes are missing.

§ Outcomes that used diaries to capture PROs are excluded:

2012 Protocols: primary 5, secondary 10; 2012 Publications: primary 2, secondary 5

2016 Protocols: primary 5, secondary 9; 2016 Publications: primary 6, secondary 1

Table 4: Quality of PRO reporting among published trials according to the Consolidated Standards of Reporting Trials (CONSORT) patient-reported outcomes (PRO) Extension Checklist

CONSORT-PRO item *	2012 (n=26)	2016 (n=36)
Identifying PRO in abstract	22 (84%)	28 (82%)
Rationale of choosing a PRO	9 (32%)	15 (44%)
PRO hypothesis mentioned	6 (24%)	19 (54%)
Evidence for validation of instrument used to capture PRO *‡	15 (62%)	20 (66%)
Method of PRO collection described ‡	7 (28%)	15 (44%)
Mention of a minimal clinically important difference for the PRO ‡	12 (44%)	12(35%)
Sample size calculation adequately described (statistical test & alpha value & statistical power)	18 (68%)	31 (91%)
Handling of missing PRO data described	15 (56%)	22 (65%)
Reporting of a participant flow diagram	23 (88%)	32 (94%)
Reporting of baseline data for PROs	17 (65%)	26 (76%)
Results provided for each domain and time point §	3 (42%)	2 (20%)
PRO-specific limitations/implications for generalizability reported	1 (4%)	2 (6%)
Interpretation in relation to clinical outcome provided ¶	2 (9%)	2 (12%)

* We did not consider CONSORT PRO items 4a (participants), 16 (numbers analyzed), 18 (ancillary analyses), because these appeared equally relevant for PROs and non-PROs
† Outcomes that used diaries as a tool to capture PROs were excluded: 2 from 2012 and 6 from 2016
‡ These items are all components of CONSORT PRO item 6a (outcomes) which we assessed separately, because each component appeared specifically relevant for PROs
§ non-multidimensional PROs were excluded: 19 from 2012 and 26 from 2016
¶ Trials only planning surrogate outcomes were excluded: 5 from 2012, 20 from 2016

Disclosures

BvN is currently employed by Roche Pharma AG, Grenzach-Wyhlen, Germany. All other authors have no conflicts of interest to declare.

Ethics approval and consent to participate

All participating ethics committees were project partners.

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Authors' contributions

AO, SH, EvE, and MB designed the main study. ATH, DG, AO, and MB designed the present substudy. RS developed the web-tool for data extractions. ATH, DG, BvN, BS, and MB coordinated data extraction from protocols and results publications. ATH performed statistical analyses. ATH, JWB, and MB wrote the first draft of the manuscript. All other authors were involved in data collection and critically revised the manuscript. All authors approved the final version before submission.

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Abstract

This cross-sectional study compares randomized clinical trial protocols to assess the prevalence and reporting quality of planned subgroup analyses over time.

Introduction

Well-researched and methodologically sound study protocols are important for the credibility of randomized clinical trials (RCTs) [1]. This is true for the main analysis and subgroup analyses [2]. A 2014 study [3].of RCT protocols approved by ethics committees between 2000 and 2003 found that almost 30% of protocols specified at least 1 subgroup analysis. However, most of them lacked essential details, such as the definition of subgroup variables, scientific rationales, hypotheses, or a description of statistical methods. In the present study, we compared these findings with 2 more recent samples of RCT protocols approved in 2012 and 2016 to assess the prevalence and reporting quality of planned subgroup analyses over time. In addition, we determined the proportion of planned subgroup analyses based on molecular and genetic markers.

Methods

This cross-sectional study follows the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline. Approval by the ethics committee of Northern West and Central Switzerland and informed consent were waived because the study did not involve patients or the public in the design, conduct, reporting, or dissemination plans of the research.

This study uses data from 3 retrospective cohorts of RCT protocols approved between 2000 and 2003 [3], 2012, and 2016 [1]. The examined protocols were approved by research ethics committees in Switzerland, Germany, and Canada. They constitute random samples of all approved RCT protocols at participating ethics committees. Investigators trained in clinical research methods (MSc or PhD) recorded, independently and in duplicate, RCT characteristics and details about subgroup analysis [1, 3]. Disagreements were resolved by discussion and consensus. We descriptively summarized the characteristics of the 3 cohorts focusing on the planning of subgroup analyses in RCT protocols in November and December 2020; comparative statements are not inferential. The present study is 1 of 5 prespecified subprojects of the Adherence to SPIRIT Recommendations (ASPIRE) study[1].

Results

This study included 894 protocols approved between 2000 and 2003, 257 protocols approved in 2012, and 292 protocols approved in 2016. At all 3 time points, approximately one-third of RCT protocols included plans for at least 1 subgroup analysis (2000-2003: 252 [28.2%]; 2012: 93 [36.2%]; 2016: 96 [32.9%]) (Table 1). At each time point, RCT protocols planning subgroup

analyses were more frequently industry sponsored, had a multicenter design, and had a larger sample size than RCT protocols without planned subgroups. Subgroup analyses were particularly frequent in protocols of oncology and cardiovascular RCTs. The number of subgroup analyses per study, although frequently not reported, likely increased over time (2000 to 2003: median, 3 [IQR, 1-6]; 2012: median, 6 [IQR, 4-23.5]; 2016: median, 6 [IQR, 3-13]) (Table 2). The most frequent subgroup defining variables used in 2012 and 2016 (not assessed in the oldest sample) were age (2012: 44 of 93 [47.3%]; 2016: 42 of 96 [43.7%]) and sex (2012: 37 of 93 [39.7%]; 2016: 38 or 96 [39.5%]). Molecular or genetic markers were subgroup-defining variables in 13 of 93 (14.0%) RCT protocols approved in 2012 and 16 of 96 (16.7%) RCT protocols approved in 2016. The reporting of subgroup-specific hypotheses increased over time (2000 to 2003: 17 of 252 protocols [6.7%]; 2012: 9 of 93 protocols [9.7%]; 2016: 16 of 96 protocols [16.7%]) as did the number of plans that included a hypothesis sufficiently detailed to anticipate a direction of effect (2000 to 2003: 10 of 252 protocols [4.0%]; 2012: 9 of 93 protocols [9.7%]; 2016: 16 of 96 protocols [14.7%]). At all 3 time points, approximately one-third of subgroup analysis plans specified a statistical test for interaction (2000 to 2003: 87 of 252 protocols [34.5%]; 2012: 31 of 93 protocols [33.3%]; 2016: 26 of 96 protocols [27.1%]).

Discussion

The proportion and characteristics of RCT protocols with planned subgroup analyses appeared stable over time. Although the increasing proportion of hypothesis-supported subgroup analyses is encouraging, basic scientific principles, such as researching prior knowledge, limiting the number of analyses, and using appropriate statistics, continue to be violated in the majority of RCT protocols with planned subgroups. This is remarkable given the abundance of methodological guidance available [2, 4]. Study limitations include the poor reporting of subgroup analysis plans in some trial protocols and the lack of access to statistical analysis plans developed in later phases of trials. Considering the increasing importance of subgroup analyses to inform precision medicine [5, 6], investigators and regulators should pay more attention to the methodological quality of subgroup analysis plans.

Table1-Characteristics of included RCT protocols

Trial characteristics	Trial approval 2000-2003; No. (%)			Trial approval 2012; No. (%)			Trial approval 2016; No. (%)		
	SGA not planned n=642 (71.8%)	SGA planned n=252 (28.2%)	All trials n= 894	SGA not planned n=164 (63.8%)	SGA planned n= 93 (36.2%)	All trials n= 257	SGA not planned n=196 (67.1%)	SGA planned n=96 (32.9%)	All trials n= 292
Target Sample Size									
Median (Q1-Q3)	200 (80-471)	521 (229-1030)	260 (100-610)	16 (71.5-432)	600 (354-1500)	300 (100-720)	164 (75-416)	303 (150-600)	199 (100-490)
Center status									
Multicenter	500 (77.9)	241(95.6)	741 (82.9)	119 (72.6)	91(97.8)	210 (81.7)	131(66.8)	84 (87.5)	215 (73.6)
Single center	139 (21.7)	10 (4.0)	149 (16.7)	45 (27.4)	2 (2.2)	47 (18.3)	65 (33.2)	12 (12.5)	77(26.4)
Unclear	3 (0.5)	1 (0.4)	4 (0.4)	0	0	0	0	0	0
Study Design									
Parallel	592 (92.2)	244 (96.8)	836 (93.5)	145 (88.4)	86 (92.4)	231 (89.9)	172 (87.8)	95 (99.0)	267(91.4)
Crossover	40 (6.2)	1 (0.4)	41 (4.6)	10 (6.1)	1 (1.1)	11 (4.3)	11 (5.6)	1 (1.0)	12 (4.1)
Factorial	9 (1.4)	6 (2.4)	15 (1.7)	3 (1.8)	4 (4.3)	7 (2.7)	6 (3.0)	0	6 (2.1)
Other	1 (0.2)	1 (0.4)	2 (0.2)	6 (3.7)	2 (2.2)	8(3.1)	7 (3.6)	0	7 (2.4)
Study intention									
Superiority	456 (71.0)	196 (77.8)	652 (72.9)	130 (79.3)	73 (78.5)	203 (79.0)	160 (81.6)	79 (82.3)	239 (81.8)
Non-inferiority	95 (14.8)	44 (17.5)	139 (15.5)	23 (14.0)	19 (20.4)	42 (16.3)	30 (15.3)	14 (14.6)	44 (15.1)
Unclear	91 (14.2)	12 (4.8)	103 (11.5)	11 (6.7)	1 (1.1)	12 (4.7)	6 (3.1)	3 (3.1)	9 (3.1)
Sponsorship									
Industry	356 (55.5)	195 (77.4)	551 (61.6)	69(42.1)	69 (74.2)	138 (53.7)	73 (37.2)	57 (59.4)	130 (44.5)
Investigator	286 (44.5)	57(22.6)	343 (38.4)	95(57.9)	24 (25.8)	119 (46.3)	123 (62.8)	39 (40.6)	162(55.5)
Clinical area									
Oncology	113 (17.6)	42(16.3)	155 (17.3)	22 (13.4)	25 (26.9)	47 (18.3)	27(13.8)	24 (25.0)	51(17.5)
Cardiovascular	59 (9.2)	49 (19.5)	108 (12.1)	8 (4.9)	19 (20.4)	27 (10.5)	15 (7.7)	20 (20.8)	35 (12.0)
Infectious diseases	60 (9.3)	27 (10.8)	87 (9.7)	6 (3.7)	3 (3.2)	9 (3.5)	4 (2.0)	3 (3.1)	7 (2.4)
Surgery	75 (11.7)	18 (7.2)	93 (10.4)	27(16.5)	10 (10.8)	37 (14.4)	21 (10.7)	10 (10.4)	31(10.6)
Pediatrics	34 (5.3)	11(4.4)	45 (5.0)	11 (6.7)	3 (3.2)	14 (5.4)	11 (5.6)	8 (8.3)	19 (6.5)
Other	301 (46.9)	105 (41.7)	406 (45.4)	90 (54.9)	33 (35.5)	123 (47.9)	118 (60.2)	31(32.3)	149 (51.0)

Abbreviations: RCT, randomized clinical trial; SGA, subgroup analysis; Q1-Q3, 25th and 75th percentile

Table2-Characteristics of subgroup analyses in RCT protocols that planned at least one subgroup analysis

Characteristics of subgroup analyses	Trial approval 2000-2003 (n= 252); No. (%)	Trial approval 2012 (n= 93); No. (%)	Trial approval 2016 (n=96); No. (%)
Hypothesis given	17 (6.7)	9 (9.7)	16 (16.7)
Direction of subgroup effect anticipated	10 (4.0)	9 (9.7)	14 (14.6)
Interaction test planned	87 (34.5)	31 (33.3)	26 (27.1)
Subgroup outcome variable explicitly mentioned	NA	68 (73.1)	71 (74.0)
Exploratory nature explicitly mentioned	NA	33 (35.5)	22 (22.9)
Subgroup analysis considered in sample size calculation	NA	8 (8.6)	12 (12.5)
Most frequent subgroup variables*			
Age	NA	44 (47.3)	42 (43.7)
Sex	NA	37 (39.7)	38 (39.5)
Race/ Ethnicity	NA	25 (26.8)	22 (22.9)
Region	NA	23 (24.7)	14 (14.5)
Molecular/genetic markers	NA	13 (14.0)	16 (16.7)
Body mass index	NA	8 (8.6)	4 (4.1)
Number of subgroup analyses			
Median (Q1-Q3)	3 (1-6)	6 (4-23.5)	6 (3-13)
Not Reported	30 (11.9)	31 (33.3)	43 (44.8)

* More than one category possible
Abbreviations: RCT, randomized clinical trial; NA, not available

Author Contributions

Ms Taji Heravi and Dr Briel had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Ms Taji Heravi, Drs Gryaznov and Schandelmaier contributed equally.
Concept and design: Taji Heravi, Schandelmaier, Kasenda, Briel.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Taji Heravi, Gryaznov, Briel.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Taji Heravi, Schandelmaier.
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Administrative, technical, or material support: Taji Heravi, Gryaznov, Briel.
Supervision: Kasenda, Briel.

Conflict of Interest Disclosures

Dr Kasenda is currently employed by iOMEDICO AG, Freiburg, Germany and reported receiving personal fees from Roche, Riemser, and Astellas outside the submitted work. Dr Gryaznov reported being currently employed by Idorsia Pharmaceuticals. Dr Briel reported receiving grants from the Swiss Federal Office of Public Health. No other disclosures were reported.

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Additional Information

All participating ethics committees were project partners

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4 Discussion and future steps

4.1 Understanding recruitment patterns: implications and strategies for improving recruitment

For trialists, understanding the recruitment pattern of their study is necessary to help them complete the recruitment successfully. Our study revealed that almost 70% of trials show a linear recruitment pattern. This suggests that if participant recruitment in a trial is slow in the beginning, this pace tends to persist over time, resulting in a continued slow recruitment trajectory. Trialists must pay attention and look out for warning signs and not have false hopes or passively wait for improvements. Instead, when observing a slow trend, proactive interventions are necessary.

Finding effective strategies for accelerating or managing a successful recruitment remains challenging and limited. Here are some examples and groups that provide different approaches. The Clinical Trials Transformation Initiative (CTTI) group suggested several essential aspects to ensure successful recruitment planning. These aspects include recommendations for better design and protocol development, feasibility assessment, site selection, and implementing a monitoring tool [1]. However, these recommendations are not straightforward and pose open-ended questions to guide the planning process effectively. The Cochrane review on interventions for improving recruitment has highlighted four different interventions through Studies Within A Trial (SWATs), which are independent research studies integrated into ongoing trials: [2]: telephone reminders for non-responders, Opt-out procedures, financial incentive with the trial invitation, and open design trials [3], as telephone reminders and open design trials seems to supported by high-certainty evidence [4]. However, it's important to note that certain approaches, like open trials, may raise methodological concerns, such as performance bias [5]. The Trial Forge SWAT Network has generated new priorities concerning recruitment strategies for future randomized SWAT designs in 2024. These include questions such as, 'How can patient and public involvement be optimized to enhance participant recruitment in trials?' and 'What methods yield the highest efficacy in utilizing videos to bolster trial recruitment?' [6].

4.2 Advancing clinical trial methodology

Health researchers universally acknowledge that methodology is one of the key aspects for enhancing research quality [7, 8]. Efforts have been made at different levels through international collaborations, guidelines, and regulatory laws to enhance research methodology.

The TRIAL FORGE initiative (https://www.trialforge.org/) emerged with a mission to enhance practices within RCTs. Its core objective is to advance clinical research by advocating for an evidence-based approach to trial methodology. In the United States, the CTTI, a collaboration between the Food and Drug Administration (FDA) and academia, is working to improve the quality of clinical trials. They developed multiple recommendations and tools addressing multiple aspects of trial methodology [9]. Core Outcome Measures in Effectiveness Trials (COMET) is an initiative that aims to improve the selection and reporting of outcomes in clinical trials. By standardizing outcomes across trials, COMET helps ensure that trial results are comparable and relevant to patients and healthcare providers [10]. The PROTEUS-Trials Consortium (Patient-Reported Outcomes Tools: Engaging Users & Stakeholders) was initiated to promote patient-centered care and research through enhanced PRO use in clinical trials [11]. Switzerland has launched several initiatives aiming at improving the quality of clinical research. These efforts encompass the enhancement of clinical research infrastructure, including the establishment of Clinical Trial Units (CTUs) and the Swiss Clinical Trial Organization (SCTO), serving as the central platform for national patient-oriented clinical research collaboration. Within the SCTO the Swiss Clinical Trials Empirical Assessment & Methods (STEAM) group was created aiming to improve the information sharing, coordination and collaboration of various groups performing meta-research in Switzerland [12]. The Enhancing the QUAlity and Transparency Of health Research network (EQUATOR Network, www.equator-network.org) serves as a valuable resource, hosting a comprehensive library of reporting guidelines for various study designs, including reporting PROs in RCTs [13, 14]. Apart from all different associations and research groups, so many different commentaries, meta-studies, simulation studies, and guidance papers have been published. Yet, empirical evidence and results from this PhD thesis, ASPIRE subprojects, reveal persistent problems in different methodological aspects of RCTs.

Our study on non-registration, discontinuation, non-publication rates show that these aspects are still a major challenge in clinical research especially for investigator-initiated trials. Our investigation of the adherence between planning and reporting of PROs and the quality of PRO reporting highlighted deficiencies, indicating that merely having a reporting guideline is insufficient to ensure its widespread adoption among researchers. This trend extends to our review of quality of subgroup analysis planning in a repeated cross-sectional study of RCT

protocols approved in 2000-3, 2012, and 2016 [15]. We identified substantial deficiencies, particularly in detailing characteristics such as pre-specifying hypotheses for subgroup analyses. This pattern persists in recent studies, including a sample of cancer trials from 2004 to 2020, as highlighted by Sherry et al [16].

Once more, this underscore concerns regarding the effective implementation of available guidance and methods, highlighting the need and action for stricter rules. Improving these areas is essential for enhancing the transparency and reliability of clinical research.

4.3 Future steps in improving recruitment

I would like to suggest three further projects to better understand participant recruitment in clinical trials and to address its challenges more comprehensively.

I propose using our dataset to validate the Bayesian model developed by Jiang et al. [17, 18] which is a recruitment model that provides a freely available software package (written for R [www.r-project.org]) for recruitment prediction. This model is particularly suitable for validation because it integrates prior knowledge with ongoing data, offering a dynamic and potentially more accurate prediction method. Validating this model would help determine its reliability and usability in real-world scenarios, potentially providing trialists with a powerful tool to enhance recruitment strategies.

Secondly, the challenge of slow recruitment in clinical trials is complex. What is missing is a simple tool to identify recruitment issues and provide actionable strategies. Currently, our team has begun compiling a list of problems and potential solutions, but it's currently only available in German. Moving forward, continuous research is essential to identify and propose effective solutions. What's required is an updatable checklist or tool, housed in a centralized database, guiding trialists through each step, enabling them to efficiently address recruitment challenges.

Thirdly, debates surround the efficiency of innovative trial designs like Trials-within-Cohorts (TwiCs) [19, 20] and Platform trials [21], which are proposed to enhance recruitment. However, conclusive evidence supporting this claim is still lacking. To better understand this concept, one approach could be to apply the same methodology as our RECRUIT-IT project and compare the recruitment patterns among these three groups. Our group has already conducted a systematic review on existing TWICS [under review] and Platform trials [22]. Using these databases to contact the representatives and PIs and request the recruitment data of trials can be the first step.

4.4 Future steps in advancing clinical trial methodology

Our mission as methodologists is to enhance not only the methodology but ensuring the implementation of appropriate methods within research practices. It is important to dive deeper into understanding why certain methodological aspects are underused. Identifying barriers, challenges, and user preferences in implementation is crucial for effecting change. While some studies have begun to address these issues, I think there is need for continued efforts to fully grasp these complexities and overcome obstacles [23-26].

Several ways to enhance clinical research methodology was proposed and worth to continue. Collaboration among diverse stakeholders, including researchers, policymakers, clinicians, journal publishers, ethics committees, regulatory agencies, funders, and patient representatives, fosters concerted efforts to ensure methodological implementation in clinical research. Educational workshops and conferences serve as another avenue to inform stakeholders about challenges beyond methodological implementation. Furthermore, recognizing researchers' needs is pivotal. By doing so, we gain insight into the underlying challenges behind compliance with regulations and the reasons for researchers' reluctance to accept them. For example, researchers may hesitate to publish negative results or discontinue trials due to feelings of failure [27]. This highlights the significance of implementing support programs and regulations that acknowledge investigators' emotions, fostering transparency and facilitating learning. Additionally, making methodological recommendations more accessible is crucial, as currently, they are scattered across the web. A colleague in our group has taken the initiative to address this issue by launching a living database for methods guidance called LIbrary of Guidance for HealTh Scientists (LIGHTS, www.lights.science) [28], which assists health researchers in finding suitable guidance for their projects. Further, mandating adherence to methodological standards [24, 29], and involving a methodologist in the design [30] by journals and ethics committees, along with continued meta-research efforts, can identify prevalent issues and pave the way for solutions. While progress is evident, the journey ahead demands sustained commitment and collaboration.

Towards this goal and focusing on methodology aspects discussed in this PhD work, I would suggest conducting the following studies.

Qualitative research, such as semi-structured interviews with trialists, to understand why crucial information about subgroup analysis and PROs is often omitted during the planning and reporting phases. Additionally, it would be valuable to investigate why certain outcomes fail to be published or mentioned in publications at all. I hypothesize that a lack of awareness regarding the importance of transparency and difficulties in understanding the given checklists

may be contributing factors. However, it is essential to systematically examine these issues based on evidence to gain a deeper understanding.

Based on one of the studies conducted by our group, it is surprising to find that lack of knowledge of investigators is a factor contributing to non-registration in Switzerland [31]. This underscores the need for collaborative efforts to address these challenges. It requires a national and international commitment to advance regulations and raise awareness about basic methodological aspects in clinical trials. This can be achieved through workshops, fostering rule-making processes and continuous evaluation of registration, discontinuation, and publication availability of results and protocols. By working together, we can promote transparency and adherence to best practices in clinical research.

4.5 Closing remarks

In this PhD work, we examined trial recruitment patterns and found that, recruitment trajectories predominantly follow a linear path. This finding signals a cautionary note for trialists, suggesting that significant changes in recruitment rates are unlikely without proactive intervention. Furthermore, our research indicates issues in terms of pre-registration, discontinuation, and non-publication rates, highlighting persistent challenges in ensuring transparency in clinical research. Additionally, despite existing regulatory guidelines and checklists, the planning and reporting quality of PROs and subgroup analyses remain poor.

As health researchers and methodologists, it is essential for us to champion the implementation of robust methods to elevate the quality of our research. By embracing this commitment, we not only enhance the credibility of our findings but also open the door to big improvements in healthcare. Collaboration among diverse stakeholders in clinical research ensures methodological implementation and addresses challenges beyond implementation through educational initiatives. Recognizing researchers' needs, mandating adherence to standards, and improving accessibility of methodological recommendations are vital steps toward fostering transparency and advancing clinical research.

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5 Further publications

5.1 Characteristics, Progression, and Output of Randomized Platform Trials: A Systematic Review

Alexandra Griessbach, Christof Manuel Schönenberger, **Ala Taji Heravi**, Viktoria Gloy, Arnav Agarwal, Tim Jonas Hallenberger, Stefan Schandelmaier, Perrine Janiaud, Alain Amstutz, Manuela Covino, David Mall, Benjamin Speich, Matthias Briel.

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Abstract

Importance: Platform trials have become increasingly common, and evidence is needed to determine how this trial design is actually applied in current research practice.

Objective: To determine the characteristics, progression, and output of randomized platform trials.

Evidence review: In this systematic review of randomized platform trials, Medline, Embase, Scopus, trial registries, gray literature, and preprint servers were searched, and citation tracking was performed in July 2022. Investigators were contacted in February 2023 to confirm data accuracy and to provide updated information on the status of platform trial arms. Randomized platform trials were eligible if they explicitly planned to add or drop arms. Data were extracted in duplicate from protocols, publications, websites, and registry entries. For each platform trial, design features such as the use of a common control arm, use of nonconcurrent control data, statistical framework, adjustment for multiplicity, and use of additional adaptive design features were collected. Progression and output of each platform trial were determined by the recruitment status of individual arms, the number of arms added or dropped, and the availability of results for each intervention arm.

Findings: The search identified 127 randomized platform trials with a total of 823 arms; most trials were conducted in the field of oncology (57 [44.9%]) and COVID-19 (45 [35.4%]). After a more than twofold increase in the initiation of new platform trials at the beginning of the COVID-19 pandemic, the number of platform trials has since declined. Platform trial features were often not reported (not reported: nonconcurrent control, 61 of 127 [48.0%]; multiplicity adjustment for arms, 98 of 127 [77.2%]; statistical framework, 37 of 127 [29.1%]). Adaptive design features were only used by half the studies (63 of 127 [49.6%]). Results were available for 65.2% of closed arms (230 of 353). Premature closure of platform trial arms due to recruitment problems was infrequent (5 of 353 [1.4%]).

Conclusions and relevance: This systematic review found that platform trials were initiated most frequently during the COVID-19 pandemic and declined thereafter. The reporting of platform features and the availability of results were insufficient. Premature arm closure for poor recruitment was rare.

5.2 Antibody Response After the Third SARS-CoV-2 Vaccine in Solid Organ Transplant Recipients and People Living With HIV (COVERALL-2)

Alexandra Griessbach, Frédérique Chammartin, Irene A. Abela, Patrizia Amico, Marcel P. Stoeckle, Anna L. Eichenberger, Barbara Hasse, Dominique L. Braun, Macé M. Schuurmans, Thomas Müller, Michael Tamm, Annette Audigé, Nicolas J. Mueller, Andri Rauch, Huldrych F. Günthard, Michael T. Koller, Alexandra Trkola, Selina Epp, Alain Amstutz, Christof M. Schönenberger, **Ala Taji Heravi**, Matthaios Papadimitriou-Olivgeris, Alessio Casutt, Oriol Manuel, Katharina Kusejko, Heiner C. Bucher, Matthias Briel, Benjamin Speich, and the Swiss HIV Cohort Study and the Swiss Transplant Cohort Study.

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Abstract

Background: After basic immunization with 2 mRNA SARS-CoV-2 vaccine doses, only a small proportion of patients who are severely immunocompromised generate a sufficient antibody response. Hence, we assessed the additional benefit of a third SARS-CoV-2 vaccine in patients with different levels of immunosuppression.

Methods: In this observational extension of the COVERALL trial (Corona Vaccine Trial Platform), we recruited patients from the Swiss HIV Cohort Study and the Swiss Transplant Cohort Study (ie, lung and kidney transplant recipients). We collected blood samples before and 8 weeks after the third SARS-CoV-2 vaccination with either mRNA-1273 (Moderna) or BNT162b2 (Pfizer-BioNTech). The primary outcome was the proportion of participants showing an antibody response (Elecsys Anti-SARS-CoV-2 S test; threshold ≥100 U/mL) 8 weeks after the third SARS-CoV-2 vaccination. We also compared the proportion of patients who reached the primary outcome from basic immunization (the first and second vaccines) to the third vaccination.

Results: Nearly all participants (97.2% [95% CI, 95.9%-98.6%], 564/580) had an antibody response. This response was comparable between mRNA-1273 (96.1% [95% CI, 93.7%-98.6%], 245/255) and BNT162b2 (98.2% [95% CI, 96.7%-99.6%], 319/325). Stratification by

cohort showed that 99.8% (502/503) of people living with HIV and 80.5% (62/77) of recipients of solid organ transplants achieved the primary endpoint. The proportion of patients with an antibody response in solid organ transplant recipients improved from the second vaccination (22.7%, 15/66) to the third (80.5%, 62/77).

Conclusions: People living with HIV had a high antibody response. The third vaccine increased the proportion of solid organ transplant recipients with an antibody response.

Clinical Trials Registration: NCT04805125 (ClinicalTrials.gov).

Keywords: HIV; SARS-CoV-2; organ transplant; vaccine.

5.3 Antibody Response After Third Vaccination With mRNA-1273 or BNT162b2: Ex-tension of a Randomized Controlled SARS-CoV-2 Noninferiority Vaccine Trial in Patients With Different Levels of Immunosuppression (COVERALL-2)

Alexandra Griessbach, Frédérique Chammartin, Irene A. Abela, Patrizia Amico, Marcel P. Stoeckle, Anna L. Eichenberger, Barbara Hasse, Dominique L. Braun, Macé M. Schuurmans, Thomas Müller, Michael Tamm, Annette Audigé, Nicolas J. Mueller, Andri Rauch, Huldrych F. Günthard, Michael T. Koller, Alexandra Trkola, Selina Epp, Alain Amstutz, Christof M. Schönenberger, **Ala Taji Heravi**, Matthaios Papadimitriou-Olivgeris, Alessio Casutt, Oriol Manuel, Katharina Kusejko, Heiner C. Bucher, Matthias Briel, Benjamin Speich, and the Swiss HIV Cohort Study and the Swiss Transplant Cohort Study.

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Abstract

Extension of the COVERALL (COrona VaccinE tRiAL pLatform) randomized trial showed noninferiority in antibody response of the third dose of Moderna mRNA-1273 vaccine (95.3% [95% confidence interval, 91.9%-98.7%]) compared to Pfizer-BioNTech BNT162b2 vaccine (98.1% [95% CI, 95.9%-100.0%]) in individuals with different levels of immunosuppression (difference, -2.8% [95% CI, -6.8% to 1.3%]).

Keywords: HIV; Organ transplant; SARS-CoV-2; Vaccine; randomized trial.

5.4 Effects of remdesivir in patients hospitalised with COVID-19: a systematic review and individual patient data meta-analysis of randomised controlled trials

Alain Amstutz, Benjamin Speich, France Mentré, Corina Silvia Rueegg, Drifa Belhadi, Lambert Assoumou, Charles Burdet, Srinivas Murthy, Lori Elizabeth Dodd, Yeming Wang, Kari A.O. Tikkinen, Florence Ader, Maya Hites, Maude Bouscambert, Mary Anne Trabaud, Mike Fralick, Todd Campbell Lee, Ruxandra Pinto, Andreas Barratt-Due, Fridtjof Lund-Johansen, Fredrik Müller, Olli P.O. Nevalainen, Bin Cao, Tyler Bonnett, Alexandra Griessbach, **Ala Taji Heravi**, Christof Schönenberger, Perrine Janiaud, Laura Werlen, Soheila Aghlmandi, Stefan Schandelmaier, Yazdan Yazdanpanah, Dominique Costagliola, Inge Christoffer Olsen, Matthias Briel.

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Lancet Respir Med, 2023 Feb.
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Abstract

Background: Interpretation of the evidence from randomised controlled trials (RCTs) of remdesivir in patients treated in hospital for COVID-19 is conflicting. We aimed to assess the benefits and harms of remdesivir compared with placebo or usual care in these patients, and whether treatment effects differed between prespecified patient subgroups.

Methods: For this systematic review and meta-analysis, we searched PubMed, Embase, the Cochrane COVID-19 trial registry, ClinicalTrials.gov, the International Clinical Trials Registry Platform, and preprint servers from Jan 1, 2020, until April 11, 2022, for RCTs of remdesivir in adult patients hospitalised with COVID-19, and contacted the authors of eligible trials to request individual patient data. The primary outcome was all-cause mortality at day 28 after randomisation. We used multivariable hierarchical regression—adjusting for respiratory support, age, and enrollment period to investigate effect modifiers. This study was registered with PROSPERO, CRD42021257134.

Findings: Our search identified 857 records, yielding nine RCTs eligible for inclusion. Of these nine eligible RCTs, individual data were provided for eight, covering 10 480 patients hospitalised with COVID-19 (99% of such patients included in such RCTs worldwide) recruited

between Feb 6, 2020, and April 1, 2021. Within 28 days of randomisation, 662 (12·5%) of 5317 patients assigned to remdesivir and 706 (14·1%) of 5005 patients assigned to no remdesivir died (adjusted odds ratio [aOR] 0·88, 95% CI 0·78–1·00, p=0·045). We found evidence for a credible subgroup effect according to respiratory support at baseline (pinteraction=0·019). Of patients who were ventilated—including those who received high-flow oxygen—253 (30·0%) of 844 patients assigned to remdesivir died compared with 241 (28·5%) of 846 patients assigned to no remdesivir (aOR 1·10 [0·88–1·38]; low-certainty evidence). Of patients who received no oxygen or low-flow oxygen, 409 (9·1%) of 4473 patients assigned to remdesivir died compared with 465 (11·2%) of 4159 patients assigned to no remdesivir (0·80 [0·70–0·93]; high-certainty evidence). No credible subgroup effect was found for time to start of remdesivir after symptom onset, age, presence of comorbidities, enrolment period, or corticosteroid use. Remdesivir did not increase the frequency of severe or serious adverse events. Interpretation This individual patient data meta-analysis showed that remdesivir reduced mortality in patients hospitalised with COVID-19 who required no or conventional oxygen support, but was underpowered to evaluate patients who were ventilated when receiving remdesivir. The effect size of remdesivir in patients with more respiratory support or acquired immunity and the cost-effectiveness of remdesivir remain to be further elucidated.

Funding: The European Union’s Horizon 2020 research and innovation program.

5.5 Reproducibility and Scientific Integrity of Big Data Research in Urban Public Health and Digital Epidemiology: A Call to Action

Ana Cecilia Quiroga Gutierrez, Daniel J. Lindegger, **Ala Taji Heravi**, Thomas Stojanov, Martin Sykora, Suzanne Elayan, Stephen J. Mooney, John A. Naslund, Marta Fadda, and Oliver Gruebner.

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Abstract

The emergence of big data science presents a unique opportunity to improve public-health research practices. Because working with big data is inherently complex, big data research must be clear and transparent to avoid reproducibility issues and positively impact population health. Timely implementation of solution-focused approaches is critical as new data sources and methods take root in public-health research, including urban public health and digital epidemiology. This commentary highlights methodological and analytic approaches that can reduce research waste and improve the reproducibility and replicability of big data research in public health. The recommendations described in this commentary, including a focus on practices, publication norms, and education, are neither exhaustive nor unique to big data, but, nonetheless, implementing them can broadly improve public-health research. Clearly defined and openly shared guidelines will not only improve the quality of current research practices but also initiate change at multiple levels: the individual level, the institutional level, and the international level.

Keywords: reproducibility; big data; digital epidemiology; urban public health.

5.6 Report: Low-dose CT screening for lung cancer

Soheila Aghlmandi, Arjun Bhadhuri, Prof. Heiner C. Bucher, Koen de Nijs, Hannah Ewald Dominik Glinz, Viktoria Gloy, Alexandra Griessbach, Dr. David Shaw, **Ala Taji Heravi**, Kevin ten Haaf, Yuki Tomonaga.

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URL: https://edoc.unibas.ch/90304/

Summary

Background: Lung cancer is the most important malignancy causing roughly 3,200 deaths in Switzerland each year and is most prevalent in smoking individuals. Individuals with a late-stage diagnosis of lung cancer have a poor prognosis. Low Density Computed Tomography (LDCT) may be a promising screening intervention for early diagnosis and treatment of lung cancer in high-risk populations to reduce morbidity and mortality due to lung cancer.

Aims: Based on the UK Health Technology Assessment (HTA) 'Low-dose computed tomography for lung screening in high-risk populations: a systematic review and economic evaluation' by Snowsill T et al. (issued in November 2018) an updated HTA report on the relative effectiveness and cost-effectiveness of LDCT screening for lung cancer in Switzerland was conducted which also addresses the ethical issues related to LDCT screening.

Methods: *Clinical effectiveness*: An updated literature search based on the one provided in the report by Snowsill was conducted. The search was adapted and extended for additional terms and comprised Medline via OvidSP, Embase, Web of Science via Clarivate Analytics, and the Cochrane Central Register of Controlled Trials (CENTRAL) via Cochrane Collaboration and the trial registries clintrials.gov and the WHO registry. Two assessors checked independently all literature items for randomised controlled trials comparing LDCT screening versus control or chest X-ray (CXR) for lung cancer in smoking individuals or heavy former smokers. Critical outcomes were lung cancer and overall mortality, and complications from invasive workup of false positive scans. Important outcomes were the number of false-positive scans, indeterminate scans, follow-up assessment and investigations with LDCT, the number of lung cancer detected and their stages, psychological distress, overdiagnosis, smoking cessation rate, type of cancer treatment, and quality of life. Data abstraction of eligible

trials was done in duplicate. Trials with ≥5 years of follow-up were considered for further assessment and critical binary outcomes that were available in both trial arms were pooled using a random effect model. Risk of bias was assessed with the GRADE tool. No continuous data was pooled, as too little data were reported in individual trials. In a sensitivity analysis for the critical outcome of lung cancer and overall mortality an indirect comparison of trials comparing 12 LDCT screening versus no screening, LDCT screening versus CXR screening, and CXR screening versus no screening was conducted.

Cost-effectiveness and budget impact: A systematic literature search of the economic literature on lung cancer screening based on the HTA published by Snowsill et al. in 2018 was conducted in Medline (via Ovid), EMBASE (via Ovid), and Web of Science (via Clarivate Analytics) in December 2020. Moreover, a non-systematic search update was conducted in Pubmed in October 2021 to identify potentially relevant articles published in 2021. All articles were screened by title, abstract, and if necessary, by full text review by two independent reviewers. Data extraction and quality assessment according to the Consensus on Health Economic Criteria (CHEC)-list for economic evaluations was conducted for all eligible articles. Population demographics, study characteristics, and main results were summarised and briefly described. The cost-effectiveness analysis was based on a newly programmed version of the MIcrosimulation SCreening ANalysis (MISCAN) Lung model (a stochastic, microsimulation model). Like in our previous Swiss cost-effectiveness analysis based on NLST-effectiveness data, we modelled a cohort of 100,000 Swiss persons born between 1940 and 1980. Effectiveness data from the Dutch–Belgian lung cancer screening trial (NELSON) were used to calibrate the model. The inclusion criteria for patient eligibility to screening were based on the NLST, on the NELSON, and on the PLCOm2012 risk assessment criteria. Costs included costs for LDCT screen and invitation, risk-assessment, LDCT follow-up, biopsy, and treatment (divided by care phase and including immunotherapy costs as part of the terminal care costs). The analyses were conducted using a healthcare perspective, a lifetime horizon, and a discount rate of 3% (for both costs and effects). The budget impact analysis was based on the results of the cost-effectiveness analysis. Undiscounted costs of selected screening scenarios were compared to no screening.

Ethics: Empirical research on patient attitudes as well as analytical literature on ethical issues was identified using purposive sampling on Pubmed and Google Scholar. Abstracts were selected for screening if they referred to ethical issues relating to screening or patient attitudes to screening, but only those that focused on these topics were included in the review. From the papers included, ethical issues were identified and categorised. Only one unanticipated ethical issue emerged from the literature review; one further ethical issue emerged during the ethical analysis. Following the identification of issues, they were categorised into two main

groups: Clinical ethical issues concerning screening, and wider 13 issues concerning justice and discrimination. Each issue was subjected to normative analysis via the application of key ethical principles and the available arguments in the ethical literature.

Results: *Clinical effectiveness:* Thirteen trials comparing LDCT with no screening or CXR were identified and of those 7 trials had ≥5 years of follow-up which included 88,006 subjects for the primary critical outcome analyses. Three additional ongoing trials were found. For the network analysis 3 trials comparing CXR to no screening, 6 trials comparing LDCT with no screening and one trial comparing LDCT with CXR were available. For the critical mortality outcomes risk of bias in trials was judged as moderate. There was considerable variation in screening programmes in terms of screening intensity, with most trials conducting 3 to 5 screening rounds, the definition of a positive node and as a consequence the necessary work-up investigations. Only one trial (NELSON) used a volume-based and not diameter-based definition of a positive node. The risk ratio (RR) of death from lung cancer of LDCT compared with no screening or CXR in 7 trials with ≥ 5 years of follow up was 0.80 (95%CI 0.72 to 0.88; test for heterogeneity I2 = 0%). In the network analysis the league table for the pooled direct and indirect comparisons of trials comparing LDCT with CXR or no screening or CXR with no screening indicated that CXR compared to LDCT had a statistically significant higher risk ratio for death from lung cancer, LDCT compared to no screening a statistically significant lower RR of death from lung cancer and CXR compared to no screening had no effect on lung cancer mortality. The RR of death from all causes of LDCT compared with no screening or CXR (7 trials) was 0.96 (95%CI 0.92 to 1.00; I2 = 0%). Two trials (NELSON and NLST) contributed roughly 75% of weight to the pooled summary of all mortality outcome data. In the network meta-analysis no statistically significant difference in overall mortality was found between any direct or indirect comparison. Obviously, more lung cancers were detected with LDCT and patients with LDCT compared to control were more likely to be diagnosed with lung cancers in earlier stages (I and II) (RR 2.69, 95% CI 1.94 to 3.74, I2 = 80%, 7 trials). Three trials assessed psychological effects that may be associated with LDCT screening but only one trial (DLCST) evaluated the entire trial population. All trials had validity issues due to the relative subjectivity of outcomes assessments, lack of blinding, and loss to follow-up. No uniform picture in terms of psychological consequences from screening with LDCT can be drawn. In DLCST following the first and prior to the second screening round mean scores for anxiety were lower in the screening group, but likely not clinically relevant. During screening rounds, 2 – 5 participants in the control group experienced statistically significantly more negative psychosocial consequences in seven of nine health scales compared to the LDCT group. 14 Two trials evaluate smoking behaviour change in relation to lung cancer screening at the broadest study

population level but did not show that LDCT screening was associated with higher quit rates when compared to control. The definition of a positive node or findings in LDCT varied between trials and diagnostic work algorithms also differed. The range of any found thorax abnormality or protocol defined in determinate scans during screening programs was wide and between 4.5% in MILD and 47.5% in the UKLS trial. The range of false positive scans (defined as the ratio of the [difference between recall scans/work-ups and screening detected lung cancers] and screened individuals) was also large between trials and varied between 1.2% in NELSON, 3.0% in DLCST, and 45.3% in the NLST trial. Trials with defined workup algorithms had considerably lower false positive rates. The rate of invasive procedures from false positive scans in individuals in need of a recall scan or diagnostic work-up ranged from 2.6% to 9.6%; data on complications from false positive LDCT was, however, very scarce. Rates of invasive procedures per screened individual varied between 0.5% and 11.4%.

Cost-effectiveness and budget impact: A total of 43 cost-effectiveness analyses were included in the systematic review. According to the CHEC checklist, the quality of reporting differed substantially between studies. The included studies showed high heterogeneity in the interventions (e.g., single, annual, biennial, triennial LDCT screening), comparators (no screening or CXR), the main source of effectiveness assumptions (e.g., NLST, NELSON, ELCAP, etc.), perspective (e.g., healthcare, payer, insurer, societal), and time horizon (from 1 year to lifetime). In general, a common theme in the study results was that LDCT screening is more costly and more effective than no screening or CXR (NB: studies based on NLST generally assumed that CXR was equal to no screening). In most cases, the incremental cost effectiveness ratios (ICERs) were below USD/EUR/GBP/NZD/CAD 100,000 per life year gained (LYG) or per quality-adjusted life-year (QALY) gained. Studies based on the recently published NELSON study seemed to lead to improved ICERs for LDCT screening if compared with studies based on NLST or other trials. Many studies emphasized that the screening strategy (e.g., inclusion criteria for lung cancer screening), the cost of LDCT scans, the effectiveness of screening (sensitivity and stage shift leading to lung cancer detection in early stages) and the incidence/prevalence of lung cancer are key factors affecting the cost-effectiveness of screening. To compare the previously published analyses based on NLST effectiveness with the new estimations based on NELSON effectiveness, a total of 2,972 scenarios were modelled. The results showed that scenarios based on NELSON effectiveness led to more LYG if compared to the original scenarios based on NLST effectiveness. The average cost-effectiveness ratios (ACERs) comparing each scenario with no 15 screening for the models based on NELSON effectiveness led to ACERs ranging between CHF 14,452 to CHF 37,959 per QALY gained. The no screening scenario estimated the detection of 6,784 lung cancer cases and a total of 4,674 lung cancer deaths per 100,000 persons. The introduction of lung cancer screening led to a higher number of detected lung cancer cases

and a lower number of cancer deaths. For the scenarios on the efficiency frontier, the number of detected lung cancer cases ranged between 6,799 (+15 cases per 100,000 persons compared to no screening) and 6,981, (+197 cases per 100,000 persons compared to no screening), while the number of lung cancer deaths would range between 4,471 (-4.3%) and 3,593 (-23.1%). In our previous study, the number of false positive screens per 100,000 persons (based on NLST effectiveness) were particularly high, ranging between 7,651 and 63,435. The new analyses based on NELSON false-positive rates showed a drastic decrease, with false positive screens ranging between 360 and 8,290 per 100,000 persons. Depending on the screening scenario, the number of individuals needed to screen per LYG would range between 2 and 3 (i.e. you need to screen 2-3 persons at risk to gain one life-year), while the number of individuals needed to screen per death avoided would range between 21 and 41. The number of LDCT screens per lung cancer death avoided would range between 155 and 434 LDCT screens per LYG. In the budget impact analysis, the total costs related to lung cancer treatment in Switzerland in the absence of screening were estimated to increase from CHF 474 million in 2023 to CHF 724 million in 2037. Compared to no screening, the budget impact of all screening scenario was higher. Over a period of 15 years, the total costs of lung cancer in the no screening scenario were estimated to reach CHF 9.4 billion, while the costs for three selected scenarios on the efficiency frontier ranged between CHF 10.2 billion and CHF 12.6 billion (i.e., +9% and +34% compared to no screening, respectively).

Ethics: Screening raises many ethical issues regarding access, stigmatisation, shared decision making and treatment modalities. These can all be addressed with careful design of screening campaigns and patient interaction, but particular care should be taken to avoid overstating the prospective benefits of screening. Perceptions of lung cancer as a “self-inflicted” disease are held by some citizens, but this view is not prevalent and screening is perceived positively by a majority. Screening also raises issues concerning just distribution of resources, with hundreds of patients needing to be screened to prevent one death from lung cancer and a high financial cost per averted death, and little impact on overall mortality. Implementation of screening would benefit those in lower socioeconomic groups and certain ethnic groups to a greater extent than other populations, but failure to implement screening would not amount to discrimination against these groups. Excluding other high-risk groups other than (ex-)smokers would also not be discriminatory given the differential balance of costs and benefits. 16

Conclusion: LDCT screening for lung cancer is associated with a reduced mortality from lung cancer but does not reduce overall mortality. Psychological consequences of screening (e.g. anxiety or depression) remain unclear and LDCT screenings does not seem to increase quit rates from smoking. False positive findings from LDCT remain a concern and important differences in false positive rates, repeated scans and invasive work-ups were found between

trials. Volumed-based definitions of suspicious nodes, repeated scans and strict work-up protocols as applied in the large NELSON trial reduce false positive scans. The great majority of the published cost-effectiveness analyses concluded that lung cancer screening may be a cost-effective intervention. Analyses based on data from the NELSON trial confirmed the positive results obtained in previous analyses based on the results of the NLST. The results of the cost effectiveness analysis suggested that most lung cancer screening strategies may be cost-effective in Switzerland (assuming a threshold of CHF 100,000 per QALY gained). The cost-effectiveness and budget impact were highly dependent on screening intervals and smoking eligibility criteria. Although being more expensive than biennial and triennial screening strategies, annual screening showed the greatest potential reduction in lung cancer mortality and the highest increase of QALY gained. Whether lung cancer screening represents a fair distribution of harms and burdens for the benefit conferred is a subjective judgment. Even if screening is deemed cost-effective in a financial sense, there is little impact on overall mortality and the number of patients needed to screen and the number of false positives incurred to prevent each lung cancer death may be too high to merit implementation. Whatever decision is ultimately made about screening, whether at the patient level or the health systems level, any values underlying that decision must be articulated clearly, along with the empirical evidence informing that decision.

5.7 Towards full clinical trial registration and results publication: longitudinal meta-research study in Northwestern and Central Switzerland

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Abstract

Objective: The registration of clinical trials is required by law in Switzerland. We investigated (1) the proportion of registered and prospectively registered clinical trials, (2) the availability of results for ethically approved trial protocols, (3) factors associated with increased registration, and (4) reasons for non-registration.

Design and setting: We included all clinical trials with mandatory prospective registration, which were approved by the ethics committee of Northwestern and Central Switzerland between January 1, 2016, and December 31, 2020.

Methods: We extracted relevant trial characteristics from the Swiss Business Administration System for Ethics Committees and systematically searched the International Clinical Trials Registry Platform and primary trial registries for corresponding registry entries. We used multivariable logistic regression to examine the association between trial characteristics and registration. We qualitatively assessed reasons for non-registration of trials through an email questionnaire for trial investigators.

Results: Of 473 included clinical trials, 432 (91%) were registered at all and 326 (69%) were prospectively registered. While the percentages of registration and prospective registration of investigator-sponsored trials increased from 85 to 93% and from 59 to 70% over 5 years, respectively, industry-sponsored trials consistently remained at a high level of prospective registration (92 to 100%). Trials with multiple centres, higher risk category, or methodological support from the local clinical trials unit were independently associated with increased registration rates. Of 103 clinical trials completed before August 2020, results were available

for 70% of industry-sponsored trials and 45% of investigator-sponsored trials as peer-reviewed journal publications or in trial registries. Most common reasons for non-registration provided by investigators were lack of time or resources (53%), lack of knowledge (22%), and lack of reminders by the ethics committee (36%).

Conclusions: In Northwestern and Central Switzerland about 10% of clinical trials remained unregistered despite the obligation by law. More support for investigators and stricter enforcement by regulators are needed to improve the transparency of investigator-sponsored trials in particular.

5.8 Scoping review and characteristics of publicly available checklists for assessing clinical trial feasibility

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Abstract

Background: Whether there is sufficient capacity and capability for the successful conduct and delivery of a clinical trial should be assessed by several stakeholders according to transparent and evidence-based criteria during trial planning. For this openly shared, user-tested, and validated tools are necessary. Therefore, we systematically examined the public availability and content of checklists which assess the study-level feasibility in the planning phase of clinical trials.

Methods: In our scoping review we systematically searched Medline, EMBASE, and Google (last search, June 2021). We included all publicly available checklists or tools that assessed study level feasibility of clinical trials, examined their content, and checked whether they were user-tested or validated in any form. Data was analysed and synthesised using conventional content analysis.

Results: A total of 10 publicly available checklists from five countries were identified. The checklists included 48 distinct items that were classified according to the following seven different domains of clinical trial feasibility: regulation, review and oversight; participant recruitment; space, material and equipment; financial resources; trial team resources; trial management; and pilot or feasibility studies. None of the available checklists appeared to be user-tested or validated.

Conclusions: Although a number of publicly available checklists to assess the feasibility of clinical trials exist, their reliability and usefulness remain unclear. Openly shared, user-tested, and validated feasibility assessment tools for a better planning of clinical trials are lacking.

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

Christof Manuel Schönenberger, Alexandra Griessbach, **Ala Taji Heravi**, Dmitry Gryaznov, Viktoria L Gloy, Szimonetta Lohner, Katharina Klatte, Nilabh Ghosh, Hopin Lee, Anita Mansouri, Ioana R. Marian, Ramon Saccilotto, Edris Nury, Jason W. Busse, Belinda von Niederhäusern, Dominik Mertz, Anette Blümle, Ayodele Odutayo, Sally Hopewell, Benjamin Speich, Matthias Briel.

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Journal of Clinical Epidemiology, 2022 May.
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Abstract

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

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

5.10 Reporting quality of clinical trial protocols: a repeated cross-sectional study aboutthe Adherence to SPIrit Recommendations in Switzerland, CAnada and Germany (ASPIRE-SCAGE)

Dmitry Gryaznov; Belinda von Niederhäusern; Benjamin Speich; Benjamin Kasenda; Elena Ojeda-Ruiz; Anette Blümle; Stefan Schandelmaier; Dominik Mertz; Ayodele Odutayo; Yuki Tomonaga; Alain Amstutz; Christiane Pauli-Magnus; Viktoria Gloy; Szimonetta Lohner; Karin Bischoff; Katharina Wollmann; Laura Rehner; Joerg J Meerpohl; Alain Nordmann; Katharina Klatte; Nilabh Ghosh; **Ala Taji Heravi**; Jacqueline Wong; Ngai Chow; Patrick Jiho Hong; Kimberly Mc Cord; Sirintip Sricharoenchai; Jason W. Busse; Arnav Agarwal; Ramon Saccilotto; Matthias Schwenkglenks; Giusi Moffa; Lars G. Hemkens; Sally Hopewell; Erik von Elm; Matthias Briel.

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Abstract

Objectives: Comprehensive protocols are key for the planning and conduct of randomised clinical trials (RCTs). Evidence of low reporting quality of RCT protocols led to the publication of the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) checklist in 2013. We aimed to examine the quality of reporting of RCT protocols from three countries before and after the publication of the SPIRIT checklist.

Design: Repeated cross sectional study.

Setting: Swiss, German and Canadian research ethics committees (RECs).

Participants: RCT protocols approved by RECs in 2012 (n=257) and 2016 (n=292).

Primary and secondary outcome measures: The primary outcomes were the proportion of reported SPIRIT items per protocol and the proportion of trial protocols reporting individual SPIRIT items. We compared these outcomes in protocols approved in 2012 and 2016, and built regression models to explore factors associated with adherence to SPIRIT. For each protocol, we also extracted information on general trial characteristics and assessed whether

individual SPIRIT items were reported RESULTS: The median proportion of reported SPIRIT items among RCT protocols showed a non-significant increase from 72% (IQR, 63%-79%) in 2012 to 77% (IQR, 68%-82%) in 2016. However, in a preplanned subgroup analysis, we detected a significant improvement in investigator-sponsored protocols: the median proportion increased from 64% (IQR, 55%-72%) in 2012 to 76% (IQR, 64%-83%) in 2016, while for industry-sponsored protocols median adherence was 77% (IQR 72%-80%) for both years. The following trial characteristics were independently associated with lower adherence to SPIRIT: single-centre trial, no support from a clinical trials unit or contract research organisation, and investigator-sponsorship.

Conclusions: In2012, industry-sponsored RCT protocols were reported more comprehensively than investigator-sponsored protocols. After publication of the SPIRIT checklist, investigator-sponsored protocols improved to the level of industry-sponsored protocols, which did not improve.

Keywords: Clinical trials; EPIDEMIOLOGY; Protocols & guidelines.

5.11 Nonregistration, discontinuation, and nonpublication of randomized trials: A repeated meta-research analysis

Benjamin Speich, Dmitry Gryaznov, Jason W. Busse, Viktoria L Gloy, Szimonetta Lohner, Katharina Klatte, **Ala Taji Heravi**, Nilabh Ghosh, Hopin Lee, Anita Mansouri, Ioana R. Marian, Ramon Saccilotto, Edris Nury, Alexandra N Griessbach, Christof Schönenberger, Dominik Mertz, Anette Blümle, Belinda von Niederhäusern, Sally Hopewell, Ayodele Odutayo, Matthias Briel, and the ASPIRE study group.

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Abstract

Background: We previously found that 25% of 1,017 randomized clinical trials (RCTs) approved between 2000 and 2003 were discontinued prematurely, and 44% remained unpublished at a median of 12 years follow-up. We aimed to assess a decade later (1) whether rates of completion and publication have increased; (2) the extent to which nonpublished RCTs can be identified in trial registries; and (3) the association between reporting quality of protocols and premature discontinuation or nonpublication of RCTs.

Methods and findings: We included 326 RCT protocols approved in 2012 by research ethics committees in Switzerland, the United Kingdom, Germany, and Canada in this meta research study. Pilot, feasibility, and phase 1 studies were excluded. We extracted trial characteristics from each study protocol and systematically searched for corresponding trial registration (if not reported in the protocol) and full text publications until February 2022. For trial registrations, we searched the (i) World Health Organization: International Clinical Trial Registry Platform (ICTRP); (ii) US National Library of Medicine (ClinicalTrials.gov); (iii) European Union Drug Regulating Authorities Clinical Trials Database (EUCTR); (iv) ISRCTN registry; and (v) Google. For full text publications, we searched PubMed, Google Scholar, and Scopus. We recorded whether RCTs were registered, discontinued (including reason for discontinuation), and published. The reporting quality of RCT protocols was assessed with the 33-item SPIRIT checklist. We used multivariable logistic regression to examine the association between the independent variables protocol reporting quality, planned sample size, type of control (placebo

versus other), reporting of any recruitment projection, single-center versus multicenter trials, and industry versus investigator sponsoring, with the 2 dependent variables: (1) publication of RCT results; and (2) trial discontinuation due to poor recruitment.Of the 326 included trials, 19 (6%) were unregistered. Ninety-eight trials (30%) were discontinued prematurely, most often due to poor recruitment (37%; 36/98). One in 5 trials (21%; 70/326) remained unpublished at 10 years follow-up, and 21% of unpublished trials (15/70) were unregistered. Twenty-three of 147 investigator-sponsored trials (16%) reported their results in a trial registry in contrast to 150 of 179 industry-sponsored trials (84%).The median proportion of reported SPIRIT items in included RCT protocols was 69% (interquartile range 61% to 77%). We found no variables associated with trial discontinuation; however, lower reporting quality of trial protocols was associated with nonpublication (odds ratio, 0.71 for each 10% increment in the proportion of SPIRIT items met; 95% confidence interval, 0.55 to 0.92; p = 0.009). Study limitations include that the moderate sample size may have limited the ability of our regression models to identify significant associations.

Conclusions: We have observed that rates of premature trial discontinuation have not changed in the past decade. Nonpublication of RCTs has declined but remains common; 21% of unpublished trials could not be identified in registries. Only 16% of investigator-sponsored trials reported results in a trial registry. Higher reporting quality of RCT protocols was associated with publication of results. Further efforts from all stakeholders are needed to improve efficiency and transparency of clinical research.

5.12 Reliability of trial information across registries for trials with multiple registrations: A systematic review

Benjamin Speich, Viktoria L Gloy, Katharina Klatte, Dmitry Gryaznov, **Ala Taji Heravi**, Nilabh Ghosh, Ioana R. Marian, Hopin Lee, Anita Mansouri, Szimonetta Lohner, Ramon Saccilotto, Edris Nury, An-Wen Chan, Anette Blümle, Ayodele Odutayo, Sally Hopewell, Matthias Briel, and the ASPIRE study group.

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Abstract

Importance: Clinical trial registries are important for gaining an overview of ongoing research efforts and for deterring and identifying publication bias and selective outcome reporting. The reliability of the information in trial registries is uncertain.

Objective: To assess the reliability of information across registries for trials with multiple registrations.

Evidence Review: For this systematic review, 360 protocols of randomized clinical trials (RCTs) approved by research ethics committees in Switzerland, the UK, Canada, and Germany in 2012 were evaluated. Clinical trial registries were searched from March to September 2019 for corresponding registrations of these RCTs. For RCTS that were recorded in more than 1 clinical trial registry, key trial characteristics that should be identical among all trial registries (ie, sponsor, funding source, primary outcome, target sample size, trial status, date of first patient enrollment, results available, and main publication indexed) were extracted in duplicate. Agreement between the different trial registries for these key characteristics was analyzed descriptively. Data analyses were conducted from May 1 to November 30, 2020. Representatives from clinical trial registries were interviewed to discuss the study findings between February 1 and March 31, 2021.

Findings: The analysis included 197 RCTs registered in more than 1 trial registry (151 in 2 registries and 46 in 3 registries), with 188 trials in ClinicalTrials.gov, 185 in the European Union Drug Regulating Authorities Clinical Trials Database (EudraCT), 20 in ISRCTN, and 47 in other

registries. The agreement of key information across all registries was as follows: 178 of 197 RCTs (90%; 95% CI, 85%-94%) for sponsor, 18 of 20 (90%; 95% CI, 68%-99%) for funding source (funding was not reported on ClinicalTrials.gov), 154 of 197 (78%; 95% CI, 72%-84%) for primary outcome, 90 of 197 (46%; 95% CI, 39%-53%) for trial status, 122 of 194 (63%; 95% CI, 56%-70%) for target sample size, and 43 of 57 (75%; 95% CI, 62%-86%) for the date of first patient enrollment when the comparison time was increased to 30 days (date of first patient enrollment was not reported on EudraCT). For results availability in trial registries, agreement was 122 of 197 RCTs (62%; 95% CI, 55%-69%) for summary data reported in the registry and 91 of 197 (46%; 95% CI, 39%-53%) for whether a published article with the main results was indexed. Different legal requirements were stated as the main reason for inconsistencies by representatives of clinical trial registries.

Conclusions and Relevance: In this systematic review, for a substantial proportion of registered RCTs, information about key trial characteristics was inconsistent across trial registries, raising concerns about the reliability of the information provided in these registries. Further harmonization across clinical trial registries may be necessary to increase their usefulness.

5.13 Reporting quality of trial protocols improved for non-regulated interventions but not regulated interventions: A repeated cross sectional study

Szimonetta Lohner, Dmitry Gryaznov, Belinda von Niederhäusern, Benjamin Speich, Benjamin Kasenda, Elena Ojeda-Ruiz, Stefan Schandelmaier, Dominik Mertz, Ayodele Odutayo, Yuki Tomonaga, Alain Amstutz, Christiane Pauli-Magnus, Viktoria Gloy, Karin Bischoff, Katharina Wollmann, Laura Rehner, Joerg J Meerpohl, Alain Nordmann, Katharina Klatte, Nilabh Ghosh, **Ala Taji Heravi**, Jacqueline Wong, Ngai Chow, Patrick Jiho Hong, Kimberly Mc Cord, Sirintip Sricharoenchai, Jason W. Busse, Arnav Agarwal, Ramon Saccilotto, Matthias Schwenkglenks, Giusi Moffa, Lars G. Hemkens, Sally Hopewell, Erik von Elm, Anette Blümle, Matthias Briel.

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Journal of Clinical Epidemiology, 2021 May.
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Abstract

Objectives: To investigate the adherence of randomised controlled trial (RCT) protocols evaluating non-regulated interventions (including dietary interventions, surgical procedures, behavioural and lifestyle interventions, and exercise programmes) in comparison with regulated interventions to the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) 2013 Statement.

Methods: We conducted a repeated cross-sectional investigation in a random sample of RCT protocols approved in 2012 (n = 257) or 2016 (n = 292) by research ethics committees in Switzerland, Germany, or Canada. We investigated the proportion of accurately reported SPIRIT checklist items in protocols of trials with non-regulated as compared to regulated interventions.

Results: Overall, 131 (24%) of trial protocols tested non-regulated interventions. In 2012, the median proportion of SPIRIT items reported in these protocols (59%, interquartile range [IQR], 53%-69%) was lower than in protocols with regulated interventions (median, 74%, IQR, 66%-80%). In 2016, the reporting quality of protocols with non-regulated interventions (median,

75%, IQR, 62%-83%) improved to the level of regulated intervention protocols, which had not changed on average.

Conclusions: Reporting of RCT protocols evaluating non-regulated interventions improved between 2012 and 2016, although remained suboptimal. SPIRIT recommendations need to be further endorsed by researchers, ethics committees, funding agencies, and journals to optimize reporting of RCT protocols.

Keywords: Behavioural and lifestyle interventions; Clinical trial protocol; Dietary interventions; Randomized controlled trials; Reporting guidelines; Surgical procedures.

5.14 A meta-research study revealed several challenges in obtaining placebos for investigator-initiated drug trials

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Journal of Clinical Epidemiology, 2020 November.
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Abstract

Objectives: To systematically assess the kind of placebos used in investigator-initiated randomized controlled trials (RCTs), from where they are obtained, and the hurdles that exist in obtaining them.

Study design and setting: PubMed was searched for recently published noncommercial, placebo-controlled randomized drug trials. Corresponding authors were invited to participate in an online survey.

Results: From 423 eligible articles, 109 (26%) corresponding authors (partially) participated. Twenty-one of 102 (21%) authors reported that the placebos used were not matching (correctly labeled in only one publication). The main sources in obtaining placebos were hospital pharmacies (32 of 107; 30%) and the manufacturer of the study drug (28 of 107; 26%). RCTs with a hypothesis in the interest of the manufacturer of the study drug were more likely to have obtained placebos from the drug manufacturer (18 of 49; 37% vs. 5 of 29; 17%). Median costs for placebos and packaging were US$ 58,286 (IQR US$ 2,428- US$ 160,770; n = 24), accounting for a median of 10.3% of the overall trial budget.

Conclusion: Although using matching placebos is widely accepted as a basic practice in RCTs, there seems to be no standard source to acquire them. Obtaining placebos requires substantial resources, and using nonmatching placebos is common.

Keywords: Investigator-initiated trials; Matching; Placebo; Randomized controlled trial.

5.15 Rationale and design of repeated cross-sectional studies to evaluate the reportingquality of trial protocols: the Adherence to SPIrit REcommendations (ASPIRE) study and associated projects

Dmitry Gryaznov, Ayodele Odutayo, Belinda von Niederhäusern, Benjamin Speich, Benjamin Kasenda, Elena Ojeda-Ruiz, Anette Blümle, Stefan Schandelmaier, Dominik Mertz, Yuki Tomonaga, Alain Amstutz, Christiane Pauli-Magnus, Viktoria Gloy, Karin Bischoff, Katharina Wollmann, Laura Rehner, Szimonetta Lohner, Joerg J Meerpohl, Alain Nordmann, Katharina Klatte, Nilabh Ghosh**, Ala Taji Heravi**, Jacqueline Wong, Ngai Chow, Patrick Jiho Hong, Kimberly Mc Cord, Sirintip Sricharoenchai, Jason W. Busse, Arnav Agarwal, Ramon Saccilotto, Matthias Schwenkglenks, Giusi Moffa, Lars G. Hemkens, Sally Hopewell, Erik von Elm, Matthias Briel.

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Trials, 2020 October.
DOI: 10.1186/s13063-020-04808-y

Abstract

Background: Clearly structured and comprehensive protocols are an essential component to ensure safety of participants, data validity, successful conduct, and credibility of results of randomized clinical trials (RCTs). Funding agencies, research ethics committees (RECs), regulatory agencies, medical journals, systematic reviewers, and other stakeholders rely on protocols to appraise the conduct and reporting of RCTs. In response to evidence of poor protocol quality, the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guideline was published in 2013 to improve the accuracy and completeness of clinical trial protocols. The impact of these recommendations on protocol completeness and associations between protocol completeness and successful RCT conduct and publication remain uncertain.

Objectives and methods: Aims of the Adherence to SPIrit REcommendations (ASPIRE) study are to investigate adherence to SPIRIT checklist items of RCT protocols approved by RECs in the UK, Switzerland, Germany, and Canada before (2012) and after (2016) the publication of the SPIRIT guidelines; determine protocol features associated with non-adherence to SPIRIT checklist items; and assess potential differences in adherence across

countries. We assembled an international cohort of RCTs based on 450 protocols approved in 2012 and 402 protocols approved in 2016 by RECs in Switzerland, the UK, Germany, and Canada. We will extract data on RCT characteristics and adherence to SPIRIT for all included protocols. We will use multivariable regression models to investigate temporal changes in SPIRIT adherence, differences across countries, and associations between SPIRIT adherence of protocols with RCT registration, completion, and publication of results. We plan substudies to examine the registration, premature discontinuation, and non-publication of RCTs; the use of patient-reported outcomes in RCT protocols; SPIRIT adherence of RCT protocols with non-regulated interventions; the planning of RCT subgroup analyses; and the use of routinely collected data for RCTs.

Discussion: The ASPIRE study and associated substudies will provide important information on the impact of measures to improve the reporting of RCT protocols and on multiple aspects of RCT design, trial registration, premature discontinuation, and non-publication of RCTs observing potential changes over time.

6 Supplementary materials

6.1 Supplementary material manuscript I - RECRUITment patterns In randomized clinical Trials (RECRUIT-IT- a meta-research study

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Appendix 1- STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No.	Recommendation	Page No.
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6 &7
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	6&7

		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7 &8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*7*
Bias	9	Describe any efforts to address potential sources of bias	7 &8
Study size	10	Explain how the study size was arrived at	7, protocol
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7&8
		(*b*) Describe any methods used to examine subgroups and interactions	7
		(*c*) Explain how missing data were addressed	7
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed	not applicable

		Case-control study—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	7
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	17, Figure 1
		(b) Give reasons for non-participation at each stage	8 &9
		(c) Consider use of a flow diagram	17, Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	18
		(b) Indicate number of participants with missing data for each variable of interest	Figure 1, individual tables
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	not applicable
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	not applicable

		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Table Appendix 5
		(*b*) Report category boundaries when continuous variables were categorized	not applicable
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	not applicable
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	not applicable
Discussion			
Key results	18	Summarise key results with reference to study objectives	10 &11
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	11
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11 &12
Generalisability	21	Discuss the generalisability (external validity) of the study results	12

Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	13

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

Appendix 2- Rating instructions for assessors of recruitment trajectories

Dear Assessors,

To judge the recruitment pattern more accurately, recruitment trajectories are available in the scale of months & weeks for those trials recruiting only for one year or less. Otherwise, the scale is months only.
Please answer the following questions for each trial, in the provided Excel sheet, named "RecruitmentPattern_Rating.xlsx".
Please NOTE! Discontinued trials are plotted in red color.

1- From visual inspection, how would you characterize the recruitment trajectory in the beginning/early phase of recruitment (during first 10% of the target sample size)?

- Linear: Recruitment more or less steady and linear over time;
- Accelerating: Starts slow and then increases substantially over time;
- Jump start: Starts fast with several participants recruited right away (vertical line) and then linear;
- Sigmoid/Stepped: Recruitment in a s-curve shape, i.e., with plateau in between;
- Not ratable: Not enough participants recruited to identify a pattern;
- Other (please specify): Any other pattern. Please describe. (e.g. Very slow start – plateau-like/very flat slope > 12 months)

2- From visual inspection, how would you characterize the recruitment trajectory in the middle phase of recruitment (during recruitment of about 10% to about 80% of the target sample size)?

- Linear_same: Linear/steady recruitment, same slope as in early phase;
- Linear_more steep: Linear/steady recruitment, slope is steeper than in early phase;
- Linear_less steep: Linear/steady recruitment, slope is less steep than in early phase;
- Linear_with little bump: Linear/steady recruitment, wiggly/bumpy but not a plateau (no slope (horizontal line) OR very flat slope >3months).
- Accelerating: Recruitment increases gradually/exponentially over middle phase;
- Decelerating: Steady recruitment and then slows down gradually/continuously over time;
- Sigmoid/Stepped: Recruitment interrupted by one or several plateaus;
- Not ratable: Not enough participants recruited to identify a pattern;
- Other (please specify): Any other pattern. Please describe.

3- From visual inspection, how would you characterize the recruitment trajectory in the end/late phase of recruitment (during recruitment of the last 20% of the target sample size)?

- Linear_same: Linear/steady recruitment, same slope as in middle phase;
- Linear_more steep: Linear/steady recruitment, slope is steeper than in middle phase;
- Linear_less steep: Linear/steady recruitment, slope is less steep than in middle phase;

- Accelerating: Recruitment increases gradually/exponentially over end phase;
- Decelerating: Slows down gradually/continuously over end phase;
- Sigmoid/Stepped: Recruitment interrupted by one or several plateaus;
- Not ratable: Not enough participants recruited to identify a pattern;
- Other (please specify): Any other pattern. Please describe

PLEASE NOTE!

- We consider the first 10% of the target sample size as the beginning/early phase, however, this is just rough guidance. Similarly, we consider the last 20% of the target sample size as the end/late phase of recruitment (see stratified rating above).

- If the beginning/early recruitment pattern differs from the middle pattern, the end of the beginning/early pattern (as % of the target sample size) should be estimated. If no pattern change, NA should be entered.

- If the middle recruitment pattern differs from the end/late pattern, the start of the end pattern (as % of the target sample size) should be estimated. If no pattern change, NA should be entered.

Appendix 3- Descriptions of overall recruitment pattern categories

Linear	Linear throughout	Beginning/early phase linear, jump start, or acceler ating, then a generally linear or bumpy trajectory u ntil the end.
	Linear with vertical element	As above, but in the middle part of the trajectory th ere is a “jump” or short acceleration followed by a c hange back to a linear trajectory with a similar slop e as before the vertical element.
	Classic	Linear or accelerating in the beginning, then linear i n the middle phase (largest part of the trajectory), fi nally decelerating or linear with a less steep slope t owards the end of recruitment.
Accelerating	Accelerating throughout	Accelerating trajectory from beginning to end of rec ruitment.
	Late acceleration	Beginning linear, jump start, or accelerating, then li near middle part with longer acceleration towards t he end.
	Angle to more steep	Beginning linear, jump start, or accelerating, then li near middle part with a change towards a steeper s lope which continues until the end.
Decelerating	Decelerating throughout	Beginning linear or jump start, then slope becomes gradually flatter / recruitment decelerates over the middle and end phase.
	Angle to less steep	Beginning linear, jump start, or accelerating, then linear middle part with a change towards a less steep slope which continues until the end.
Beginning/ middle/overall plateau	Mid trial slow down	The recruitment temporarily slows down in the mid dle phase and picks up again (indicating seasonalit y).
	Plateau in the middle	The recruitment trajectory includes a plateau/very fl at slope in the middle phase and then returns to a s imilar slope as before
	Very slow start	The recruitment starts out with a plateau/very flat slope for six months or more.

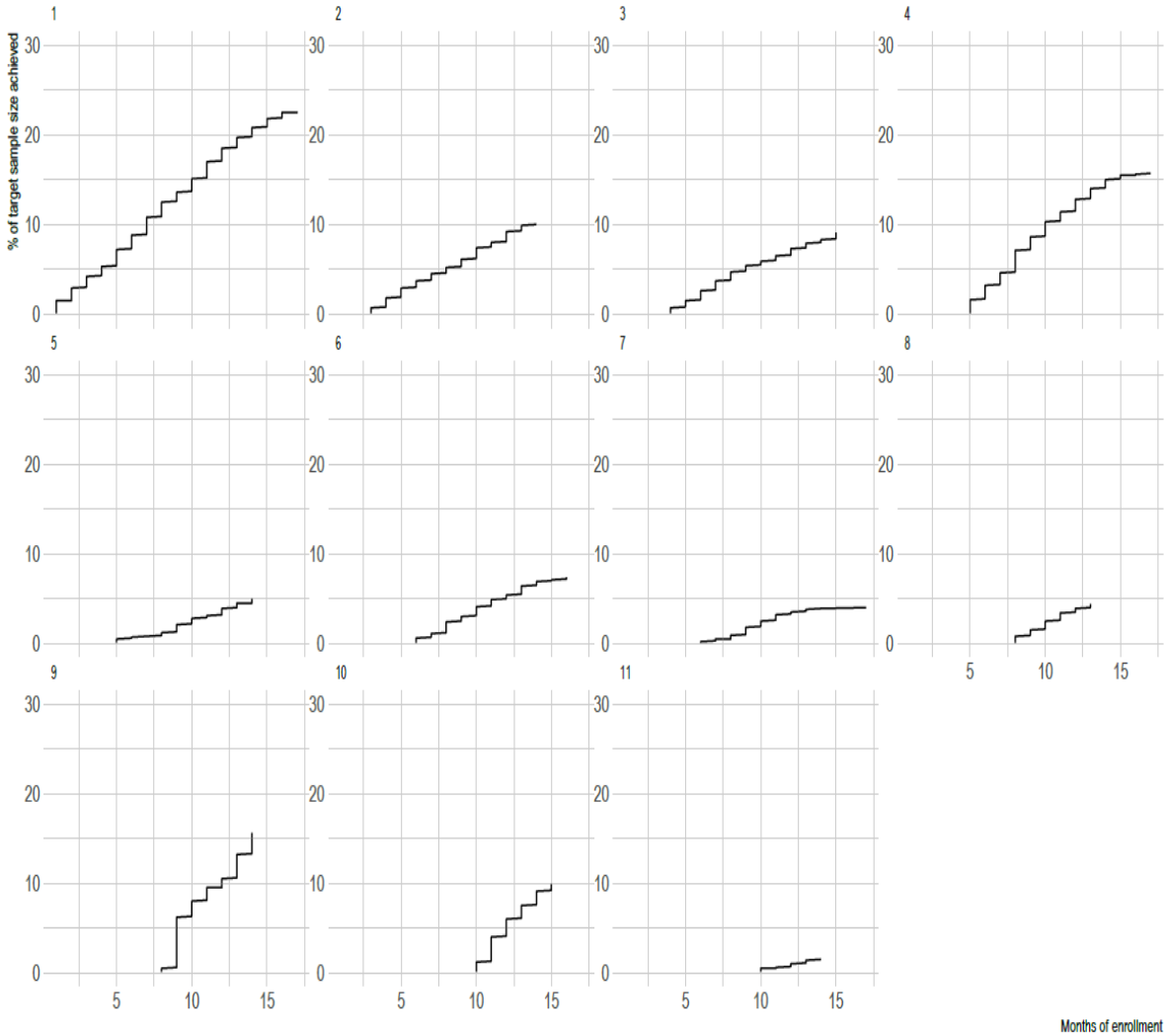
Appendix 4 – example of recruitment trajectories on site level

non_industry trial

Target sample size: 1100

Cardiovascular trial

PI_site = site number 1



Appendix 5- Trial characteristics associated with an overall linear recruitment pattern

Characteristics	Linear pattern (n=191)	Non-linear pattern (n=109)	Univariable		Multivariable	
			OR (95% CI)	P-value	OR (95% CI)	P-value
Trial network (reference: no trial network)						
Industry	65 (34.0%)	36 (33.0%)	1.13 (0.60,2.13)	0.70	1.24 (0.55,2.79)	0.61
Well-established academic trial network	83 (43.5%)	46 (42.2%)	1.13 (0.62,2.06)	0.68	1.91 (0.85,4.39)	0.12
Medical field (reference: other medical fields)						
Cardiovascular	22 (11.5%)	5 (4.6%)	2.64 (0.99,8.39)	0.07	3.03 (1.04,10.35)	0.05
Infectious disease	49 (25.7%)	39 (35.8%)	0.75 (0.42,1.34)	0.34	0.85 (0.36,2.05)	0.72
Neurology	19 (9.9%)	12 (11.0%)	0.95 (0.42,2.21)	0.90	1.24 (0.47,3.42)	0.66
Oncology	36 (18.8%)	14 (12.8%)	1.54 (0.75,3.29)	0.25	1.44 (0.64,3.34)	0.38
Time of recruitment after 2000 (vs before 2000)	57 (29.8%)	43 (39.4%)	1.51 (0.92,2.48)	0.10	1.38 (0.73,2.61)	0.40
International (vs national)	105 (55.0%)	51 (46.8%)	1.47 (0.91,2.38)	0.12	0.99 (0.97,1.02)	0.32
Planned target sample size, median (IQR)*	3.36 (1.98, 7.33)	3.00 (1.60, 7.00)	1.00 (0.98,1.02)	0.99	0.76 (0.25,2.26)	0.67

Abbreviations: RCT, randomized clinical trial; IQR, interquartile range, OR, odds ratio; CI, confidence interval.
* In increments of 100.

Appendix 6- Characteristics of RCTs with site information

	Multi-center RCTs for site analysis* (n=85)	**Multi-center RCTs without site analysis (n=132)**	**Single-center RCTs (n=17)**
Recruitment period, range	1986 -2021	1995-2015	2002-2022
Clinical area– n (%)			
Infectious Diseases	30 (35%)	45 (34%)	4 (23%)
Oncology	11 (13%)	37 (28%)	0
Surgery	8 (9%)	10 (7%)	1 (6%)
Respiratory	2 (2.5%)	0	0
Cardiovascular	11 (13%)	9 (6%)	1 (6%)
Neurology	5 (6%)	17 (13%)	1 (6%)
Psychiatry	5 (6%)	5 (3%)	0
Endocrionology	2 (2.5%)	4 (3%)	0
Other	11 (13%)		10 (59%)
Planned target Sample Size median (IQR)	550 (375-1024)	199 (105-304)	186 (84-220)
Achieved Sample Size median (IQR)	575 (408-1001)	173 (89-299)	144 (93-220)
Enrolment duration median (IQR)	22 (14-35)	26 (15-44)	16 (11-24)
Using administrative infrastructure of a network			
Investigator-sponsored RCTs with no-established trial network	23 (27%)	30 (23%)	15 (88%)
Investigator-sponsored RCTs with well-established trial network	39 (46%)	82 (62%)	1 (6%)
Industry-sponsored RCTs	23 (27%)	20 (15%)	1(6%)
Trial status			
Completed	77 (91%)	95 (72%)	13 (76%)
Stopped, due to poor recruitment	3 (3%)	19 (14%)	3 (18%)
Stopped, due to other reasons	5 (6%)	18 (14%)	1 (6%)

* RCTs with a minimum of 300 patients and with 3 to 60 recruiting sites were considered.

Appendix 7- Characteristics of RCTs with vs without PI-site information

	Multi-center RCTs with PI-site information (n=49)	Multi-center RCTs without PI-site information (n=168)
Recruitment period, range	2004-2017	1986-2021
Clinical area– n (%)		
Infectious Diseases	5 (10%)	70 (41%)
Oncology	3 (6%)	45 (27%)
Surgery	15 (31%)	3 (2%)
Respiratory	1 (2%)	1 (1%)
Cardiovascular	15 (31%)	5 (3%)
Neurology	3 (6%)	19 (11%)
Psychiatry	0	10 (6%)
Endocrionology	1 (2%)	5 (3%)
Other	6 (12%)	10 (6%)
Planned target Sample Size median (IQR)	404 (200-800)	300 (162-600)
Achieved Sample Size median (IQR)	370 (183-720)	302 (119-712)
Enrolment duration	31 (22-54)	21 (14-37)
Using administrative infrastructure of a network		
Investigator-sponsored RCTs with no-established trial network	30 (61%)	23 (14%)
Investigator-sponsored RCTs with well-established trial network	19 (39%)	102 (61%)
Industry-sponsored RCTs	0	43 (25%)
Trial status		
Completed	43 (88%)	129 (77%)
Stopped due to poor recruitment	4 (8%)	18 (11%)
Stopped due to other reasons	2 (4%)	21 (12%)

Abbreviation: PI site, principal investigator site;

Appendix 8- Spearman correlations between early recruitment and remaining recruitment

	RCTs of the AIDS Clinical Trials network (n=70)†	RCTs with other well-established trial networks (n=107)	RCTs without established trial network (n=57)
Absolute time of recruitment			
1st month accrual	0.40*	0.51*	0.37*
1st + 2nd months accrual	0.37*	0.45*	0.44*
1st + 2nd + 3rd months accrual	0.40*	0.33*	0.46*
Relative time of recruitment			
10% of recruitment time	0.63*	0.61*	0.79*
20% of recruitment time	0.70*	0.63*	0.81*
30% of recruitment time	0.67*	0.67*	0.82*

*P<0.001

† Excluded, recruited less than 5% of target sample size

6.2 Supplementary material manuscript II - non-registration, discontinuation, and non-publication of randomized trials in Switzerland, the UK, Germany, and Canada: An updated meta-research study

Benjamin Speich, **Ala Taji Heravi**, Christof Schönenberger, Lena Hausheer, Dmitry Gryaznov, Jason W. Busse, Manuela Covino, Szimonetta Lohner, Malena Chiaborelli, Johannes Schwenke, Ramon Saccilotto, Erik von Elm, Arnav Agarwal, Julian Hirt, David Mall, Alain Amstutz, Selina Epp, Dominik Mertz, Anette Blümle, Belinda von Niederhäusern, Alexandra N Griessbach, Sally Hopewell, Matthias Briel, and the ASPIRE study group

Table S1: Baseline characteristics of included randomised clinical trials, stratified by country of ethical approval

	Switzerland (n=184)	United Kingdom (n=98)	Germany (n=34)	Canada (n=30)	All RCTs (n=346)
Planned sample size, median (IQR)	200 (87-500)	228 (96-390)	304 (160-628)	269 (150-400)	220 (102-450)
Proportion of adequately reported SPIRIT items in protocol, median (IQR)	0.79 (0.72-0.83)	0.73 (0.67-0.78)	0.72 (0.63-0.77)	0.72 (0.62-0.79)	0.76 (0.68-0.81)
Single centre vs. multicentre					
Single centre	55 (29.9%)	20 (20.4%)	4 (11.8%)	4 (13.3%)	83 (24.0%)
Multicentre	129 (70.1%)	78 (79.6%)	30 (88.2%)	26 (86.7%)	263 (76.0%)
Study design					
Parallel	166 (90.2%)	94 (95.9%)	34 (100.0%)	28 (93.3%)	322 (93.1%)
Crossover	10 (5.4%)	2 (2.0%)	0 (0.0%)	0 (0.0%)	13 (3.8%)
Factorial	3 (1.6%)	1 (1.0%)	0 (0.0%)	0 (0.0%)	4 (1.2%)
Cluster	4 (2.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (1.2%)
Split body	1 (0.5%)	1 (1.0%)	0 (0.0%)	1 (3.3%)	3 (0.9%)
Placebo controlled	76 (41.3%)	43 (43.9%)	18 (52.9%)	14 (46.7%)	151 (43.6%)
Recruitment-rate reported in protocol	27 (14.7%)	38 (38.8%)	6 (17.7%)	8 (26.7%)	79 (22.8%)
Type of sponsor					
Industry	79 (42.9%)	61 (62.4%)	26 (76.5%)	16 (53.3%)	182 (52.6%)
Non-industry	105 (57.1%)	37 (37.8%)	8 (23.5%)	14 (46.7%)	164 (47.4%)

Abbreviations: RCT=randomised clinical trial; IQR=interquartile range

Table S2: Baseline characteristics of included randomised clinical trials in the current study and in the meta research studies assessing protocols receiving ethical approval in 2000-2003 [1], and 2012 [2]

	RCTs approved 2000-2003 [1] (n=894)	**RCTs approved in 2012 [2] (n=326)**	**RCTs approved in 2012 (n=346)**
Planned sample size, median (IQR)	260 (100-610)[a]	250 (100-600)	220 (102-450)
Proportion of adequately reported SPIRIT items in protocol, median (IQR)[b]	-	0.69 (0.61-0.77)	0.76 (0.68-0.81)
Single centre vs. multicentre[c]			
Single centre	149 (16.6%)	60 (18.4%)	83 (24.0%)
Multicentre	741 (82.9%)	266 (81.6%)	263 (76.0%)
Study design			
Parallel	822 (92.0%)	296 (90.8%)	322 (93.1%)
Crossover	41 (4.6%)	13 (4.0%)	13 (3.8%)
Factorial	14 (1.6%)	10 (3.1%)	4 (1.2%)
Cluster	12 (1.3%)	4 (1.2%)	4 (1.2%)
Split body	3 (0.3%)	0 (0.0%)	3 (0.9%)
Other/Unclear	2 (0.2%)	3 (0.9%)	
Placebo controlled	346 (38.7%)	131 (40.2%)	151 (43.6%)
Type of sponsor			
Industry	551 (61.6%)	179 (54.9%)	182 (52.6%)
Non-industry	343 (38.4%)	147 (45.1%)	164 (47.4%)
Country of ethical approval			
Switzerland	444 (49.7%)	165 (50.6%)	184 (53.2%)
United Kingdom	0 (0.0%)	89 (27.3%)	98 (28.3%)
Germany	272 (30.4%)	37 (11.4%)	34 (9.8%)
Canada	178 (19.9%	35 (10.7%)	30 (8.7%)

[a]12 trial protocols with missing target sample size excluded.
[b] Adherence to SPIRIT reporting guidelines was not assessed for study protocols approved in 2000-2003.
[c] For 4 protocols approved in 2000-2003 it remained unclear how many study centres were involved.
Abbreviations: RCT=randomised clinical trial; IQR=interquartile range

Table S3: Non-registration, discontinuation, and non-publication of randomised clinical trials receiving ethical approval in 2016, stratified by country of ethical approval

	Switzerland (n=184)	United Kingdom (n=98)	Germany (n=34)	Canada (n=30)	All RCTs (n=346)
Registration status					
Registered	172 (93.5%)	94 (95.9%)	31 (91.2%)	27 (90.0%)	324 (93.6%, 90.5-96.0%)
Prospectively registered	11 (11.4%)	9 (9.2%)	1 (2.9%)	2 (6.7%)	291 (84.1%, 79.8-87.8%)
Retrospectively registered	161 (87.5%)	85 (86.7%)	30 (88.2%)	25 (83.3)	33 (9.5%, 6.7-13.1%)
Not registered	12 (6.5%)	4 (4.1%)	3 (8.8%)	3 (10.0%)	22 (6.4%, 4.0-9.5%)
Completion status					
Completed	112 (60.9%)	68 (69.4%)	19 (55.9%)	21 (70.0%)	220 (63.6%, 58.3-68.7%)
Discontinued	61 (33.2%)	24 (24.5%)	12 (35.3%)	6 (20.0%)	103 (29.8%, 25.1-34.9%)
Unclear	11 (6.0%)	6 (6.1%)	3 (8.8%)	3 (10.0%)	23 (6.7%, 4.3-9.8%)
Results availability					
At any source (peer-reviewed publication or on trial registry)	138 (75.0%)	77 (78.6%)	30 (88.2%)	22 (73.3%)	267 (77.2%, 72.4-81.5%)
Peer reviewed publication	127 (69.0%)	67 (68.4%)	24 (70.6%)	18 (60.0%)	236 (68.2, 63.0-73.1%)
In trial registry	71 (38.6%)	60 (61.2%)	22 (64.7%)	19 (63.3%)	172 (49.7% 44.3-55.1%)
Results not available (neither as publication nor in trial registry	46 (25.0%)	21 (21.4%)	4 (11.8%)	8 (26.7%)	79 (22.8%, 18.5-27.6%)
Neither registered nor published	11 (6.0%)	4 (4.1%)	3 (8.8%)	3 (10.0%)	21 (6.1%, 3.8-9.1%)
Not published in journal but registered[a]	46 (80.7%)	27 (87.1%)	7 (70.0%)	9 (75.0%)	89 (80.9%, 72.3-87.8%)
Not published in journal but results available in registry[a]	11 (19.3%)	10 (32.3%)	6 (60.0%)	4 (33.3%)	31 (28.2%, 20.0-37.6%)

[a]Only a subsample of 110 trials considered (57 Switzerland, 31 United Kingdom, 10 Germany, 12 Canada) which were not published in a peer reviewed journal

Table S4: Non-publication and discontinuation in protocols approved by ethical committees in 2016 compared to protocols approved between 2000 to 2003 [1] and in 2012 [2]

	Study-protocols approved 2000-2003 [1]			Study-protocols approved in 2012 [2]			Study-protocols approved in 2016		
	Industry sponsored RCTs	**Non-industry sponsored RCTs**	**All RCTs**	**Industry sponsored RCTs**	**Non-industry sponsored RCTs**	**All RCTs**	**Industry sponsored RCTs**	**Non-industry sponsored RCTs**	**All RCTs**
Registration status[a]									
Registered	-	-	-	175/179 (97.8%)	132/147 (89.8%)	307/326 (94.2%)	177/182 (97.3%)	147/164 (89.6%)	324/346 (93.6%)
Prospectively registered	-	-	-	164/179 (91.6%)	110/147 (74.8%)	274/326 (84.0%)	168/182 (92.3%)	123/164 (75.0%)	291/346 (84.1%)
Retrospectively registered	-	-	-	10/179 (5.6%)	22/147 (15.0%)	33/326 (10.1%)	9/182 (5.0%)	24/164 (14.6%)	33/346 (9.5%)
Not registered	-	-	-	4/179 (2.2%)	15/147 (10.2%)	19/326 (5.9%)	5/182 (2.8%)	17/164 (10.4%)	22/346 (6.4%)
Completion status									
Completed	394/551 (71.5%)	181/343 (52.8%)	575/894 (64.3%)	119/179 (66.5%)	84/147 (57.1%)	203/326 (62.3%)	125/182 (68.7%)	95/164 (57.9%)	220/346 (63.6%)
Discontinued	119/551 (21.6%)	130/343 (37.9%)	249/894 (27.9%)	57/179 (31.8%)	41/147 (27.9%)	98/326 (30.1%)	50/182 (27.5%)	53/164 (32.3%)	103/346 (29.8%)
Unclear	38/551 (6.9%)	32/343 (9.3%)	70/894 (7.8%)	3/179 (1.7%)	22/147 (15.0%)	25/326 (7.7%)	7/182 (3.9%)	16/164 (9.8%)	23/346 (6.7%)
Results availability									
At any source (peer-reviewed publication or on trial registry)[a]	336/551 (61.0%)	194/343 (56.6%)	530/894 (59.3%)	172/179 (96.1%)	112/147 (76.2%)	284/326 (87.1%)	163/182 (89.6%)	104/164 (63.4%)	267/346 (77.2%)
Peer reviewed publication	336/551 (61.0%)	194/343 (56.6%)	530/894 (59.3%)	146/179 (81.6%)	100/147 (74.8%)	256/326 (78.5%)	133/182 (73.1%)	103/164 (62.8%)	236/346 (68.2)
In trial registry[a]	-	-	-	150/179 (83.8%)	23/147 (15.7%)	173/326 (53.1%)	149/182 (81.9%)	23/164 (14.0%)	172/346 (49.7%)
Reasons for discontinuation									
Poor recruitment[b]	40/119 (34%)	60/130 (46%)	100/249 (40%)	16/57 (28%)	20/41 (49%)	36/98 (37%)	16/50 (32.0%)	26/53 (49.1%)	42/103 (40.8%)
Futility	25/119 (21%)	12/130 (9%)	37/249 (15%)	15/57 (26%)	1/41 (2%)	16/98 (16%)	12/50 (24.0%)	0/53 (0.0%)	12/103 (11.7%)
Organisational/strategic reasons	20/119 (17%)	16/130 (12%)	36/249 (14%)	6/57 (11%)	0/41 (0%)	6/98 (6%)	6/50 (12.0%)	6/53 (11.3%)	12/103 (11.7%)
Harm	17/119 (14%)	7/130 (5%)	24/249 (10%)	5/57 (9%)	1/41 (2%)	6/98 (6%)	4/50 (8.0%)	2/53 (3.8%)	6/103 (5.8%)
Benefit	2/119 (2%)	7/130 (5%)	9/249 (4%)	2/57 (4%)	1/41 (2%)	3/98 (3%)	3/50 (6.0%)	2/53 (3.8%)	5/103 (4.9%)
External evidence	6/119 (5%)	2/130 (2%)	8/249 (3%)	0/57 (0%)	3/41 (7%)	3/98 (3%)	2/50 (4.0%)	0/53 (0.0%)	2/103 (1.9%)
Limited resources	1/119 (1%)	4/130 (3%)	5/249 (2%)	0/57 (0%)	1/41 (2%)	1/98 (1%)	0/50 (0.0%)	0/53 (0.0%)	0/103 (0.0%)
Unclear	6/119 (5%)	18/130 (14%)	24/249 (10%)	13/57 (23%)	14/41 (34%)	27/98 (28%)	5/50 (10.0%)	17/53 (32.1%)	22/103 (21.4%)
Other	2/119 (2%)	4/130 (3%)	6/249 (2%)	0/57 (0%)	0/41 (0%)	0/98 (0%)	2/50 (4.0%)	0/53 (0.0%)	2/103 (1.9%)

[a]Trial registration were not established in 2000-2003; hence registration was not assessed for RCT protocols approved in 2000-20003 and peer reviewed publication was the only source considered for sharing results.

Abbreviations: RCT=randomised clinical trial

Table S5: Association between discontinuation of randomised clinical trials and non-publishing of study results

	Completed RCTs (n=220)[a]	Discontinued RCTs (n=103)[a]	Odds ration (95% Confidence Interval)	*p-value*
Results available at any source (peer-reviewed publication or trial registry)	195 (88.6%)	72 (69.9%)	3.36 (1.78-6.35)	<0.001
Results available as a peer reviewed publication	181 (82.3%)	55 (53.4%)	4.05 (2.33-7.04)	<0.001
Results available in trial register	130 (59.1%)	42 (40.8%)	2.10 (1.27-3.48)	0.021

[a] Randomised clinical trials with unclear discontinuation status were excluded

Abbreviations: RCT=randomised clinical trial

Table S6 Including data from RCTs receiving ethical approval in 2012 to assess factors associated with making trial results available and discontinuation of trial due to poor recruitment

Characteristics	Multivariable		
	OR	95% CI	*P-value*
Non-availability of trial results (considering peer-reviewed publication and trial registries)			
Proportion of adequate SPIRIT reporting, median (IQR)[a]	0.72	0.61-0.85	<0.001
Planned target sample size, median (IQR)[b]	0.99	0.97-1.01	0.585
Placebo controlled (vs not placebo controlled)	1.49	0.92-2.40	0.100
Single-center (vs multicenter)	1.99	1.19-3.31	0.009
Reported recruitment projection	1.03	0.62-1.69	0.923
Industry sponsorship	0.25	0.14-0.53	<0.001
Approval in 2016 (vs 2012)	2.68	1.65-4.36	<0.001
Discontinued due to poor recruitment [c]			
Proportion of adequate SPIRIT reporting, median (IQR)[a]	1.04	0.83-1.30	0.738
Planned target sample size, median (IQR)[b]	0.96	0.91-1.01	0.082
Placebo controlled (vs not placebo controlled)	1.56	0.95-2.65	0.079
Single-center (vs multicenter)	1.11	0.57-2.13	0.752
Reported recruitment projection	0.77	0.43-1.38	0.371
Industry sponsorship	0.45	0.25-0.82	0.009
Approval in 2016 (vs 2012)	0.93	0.56-1.58	0.810

[a] In increments of 10%

[b] In increments of 100

[c] Studies with unclear discontinuation status excluded

Abbreviations: OR=odds ratio; CI= confidence Interval; IQR=interquartile range; RCT=randomised clinical trial

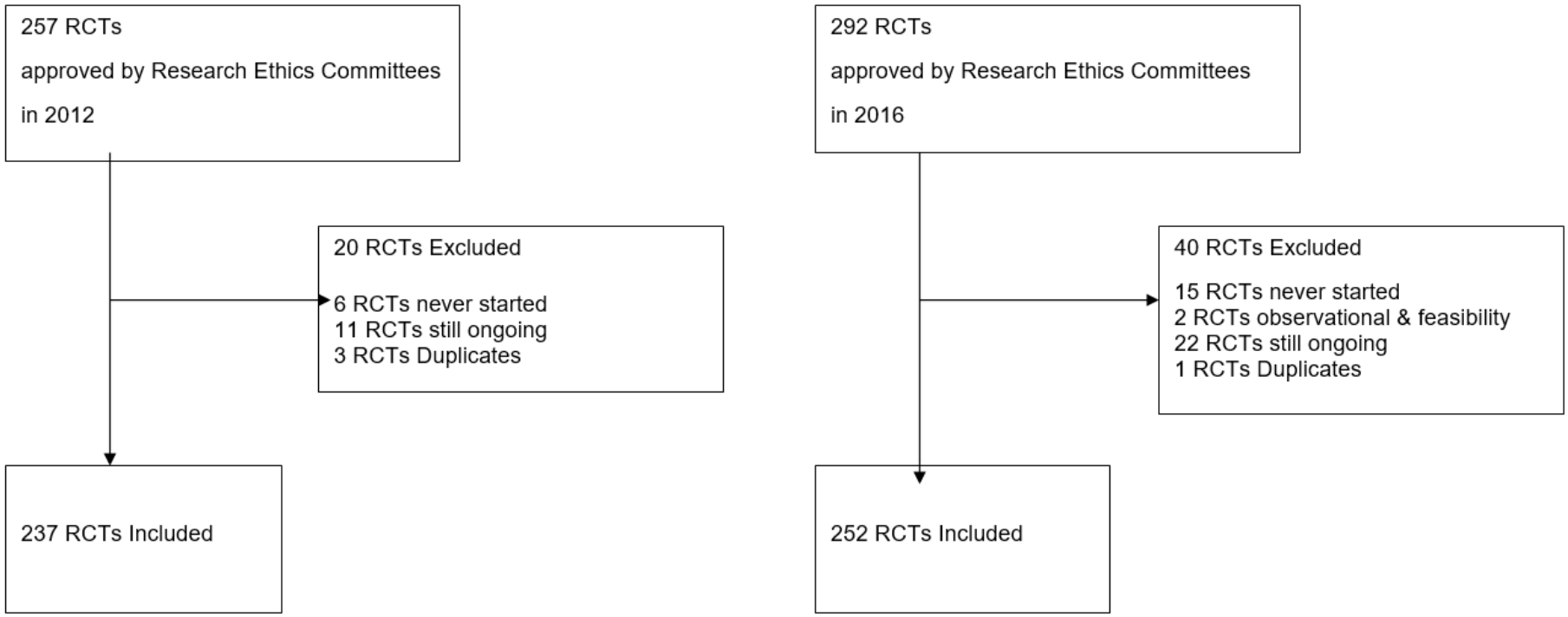
References

1. Kasenda B, von Elm E, You J, Blümle A, Tomonaga Y, Saccilotto R, et al. Prevalence, characteristics, and publication of discontinued randomized trials. JAMA. 2014;311(10):1045-51.
2. Speich B, Gryaznov D, Busse JW, Gloy VL, Lohner S, Klatte K, et al. Nonregistration, discontinuation, and nonpublication of randomized trials: A repeated metaresearch analysis. PLoS Med. 2022;19(4):e1003980.

6.3 Supplementary material manuscript III - planning and reporting of patient-reported outcomes in randomized clinical trials: a repeated cross-sectional study

Ala Taji Heravi, Dmitry Gryaznov, Jason W. Busse, Christof Manuel Schönenberger, Belinda von Niederhäusern, Lena Hausheer, Manuela Covino, Johannes Schwenke, Selina Epp, Alexandra Griessbach, Malena Chiaborelli, Arnav Agarwal, Szimonetta Lohner, Julian Hirt, Stefan Schandelmaier, Simon Egli, Moshao Amos Makhele, Alain Amstutz, Dominik Mertz, Anette Blümle, Erik von Elm, Ramon Saccilotto, Ayodele Odutayo, Sally Hopewell, Benjamin Speich, Matthias Briel, On behalf of the Adherence to SPIRIT Recommendations (ASPIRE) study group

Supplementary Figure: Trial flow diagrams



Abbreviations: RCT, randomised clinical trial

Table S1: Planning and reporting of PROs in RCTs, according to medical field

	PRO pre-specified in Surgical RCTs (n=39)	PRO pre-specified in Psychiatry RCTs (n=21)	PRO pre-specified in Neurology RCTs (n=28)	PRO pre-specified in Oncology RCTs (n=67)	PRO pre-specified in Rheumatology RCTs (n=21)	PRO pre-specified in other RCTs (n=166)
PRO as a primary outcome	**n=13**	**n=13**	**n=10**	**n=2**	**n=13**	**n=47**
No results published, N (%)	8 (61%)	4 (31%)	2 (20%)	1 (50%)	2 (15%)	21 (45%)
Published results available, N (%)	5 (39%)	9 (69%)	8 (80%)	1 (50%)	11 (85%)	26 (55%)
Reported as specified in the protocol	4 (80%)	4 (45%)	6 (75%)	1 (100%)	10 (91%)	22 (85%)
Reported differently than specified in the protocol	1 (20%)	5 (55%)	2 (25%)	0	1 (9%)	4 (15%)
PRO as a secondary outcome	**n=26**	**n=8**	**n=18**	**n=65**	**n=8**	**n=119**
No results published, N (%)	12 (46%)	4 (50%)	7 (38%)	10 (15%)	1 (13%)	26 (22%)
Published results available, N (%)	14 (54%)	4 (50%)	11 (62%)	55 (85%)	7 (87%)	93 (78%)
PROs reported as specified in the protocol	6 (43%)	0	1 (9%)	15 (27%)	1 (16%)	24 (26%)
Specified PROs not reported at all	4 (28%)	1 (25%)	4 (36.5%)	22 (40%)	2 (28%)	30 (32%)
Some PROs specified in the protocol not reported	1 (7%)	2 (50%)	1 (9%)	12 (22%)	2 (28%)	19 (21%)
Unspecified PROs reported	1(7%)	0	1 (9%)	3 (5.5%)	0	5 (5%)
Reported unspecified PROs & some pre-specified PROs unreported	2 (15%)	1 (25%)	4 (36.5%)	3 (5.5%)	2 (28%)	15 (16%)

Abbreviations: PRO=patient reported outcome; RCTs=randomized clinical trials

Table S2: Sensitivity analysis - General characteristics of RCT protocols planning PROs as primary or secondary outcomes

	Protocols approved in 2012 n= 237			Protocols approved in 2016 n= 252		
	PRO as a primary outcome (n= 33)	PRO as a secondary outcome (n=129)	No PRO (n=75)	PRO as a primary outcome (n= 47)	PRO as a secondary outcome (n=132)	No PRO (n=73)
Country of research ethics committee, n (%)						
Switzerland	19 (57.6%)	97 (75.2%)	49 (65.3%)	35 (74.5%)	105 (79.5%)	48 (65.8%)
Germany	8 (24.2%)	18 (14.0%)	11 (14.7%)	7 (14.9%)	18 (13.6%)	9 (12.3%)
Canada	6 (18.2%)	14 (10.9%)	15 (20.0%)	5 (10.6%)	9 (6.8%)	16 (21.9%)
Medical field, n (%)						
Surgical	7 (21.2%)	13 (10.1%)	10 (13.3%)	5 (10.6%)	14 (10.6%)	5 (6.8%)
Psychiatry	2 (6.1%)	2 (1.6%)	0	11 (23.4%)	6 (4.5%)	0
Neurology	6 (18.2%)	8 (6.2%)	5 (6.7%)	4 (8.5%)	10 (7.6%)	6 (8.2%)
Oncology	0	32 (24.8%)	10 (13.3%)	2 (4.3%)	33 (25.0%)	7 (9.6%)
Rheumatology	2 (6.1%)	8 (6.2%)	0	4 (8.5%)	7 (5.3%)	0
Gastro/intestinal	1 (3.0%)	7 (5.4%)	1 (1.3%)	1 (2.1%)	10 (7.6%)	2 (2.7%)
Other *	15 (45.4%)	59 (45.7%)	49 (65.4)	20 (42.6)	52 (39.4%)	53 (72.7%)
Type of intervention, n (%)						
Drug	18 (54.5%)	86 (66.7%)	50 (66.7%)	19 (40.4%)	82 (62.1%)	51 (69.9%)
Behavioral	3 (9.1%)	5 (3.9%)	0	15 (31.9%)	5 (3.8%)	1 (1.4%)
Medical device	9 (27.3%)	22 (17.1%)	14 (18.7%)	4 (8.5%)	19 (14.4%)	13 (17.8%)
Surgical	1 (3.0%)	4 (3.1%)	3 (4.0%)	3 (6.4%)	9 (6.8%)	2 (2.7%)
Other †	2 (6.1%)	12 (9.2%)	8 (10.6%)	6 (12.8%)	17 (12.9%)	6 (8.2%)
Planned sample size						
Median [IQR]	172 [80.0, 400]	315 [110, 756]	300 [118, 600]	180 [80.0, 307]	270 [120, 600]	200 [102, 370]
Sponsorship, n (%)						
Investigator	15 (45.5%)	45 (34.9%)	43 (57.3%)	31 (66.0%)	54 (40.9%)	43 (58.9%)
Industry	18 (54.5%)	84 (65.1%)	32 (42.7%)	16 (34.0%)	78 (59.1%)	30 (41.1%)
Center status, n (%)						
Single center	10 (30.3%)	20 (15.5%)	11 (14.7%)	22 (46.8%)	23 (17.4%)	18 (24.7%)
Multicenter- international	19 (57.6%)	94 (72.9%)	46 (61.3%)	15 (31.9%)	97 (73.5%)	38 (52.1%)
Multicenter- national	4 (12.1%)	15 (11.6%)	18 (24.0%)	10 (21.3%)	12 (9.1%)	17 (23.3%)

Abbreviations: PRO, patient reported outcome; RCT, randomized clinical trial

* Other category (Dermatology, Cardiovascular, Pediatrics, Respiratory, Anesthetics, Endocrinology, etc.)

† Other category (Dietary Supplement, Rehabilitation, etc.)

Abbreviation: PRO=patient reported outcome; RCTs=randomized clinical trials

Table S3: Sensitivity analysis - Planning and reporting of PROs in RCTs

	PRO pre-specified in 2012 (n=162)	PRO pre-specified in 2016 (n=179)	Total (n=341)
PRO as a primary outcome	**n= 33**	**n=47**	**n= 80**
No results published, N (%)	12 (36%)	22 (47%)	34 (43%)
Published results available, N (%)	21 (64%)	25 (53%)	46 (57%)
Reported as specified in the protocol	15 (72%)	20 (80%)	35 (76%)
Reported differently than specified in the protocol	6 (28%)	5 (20%)	11 (24%)
PRO as a secondary outcome	**n= 129**	**n=132**	**n= 261**
No results published, N (%)	26 (20%)	38 (29%)	64 (25%)
Published results available, N (%)	103 (80%)	94 (71%)	197 (75%)
PROs reported as specified in the protocol	22 (21%)	26 (28%)	48 (25%)
Specified PROs not reported at all	37 (36%)	27 (29%)	64 (32%)
Some specified PROs not reported	20 (20%)	23 (25%)	43 (22%)
Unspecified PROs reported	6 (6%)	5 (5%)	11 (6%)
Reported unspecified PROs & some pre-specified PROs unreported	18 (17%)	11 (12%)	29 (15%)

Abbreviation: PRO, patient reported outcome; RCTs, randomized clinical trials

Table S4: Sensitivity analysis - Detailed information captured by the total number of PROs in protocols and publications

	2012				2016			
	RCT-Protocol		RCT-publication		RCT-Protocol		RCT-publication	
	PRO as a primary outcome (n=35)	PRO as a secondary outcome (n=390)	PRO as a primary outcome (n=21)	PRO as a secondary outcome (n=1721)	PRO as a primary outcome (n=51)	PRO as a secondary outcome (n=405)	PRO as a primary outcome (n=26)	PRO as a secondary outcome (n=151)
Domain captured by specified PROs								
Symptoms	15 (43%)	96 (24%)	10 (48%)	37 (21%)	22 (45%)	92 (23%)	11 (42%)	21 (14%)
Physical functioning	3 (8%)	27 (7%)	1 (5%)	15 (9%)	4 (7%)	17 (4%)	3 (12%)	9 (6%)
Mental/emotional functioning	2 (6%)	23 (6%)	0	13 (8%)	5 (9%)	37 (9%)	1 (4%)	13 (8%)
Social functioning	1 (3%)	3 (1%)	0	0	1 (2%)	1 (1%)	0	1 (0.5%)
Disease-specific outcome measure	12 (34%)	93 (24%)	9 (42%)	58 (34%)	9 (17%)	92 (23%)	5 (19%)	39 (25%)
Multidimensional health-related quality of life	1 (3%)	79 (20%)	1 (5%)	29 (17%)	0	73 (19%)	0	47 (31%)
Overall sense of well-being	0	5 (1%)	0	2 (1%)	0	4 (1%)	0	7 (4%)
Satisfaction with treatment	1 (3%)	19 (5%)	0	1 (0.5%)	2 (4%)	29 (7%)	1 (4%)	4 (2%)
Utility	0	6 (2%)	0	1 (0.5%)	0	14 (3%)	0	1 (0.5%)
Other *	0	39 (10%)	0	15 (9%)	8 (16%)	46 (12%)	5 (19%)	9 (6%)
Provided evidence for validation of the instrument used to capture PROs	13 (37%)‡	162 (41%)‡	11 (52%)‡	61 (35%)‡	22 (42%)†,‡	174 (43%)‡	18 (69%)‡	73 (48%)‡
Reported how data was collected for PROs	27 (77%)	264 (67%)	7 (33%)‡	11 (6%)	30 (59%)†	259 (64%)	12 (46%)	24 (16%)

*Other: cannabis use, tolerance of treatment, abstinence, alcohol consumption

†1 RCT and 1 outcome is missing.

‡Outcomes that are use diaries as a tool to capture PRO are excluded:

2012 Protocols: primary 5, secondary 11; 2012 Publications: primary 2, secondary 5

2016 Protocols: primary 4, secondary 10; 2016 Publications: primary 6, secondary 1

Table S5: Sensitivity analysis - Quality of PRO reporting among published trials according to the Consolidated Standards of Reporting Trials (CONSORT) patient reported outcomes (PRO) Extension Checklist

CONSORT-PRO item *	2012 (n=21)	2016 (n=26)
Identifying PRO in abstract	18 (86%)	21 (81%)
Rationale of choosing a PRO	7 (33%)	14 (54%)
PRO hypothesis mentioned	5 (24%)	16 (61%)
Evidence for validation of instrument used to capture PRO *‡	11** (52%)	18 (69%)
Method of PRO collection described ‡	7** (33%)	12 (46%)
Mention of a minimal clinically important difference for the PRO ‡	8 (38%)	9 (35%)
Sample size calculation adequately described (statistical test & alpha value & statistical power)	13 (61%)	22 (85%)
Handling of missing PRO data described	10 (48%)	14 (54%)
Reporting of a participant flow diagram	18 (86%)	24 (92%)
Reporting of baseline data for PROs	16 (76%)	22 (85%)
Results provided for each domain and time point §	3 (42%)	1 (25%)
PRO-specific limitations/implications for generalizability reported	1 (4%)	2 (7%)
Interpretation in relation to clinical outcome provided ¶	1 (6%)	2 (3%)

* We did not consider CONSORT PRO items 4a (participants), 16 (numbers analyzed), 18 (ancillary analyses), because these appeared equally relevant for PROs and non-PROs
† Outcomes that used diaries as a tool to capture PROs were excluded: 2 from 2012 and 6 from 2016
‡ These items are all components of CONSORT PRO item 6a (outcomes) which we assessed separately, because each component appeared specifically relevant for PROs
§ non-multidimensional PROs were excluded: 14 from 2012 and 22 from 2016
¶ Trials only planning surrogate outcomes were excluded: 6 from 2012, 20 from 2016

7 Curriculum vitae

ALA TAJI HERAVI

Combining my statistical background with passion for clinical trials, drives advancements in research methodologies.

PERSONAL INFORMATION

January 18, 1984
Iranian
B work permit

CONTACT

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Beckenweg 11, 4056 Basel
Ala Taji Heravi

SKILL SUMMARY

- Teamwork
- Multitasking
- Project management
- Leadership
- Problem-solving

Gallup strengths

- Communication
- Woo, winning others over
- Includer
- Adaptability
- Activator

LANGUAGES

Persian
English
German

CERTIFICATES

GCP for Investigators and Study Team

CURRENT POSITION

Sep 2020 - Current
CLEAR Methods Center,
The Division of Clinical Epidemiology,
Dept. Clinical Research,
University Hospital & University of Basel,
Switzerland

Ph.D. candidate in clinical research

I am currently conducting meta-research studies primarily focusing on enhancing the planning and reporting of randomized clinical trials (RCTs). My research aims to identify and address key issues related to RCT recruitment and the quality of reporting Patient-Reported Outcomes. I am working extensively with a large dataset comprising 200,000 data points for the first time. Moreover, this research substantially improves my data analysis, project management, and critical thinking skills. In addition to my primary research, I am actively contributing to various other projects, from being involved in innovative design to systematic reviews, meta-analysis, and IPDMA.

EXPERIENCES

Jan 2020-July 2020
Dept. Clinical Research,
University Hospital & University of Basel

Research assistant

create and manage project databases, coding and analysis using R

May 2019 - Dec 2019
School of Social Work,
FHNW, Muttenz, Switzerland

Student assistant

Cleaning Data, Descriptive and multi-variable analysis using R,
Documentation of project, Literature search

May 2014 - May 2018
Dept. Biostatistics & Epidemiology,
Mashhad University of Medical Sciences,
Iran

Research assistant

Statistical consulting, Support and training researchers in the management, collection, and analysis of data

Sep 2016 - May 2018
Amar Negar Shargh Co.
Mashhad, Iran

Statistical analyst

Statistical consulting, Data collecting, cleaning, and statistical analysis

Oct 2011 - Dec 2013
Penny Markt Co.
Hamburg, Germany

Cashier

Proper sorting the sale in the shelves, The regal care, Ensure the smooth and inventory payment process, Cashing-up at the end of the day

Sep 2009 - Feb 2010
Montaserieh Research Center
Mashhad University of Medical Sciences,
Iran

Research assistant

Cleaning data, Translating medical texts from English to Persian and Persian to English

Sep 2008 - Sep 2009
Women's Health Research Center
Mashhad University of Medical Sciences,
Iran

Research assistant

Cleaning data, Translating medical texts from English to Persian and Persian to English

PROGRAMMING SKILLS

Programming

Rstudio
Stata
SPSS
SAS
MATLAB
Python

Operating Systems

Windows
MacOS

Software & Tools

Data handling/analysis
(e.g. dplyr, tidyr, data.table,...)
Visualisation
(e.g. ggplot, gganimate ...)
Office

Type Settings

Microsoft Office
LaTeX
(e.g. Overleaf, ...)

EDUCATION

Sep 2018 - July 2020
University of Basel, Switzerland — M.Sc. Epidemiology
Thesis: Conducted a mixed-methods study to compare planned and actual costs of IMPs in Swiss IITs

Sep 2011 - Incomplete
University of Hamburg, Germany — Left incomplete, Technomathematics

Sep 2003 - Sep 2007
Azad University, Mashhad, Iran — B.Sc. Statistics
Thesis: Focused on diverse clustering techniques and their practical implementation in R

EXTRACURRICULAR

- Attending the mentoring program "Zoom@Novartis", a collaboration between the University of Basel and Novartis to get insight into the industry for young researchers
- Responsible for social media at The Division of Clinical Epidemiology
- Setting up "Meet to Read" sessions at PPHS (PhD Program of Health Sciences)
- Student representative for setting up the GRACE-PhD survey at Dept. clinical research
- A voluntary member of the Red Cross