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

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ABSTRACT

Objectives

Comprehensive protocols are key for the planning and conduct of randomized 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.

Participants

RCT protocols approved by research ethics committees 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% (interquartile range [IQR], 63%-79%) in 2012 to 77% (IQR, 68%-82%) in 2016. However, in a pre-planned 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 organization, and investigator-sponsorship.

Conclusions

In 2012, 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.

Strengths and limitations of the study:

- We had full access to randomised clinical trials protocols and associated documents from research ethics committees in three countries approved in 2012 and 2016
- All Swiss research ethics committees participated in this study, we used a convenience sample of the studies approved at the German and Canadian research ethics committees
- We compared the proportion of reported SPIRIT items per protocol and the proportion of trial protocols reporting individual SPIRIT items between the years 2012 and 2016
- We built regression models to explore factors associated with adherence to SPIRIT

Key words: Randomised clinical trials, trial protocol, reporting quality, reporting guideline adherence, meta-research

INTRODUCTION

Randomised clinical trials (RCTs) are directed by their protocol, which documents the rationale, design, and planned reporting of a trial.[1] Funding agencies, research ethics committees (RECs), regulatory agencies, medical journals, systematic reviewers and other groups rely on protocols to appraise the quality of a proposed trial.[2] Incomplete protocols may compromise the safety of study participants, as well as the credibility of trial results. Empirical evidence from meta-research suggested numerous limitations in the reporting of RCT protocols including insufficient descriptions of treatment allocation methods, primary outcomes, sample size calculations, data analysis, and the roles of sponsors in trial design or access to data.[3-9] About half of protocols approved by French RECs, for instance, were estimated to have subsequent amendments to address deficiencies,[10] and a third of amendments submitted to RECs for industry-sponsored trial protocols could have been avoided by preparing more comprehensive protocols.[11 12]

In response, a minimum set of items to be addressed in trial protocols was developed by the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) Initiative, and published in January 2013.[13 14] Subsequently, a number of journals publishing trial protocols, funding agencies, and RECs endorsed the use of SPIRIT or related recommendations (e.g., www.swissethics.ch).[15] Researchers have applied the SPIRIT checklist to assess the quality of trial protocols with respect to patient reported outcomes,[16] statistical analyses,[17] and cluster-randomised trials with stepped wedge design.[18] However, there is no large-scale empirical study that has longitudinally evaluated the impact of the SPIRIT recommendations on the quality of reporting among RCT protocols.

The Adherence to SPIrit REcommendations (ASPIRE) study group is an international collaboration of researchers with a mandate to (i) evaluate the completeness of RCT protocols before and after publication of the SPIRIT statement, (ii) determine trial characteristics associated with non-adherence to SPIRIT checklist items, and (iii) investigate whether the comprehensiveness of RCT protocols varies across countries.[19] In the present

paper we report the results from our investigation of RCT protocols from Switzerland, CAnada, and GErmany (ASPIRE-SCAGE).

METHODS

The methods used to conduct the present study have previously been published.[19]

Identification of included trial protocols

We included trial protocols approved by RECs in 2012 or 2016 that assigned patients or groups of patients at random to one or more interventions to evaluate their effect on health outcomes. We excluded RCTs enrolling healthy volunteers, economic evaluations, animal studies, studies based on tissue samples, observational studies, studies involving only qualitative methods, and studies with a quasi-random method of allocation. The participating RECs in Switzerland (Basel, Bern, Geneva, Lausanne, St. Gallen, Thurgau, Ticino, Zurich), Germany (Freiburg) and Canada (Hamilton) approved this study or explicitly stated that no ethical approval was required. Details of the identification of included RCT protocols are presented in **Supplementary Figure 1**.

Data extraction

We used a web-based, password protected data extraction tool (http://squiekero.ch) for data collection and storage.[19 20] Researchers trained in trial methodology completed a calibration process to improve reliability, and then extracted relevant data from RCT protocols independently and in duplicate, including whether individual SPIRIT items were reported.[19] Disagreements were resolved by discussion. Due to limited resources 15% of included protocols were extracted by a single researcher (having extracted at least 100 RCT protocols in duplicate). All researchers extracting data from RCT protocols signed confidentiality agreements and the final database contained only coded data. Our data extraction forms are provided as **Supplementary Table 1**.

Data Analysis

The outcomes of interest were the proportion of SPIRIT checklist items that were reported among our cohorts of study protocols, and the proportion of RCT protocols addressing each SPIRIT checklist item. Our primary analysis was based on a rating approach that allowed for partial credit of individually met sub-items or components of major SPIRIT items, because it keeps the hierarchical structure of the SPIRIT checklist and it independently considers all components and sub-items of all individual SPIRIT items.[19] Other rating approaches that consider major SPIRIT items only or equally consider items and sub-items, were used in sensitivity analyses.

To investigate whether the reporting quality of RCT protocols (as defined by the proportion of reported SPIRIT checklist items) has increased from 2012 to 2016, we conducted multivariable beta regression analysis[21] with the proportion of SPIRIT items adhered to per protocol as dependent variable and the following predefined independent variables: (i) approval year (2012 *versus* 2016), (ii) investigator sponsorship *versus* industry sponsorship, (iii) planned sample size (in increments of 1000), (iv) single centre *versus* multicentre RCTs, and (v) reported methodological support from a CRO or CTU *versus* no reported support. We included interaction terms in our model to investigate potential interactions of year of approval (2012 or 2016) with either sponsorship of protocols or reported methodological support. We performed a likelihood ratio test to check if the interaction terms improved the goodness of fit of the models. To examine in a sensitivity analysis whether the comprehensiveness of RCT protocols varied across countries we stratified the median proportion of addressed SPIRIT items per protocol by country (Switzerland, Canada, Germany), by year of approval (2012 versus 2016), and by sponsorship (investigator versus industry), and added a country variable to the regression model. In further sensitivity analyses, we used hierarchical logistic regression (response is a binary variable indicating adherence to each SPIRIT item with clustering by protocol; i.e. independent variables were included in the model as fixed effects and the protocol as a random effect) instead of beta regression.[19]

For all types of regression analyses we reported coefficients or odds ratios (ORs) accompanied by 95% confidence intervals (CIs). We provided descriptive statistics as frequencies and proportions for binary data and median (interquartile range, IQR) for continuous data. We used the statistical software R version 3.6.1 for all data analysis. All statistical tests were performed using a significance level of p=0.05.

Patient and public Involvement

No patients were involved in the study.

RESULTS

Characteristics of included trial protocols

We included 549 RCT protocols in our study; 257 from 2012 and 292 from 2016 (**Table 1**). The majority of which were individually randomised, multicentre, parallel-group, superiority trials in oncology or cardiovascular medicine, and approved by a Swiss REC. About half of the protocols were investigator-sponsored and half were industry-sponsored. In 2016 there were more investigator-sponsored protocols (162/292, 55.5%) included than in 2012 (119/257, 46.3%). In 2016 the median planned sample size was lower (199; IQR, 100-490) than in 2012 (300; IQR, 100-720). Otherwise, trial characteristics were similar between cohorts. Protocols of industry-sponsored RCTs had, on average, a larger sample size, were predominantly multinational, and more frequently placebo-controlled than those of investigator-sponsored RCTs (**Table 1**).

Table 1: Characteristics of included randomised trial protocols

Characteristics	2012			2016			Overall
	Sponsorship		Total (n=257)	Sponsorship		Total (N=292)	Total (N=549)
	Industry (N=138)	Investigator (N=119)		Industry (N=130)	Investigator (N=162)		
Planned target sample size, median (IQR)	450 (184.5, 800)	150 (63, 516)	300 (100, 720)	306.5 (150,621)	141 (70, 300)	199 (100, 490)	220 (100, 597)
Planned centres							
Single centre, No. (%)	2 (1.4%)	45 (37.8%)	47 (18.3%)	4 (3.1%)	73 (45.1%)	77 (26.4%)	124 (22.6%)
Multicentre, national, No. (%)	10 (7.2%)	30 (25.2%)	40 (15.6%)	6 (4.6%)	41 (25.3%)	47 (16.1%)	87 (15.8%)
Multicentre, multinational, No. (%)	126 (91.3%)	44 (37.0%)	170 (66.1%)	120 (92.3%)	48 (29.6%)	168 (57.5%)	338 (61.6%)
Unit of randomisation							
Individuals	137 (99.3%)	113 (95.0%)	250 (97.3%)	127 (97.7%)	158 (97.5%)	285 (97.6%)	535 (97.4%)
Clusters	0 (0.0%)	4 (3.4%)	4 (1.6%)	1 (0.8%)	3 (1.9%)	4 (1.4%)	8 (1.5%)
Body parts	1 (0.7%)	2 (1.7%)	3 (1.2%)	2 (1.5%)	1 (0.6%)	3 (1.0%)	6 (1.1%)
Study design							
Parallel	135 (97.8%)	104 (87.4%)	239 (93.0%)	127 (97.7%)	147 (90.7%)	274 (93.8%)	513 (93.4%)
Crossover	2 (1.4%)	9 (7.6%)	11 (4.3%)	2 (1.5%)	10 (6.2%)	12 (4.1%)	23 (4.2%)
Factorial	1 (0.7%)	6 (5.0%)	7 (2.7%)	1 (0.8%)	5 (3.1%)	6 (2.1%)	13 (2.4%)
Study purpose							
Superiority	110 (79.7%)	93 (78.2%)	203 (79.0%)	107 (82.3%)	132 (81.5%)	239 (81.8%)	442 (80.5%)
Non-inferiority	23 (16.7%)	19 (16.0%)	42 (16.3%)	20 (15.4%)	24 (14.8%)	44 (15.1%)	86 (15.7%)
Unclear	5 (3.6%)	7 (5.9%)	12 (4.7%)	3 (2.3%)	6 (3.7%)	9 (3.1%)	21 (3.8%)
Placebo used	77 (55.8%)	30 (25.2%)	107 (41.6%)	78 (60.0%)	41 (25.3%)	119 (40.8%)	226 (41.2%)
CTU or CRO support	93 (67.4%)	56 (47.1%)	149 (58.0%)	79 (60.8%)	83 (51.2%)	162 (55.5%)	311 (56.6%)
Country							
Switzerland	91 (66.0%)	89 (74.8%)	180 (70.0%)	86 (66.2%)	131 (80.9%)	217 (74.3%)	397 (72.3%)
Canada	21 (15.2%)	19 (16.0%)	40 (15.6%)	17 (13.1%)	20 (12.3%)	37 (12.7%)	77 (14.0%)

Germany	26 (18.8%)	11 (9.2%)	37 (14.4%)	27 (20.8%)	11 (6.8%)	38 (13.0%)	75 (13.7%)

Abbreviations: CRO, contract research organization; CTU, clinical trials unit; IQR, interquartile range.

Adherence to SPIRIT in protocols from 2012 and 2016

Overall, the median proportion of reported SPIRIT items increased from 72% (IQR, 63%-79%) in 2012 to 77% (IQR, 68%-82%) in 2016 (**Table 2, Figure 1**).

Table 2: Adherence to SPIRIT items in RCT protocols

Characteristic	2012			2016		
	Sponsorship		Total 2012 (n=257)	Sponsorship		Total 2016 (n=292)
	Industry (n=138)	Investigator (n=119)		Industry (n=130)	Investigator (n=162)	
	median (IQR)	median (IQR)	median (IQR)	median (IQR)	median (IQR)	median (IQR)
Absolute number of SPIRIT items reported per protocol (out of 33)	25.5 (23.6-26.5)	21.3 (18.3, 23.7)	23.7 (20.7, 26.2)	25.3 (23.7%-26.9)	25.0 (21.3-27.3)	25.3 (22.5-27.1)
Proportion of SPIRIT items reported per protocol	77% (72%-80%)	64% (55%-72%)	72% (63%-79%)	77% (72%-82%)	76% (64%-83%)	77% (68%-82%)

Abbreviations: IQR, interquartile range

Stratifying by sponsorship, we found that the comprehensiveness increased only in investigator-sponsored RCT protocols (adherence stratified by other study characteristics can be found in **Supplementary Table 2**). The median proportion of reported SPIRIT items in investigator-sponsored protocols increased from 64% (IQR, 55%-72%) in 2012 to 76% (IQR, 64%-83%) in 2016, while it remained unchanged at 77% for both years among industry-sponsored protocols (77%, IQR 72%-80% in 2012, and 77%, IQR 72%-82% in 2016). This pattern was consistent across countries (**Supplementary Table 3**). Sensitivity analyses using different approaches to calculate the proportion of reported SPIRIT items provided similar results (**Supplementary Table 4**).

Regarding individual SPIRIT items, we found that the improvement in investigator-sponsored RCT protocols was due to an improvement in a broad range of SPIRIT items (**Supplementary Table 5**); for 25 individual items the proportion of adherent protocols improved in investigator-sponsored RCTs by 10% or more (**Supplementary Table 6**). These 25 items included descriptive (e.g. information on study registration, protocol version & date, name & contact details of sponsor) as well as methodological aspects (e.g. comparator choice explained, or allocation concealment mechanism). The largest improvements occurred with “trial registration” (SPIRIT item 2, +41.1%), “plans to disseminate trial results to key stakeholders/publication provided” (SPIRIT item 31a, +36.7%), “description of process for making amendments” (SPIRIT item 25, +34.4%), and “declaration of interests” (SPIRIT item 28, +31.6%). In industry-sponsored protocols, adherence to individual SPIRIT items remained practically stable from 2012 to 2016, i.e. items with low adherence in 2012 remained low in 2016. SPIRIT items with particularly low adherence (< 30%) in both industry- and investigator-sponsored protocols were “names of protocol contributors/authors” (SPIRT item 5a), “research question described and justified” (SPIRIT item 6a), “eligibility criteria for study centres” (SPIRIT item 10) in applicable RCTs, “location of participant recruitment” and “estimated recruitment rate” (SPIRIT item 15), “information about who will have access to the full dataset” (SPIRIT item 29), and “description of plans for granting access to full trial protocol” (SPIRIT item 31c), (**Supplementary Table 5**).

Multivariable regression analysis

Using multivariable beta or logistic regression, we found that four characteristics were independently associated with greater reporting of SPIRIT items: multicentre RCTs, RCTs with reported methodological support from CTUs or CROs, industry-sponsored RCTs, and RCTs approved in 2016 (**Supplementary Table 7, Figure 2**).

Adding the interaction term of year of approval and sponsorship to the model, improved the model fit (likelihood ratio test, Chisq =30.01, p <0.01) and provided evidence for a differential improvement in the adherence to SPIRIT over time (2012 vs 2016) for industry-sponsored and investigator-sponsored protocols suggesting that there was an improvement in investigator-sponsored protocols but not in industry-sponsored protocols. We did not find evidence for an interaction between year of approval and CTU/CRO support, i.e. protocols with or without reported support from CTUs or CROs improved to a similar extent from 2012 to 2016. Limiting our multivariable regression to investigator-sponsored protocols in an exploratory analysis, we found a notable interaction suggesting a more pronounced improvement in Swiss protocols compared with protocols from Canada or Germany (**Supplementary Table 8**).

DISCUSSION

Main findings and interpretation

This study of 549 RCT protocols approved by RECs in Switzerland, Canada, and Germany before (2012) and after (2016) the publication of the SPIRIT recommendations suggested a small overall improvement in reporting comprehensiveness. This change was driven by an increase in the median proportion of reported SPIRIT items in investigator-sponsored RCTs from 64% in 2012 to 76% in 2016. Protocols of industry-sponsored RCTs remained, on average, unchanged (median of 77% SPIRIT items reported in both years). The reporting of investigator-sponsored protocols improved for the majority of individual SPIRIT items, and was independent of the planned sample size, reported support from a CTU or CRO, and

centre status (single- vs multicentre) of RCTs. Single centre status, no reported support from a CTU or CRO, investigator sponsorship, and approval in 2012 were independently associated with lower adherence to the SPIRIT checklist. These results were similar across countries, but the improvement in investigator-sponsored RCT protocols appeared more pronounced among Swiss protocols compared with protocols approved in Canada or Germany. SPIRIT items with particularly low adherence in investigator- and industry sponsored protocols concerned the names of protocol contributors/authors, the justification of the research question, details about the planned participant recruitment, information about who will have access to the full dataset, and plans for granting access to the full trial protocol.

Our findings suggest an international improvement in the comprehensiveness of investigator-sponsored RCT protocols probably due to a combination of reasons including the publication of the SPIRIT checklist and its implementation by research institutions, funding agencies, and medical journals; the ongoing discussion about the importance of protocol publication, thoughtful planning of RCTs, and minimising reporting biases in the scientific community; and efforts to teach RCT methodology to clinician scientists in under- and postgraduate courses. The more pronounced improvement of Swiss investigator-sponsored protocols could be related to a SPIRIT-based protocol template and guidance provided by swissethics that were particularly welcomed by academic researchers or other changes in the context of the new Swiss legislation on human research from 2014.

Strengths and limitations

Strengths of our study include full access to RCT protocols and associated documents from RECs in three countries. We used standardized methods and procedures for data extraction and protocol assessment at all RECs and involved only trained methodologists in this process. This included use of piloted extraction forms with detailed written instructions as well as calibration exercises with all data extractors. More than 95% of included protocols approved in 2012 and over 80% of protocols approved in 2016 were extracted independently and in duplicate. To minimise chance associations, we considered only a limited number of

variables in our statistical models.[22] Our results proved robust in sensitivity analyses applying alternative assumptions and statistical approaches. The fact that practically all Swiss RECs participated in this study strengthens the representativeness of our data for Switzerland and the additional inclusion of a German and a Canadian REC allowed for international generalizability.

Our study has several limitations. First, we used a convenience sample of two RECs outside of Switzerland (Freiburg in Germany, Hamilton in Canada) but we cannot be certain if they are representative of other RECs in these or other countries. Second, we used RCT protocols that had already been approved by RECs, therefore SPIRIT items such as "research ethics approval" and "consent forms provided" were always fulfilled and could not discriminate more comprehensive from less comprehensive protocols. Third, although we had adequate statistical power to detect even interactions within the subgroup of investigator-sponsored protocols, the number of included protocols approved outside of Switzerland was relatively small (28%; 152/549), limiting the precision of estimates for German and Canadian protocols. Finally, our findings are not proof of causality, however, it is plausible that the publication of the SPIRIT statement at least contributed to an increase in the comprehensiveness of investigator-sponsored protocols. Investigations of a potential time trend with gradually increasing comprehensiveness of investigator-sponsored protocols by year tertiles did not suggest a continuous development, but rather a one-step-effect (**Supplementary Figure 2**).

Comparison with other studies

Few studies in the literature have used[16] or planned to use[17 18 23] the SPIRIT checklist as a tool to assess the comprehensiveness of trial protocols. One study investigated 75 RCT protocols from the UK National Institute for Health Research (NIHR) Health Technology Assessment (HTA) programme on the reporting of patient-reported outcomes and the association with general protocol completeness according to SPIRIT.[16] They found that these investigator-sponsored UK RCT protocols from 2012 and 2013 reported, on average, 63% of

SPIRIT checklist items, which is very similar to our findings for investigator-sponsored RCT protocols from 2012. Apart from the ongoing study using protocols from UK RECs (ASPIRE-UK[19]), we are not aware of any other study evaluating the comprehensiveness of RCT protocols before and after the publication of the SPIRIT statement in industry- and investigator-sponsored protocols.

There are studies assessing the quality of RCT protocols using measures other than the SPIRIT checklist. An analysis of drug trial protocols submitted to three Dutch RECs in 2010/11 focused on critical comments by RECs.[24] They found that applicants of investigator-sponsored trials received more critical comments on participant selection, methodology, and statistical analysis than applicants of industry-sponsored trials, resonating with our findings of less comprehensive investigator-sponsored protocols compared with industry protocols in 2012. Similarly, studies by Getz et al. used the proportion of protocols with substantial amendments as a measure of RCT protocol quality in the industry setting showing that more comprehensive protocols could have prevented amendments.[11 12] Finally, a study of 596 published RCT protocols from 2001 to 2011 assessed protocol quality (high versus low) based on reporting of the allocation method, allocation concealment, and intention-to-treat analysis.[25] This study found a substantial improvement in some methodological aspects of protocols (e.g. allocation concealment), but acknowledged the overall low proportion of high quality protocols with 24% in 2001-2004, 31% in 2005-2008, and 37% in 2008-2011.

Implications

Incomplete protocols may jeopardize the clinical research process at all stages with potentially harmful consequences for patients, decision-makers in health care, the scientific community, and society as a whole. Whether there is indeed an association between better reported or more comprehensive RCT protocols and better methodology, successful trial conduct, and/or publication of RCTs remains to be established. Based on the RCT sample of this study, we will examine the relationship between completeness of RCT protocols and

risks for premature discontinuation or non-publication of RCTs in a subsequent investigation [19].

Our results show improvement in the reporting quality of investigator-sponsored trial protocols such that they became consistent with industry protocols. About why industry protocols have not improved according to SPIRIT between 2012 and 2016, we can only speculate. It might be that routines and processes for writing trial protocols have been well established at companies earlier explaining our finding of consistently low adherence to specific SPIRIT items in 2012 and 2016 in industry-sponsored protocols. So, as long as regulators do not make specific protocol templates mandatory for all applicants, industry may not adapt routines and templates according to SPIRIT.

Our finding of insufficient reporting of names of protocol contributors/authors, the justification of the research question, details about the planned participant recruitment, information about who will have access to the full dataset, and plans for granting access to the full trial protocol guides involved stakeholders with respect to further needs for protocol improvement. The identified items constitute important pieces of information to enable a valid assessment of the relevance, feasibility, and transparency of planned clinical trials.

Conclusions

This before-and-after study suggests that the comprehensiveness of investigator-sponsored RCT protocols from Switzerland, Canada, and Germany improved after publication of the SPIRIT checklist, achieving a similar reporting quality as industry-sponsored protocols. Single centre status, no reported support from a CTU or CRO, investigator sponsorship, and approval in 2012 were independently associated with lower adherence to SPIRIT. Further means are needed to improve the reporting of RCT protocols particularly with respect to protocol authorship, justification of the research question, participant recruitment, access to the full dataset, and plans for granting access to the full trial protocol. Future research should clarify the relationship between protocol quality and success of subsequent trial conduct and publication.

DECLARATIONS

Ethics approval and consent to participate: All participating ethics committees are project partners.

Consent for publication: Not applicable.

Availability of data and material: Data underlying this article will be shared on reasonable request to the corresponding author

Data access, responsibility, and analysis: DG had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Competing interests: BvN is currently employed by Roche Pharma AG, Grenzach-Wyhlen, Germany. BK is currently employed by iOMEDICO AG, Freiburg, Germany. All other authors declare no financial relationships with any organization that might have an interest in the submitted work and no other relationships or activities that could appear to have influenced the submitted work.

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Authors' contributions: AO, SH, EvE, BK, and MB conceived of the study. EvE and MB acquired funding. RS developed the web-tool for data extractions. DG, BvN, BS, and MB coordinated data extraction from protocols. MB and DG wrote the first draft of the manuscript. DG, BvN, BS, BK, EOR, AB, StS, DM, YT, AA, CPM, VG, KB, KKu, LR, SIL, JM, AN, KKl, NG, ATH, JW, NC, PJHH, KMC, SiS, JWB, ArA, MS, LH, SH, EvE and MB were involved in data collection and critically revised the manuscript. All authors approved the final version before submission.

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Authors' information (optional): Not applicable

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Figure Legends

Figure 1: Proportion of reported SPIRIT items by year and study sponsorship

Figure 2: Results from a Beta regression major item approach, allowing for partial credit

Abbreviations: CTU, Clinical Trials Unit; CRO, Contract Research Organization; CI, confidence interval. *In 1000 increments. Results from two models with interaction terms are reported separately.

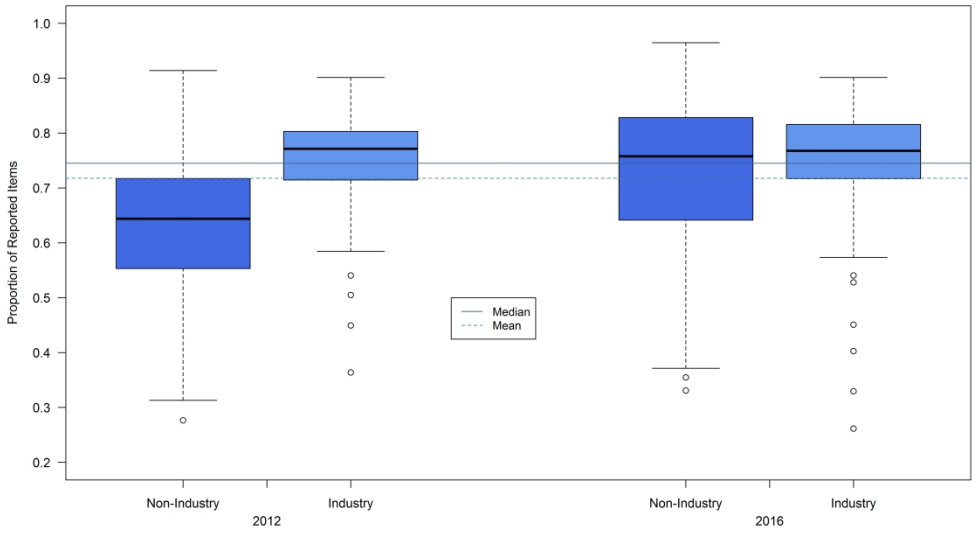


Figure 1: Proportion of reported SPIRIT items by year and study sponsorship

330x203mm (300 x 300 DPI)

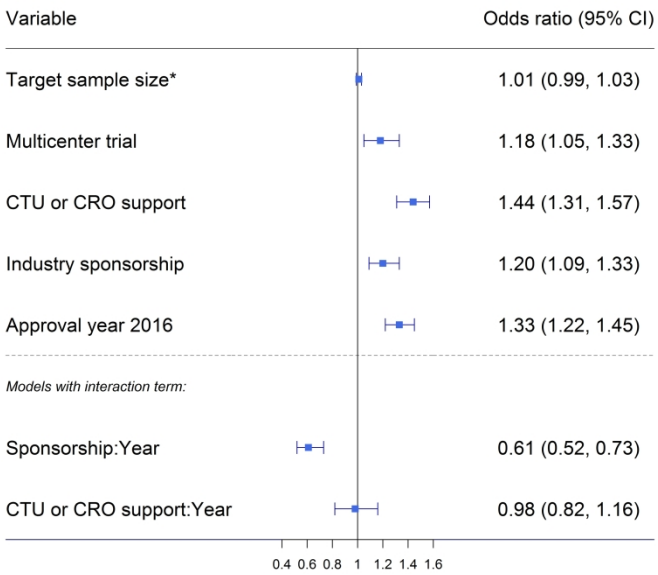


Figure 2: Results from a Beta regression major item approach, allowing for partial credit

330x203mm (300 x 300 DPI)

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

Supplementary material

1. **Supplementary Figure 1: "**Flow diagram for included randomised clinical trial protocols in ASPIRE with ethics approval in 2012 and 2016 from Switzerland, Germany, and Canada**"**
2. **Supplementary Figure 2:** Box-plots of proportions of reported SPIRIT items by year and tertile in investigator-sponsored protocols
3. **Supplementary Table 1:** Data Extraction Form
4. **Supplementary Table 2:** Adherence to SPIRIT items in RCT protocols by approval year and median target sample size, multicentre vs single centre trials, and with vs without CTU or CRO support
5. **Supplementary Table 3:** Adherence to SPIRIT items in RCT protocols by country and sponsorship
6. **Supplementary Table 4:** Sensitivity analyses of calculating the adherence to SPIRIT items for RCT protocols by sponsorship
7. **Supplementary Table 5:** Adherence to individual SPIRIT items by year and sponsorship
8. **Supplementary Table 6:** Adherence to SPIRIT items in Investigator-sponsored protocols that improved by 10% or more
9. **Supplementary Table 7:** Results from multivariable Beta and Logistic regressions for all approaches
10. **Supplementary Table 8:** Results from multivariable Beta regression, subset of Investigator-sponsored protocols

Supplementary Figure 1

Figure 1A: Flow diagram for included randomized clinical trial protocols in ASPIRE with ethics approval in 2012

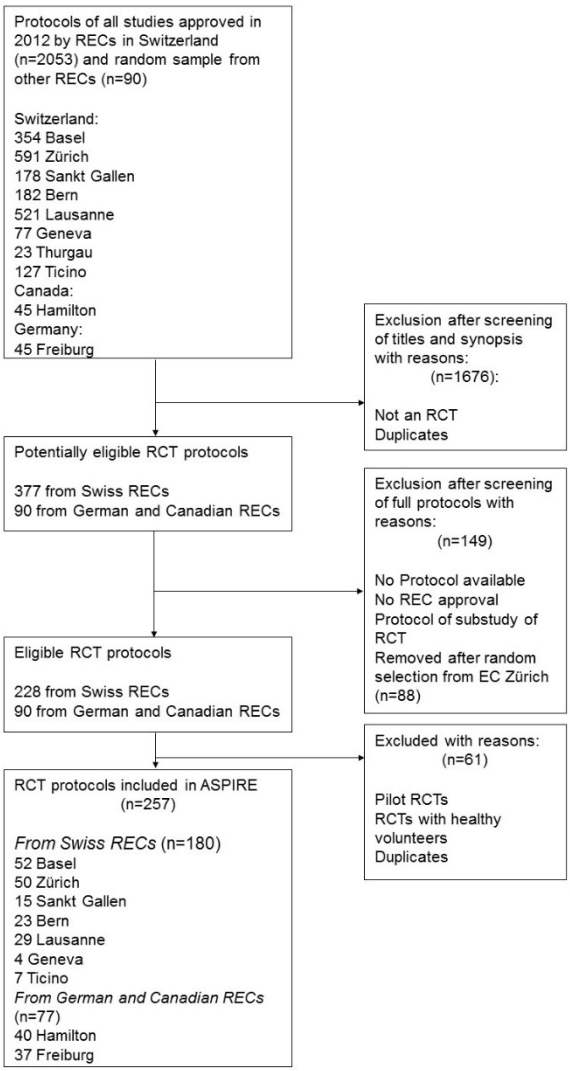
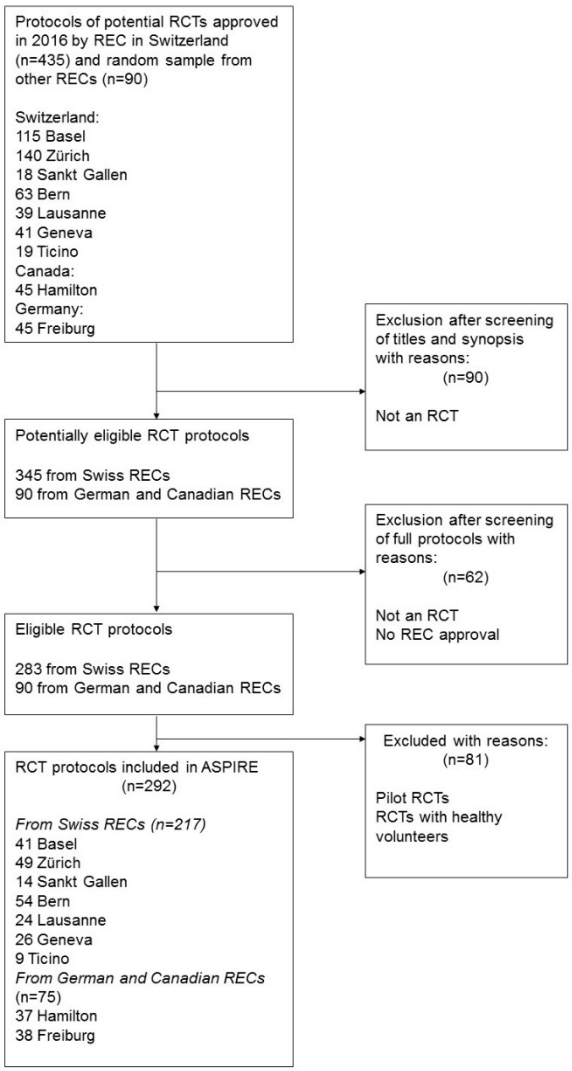


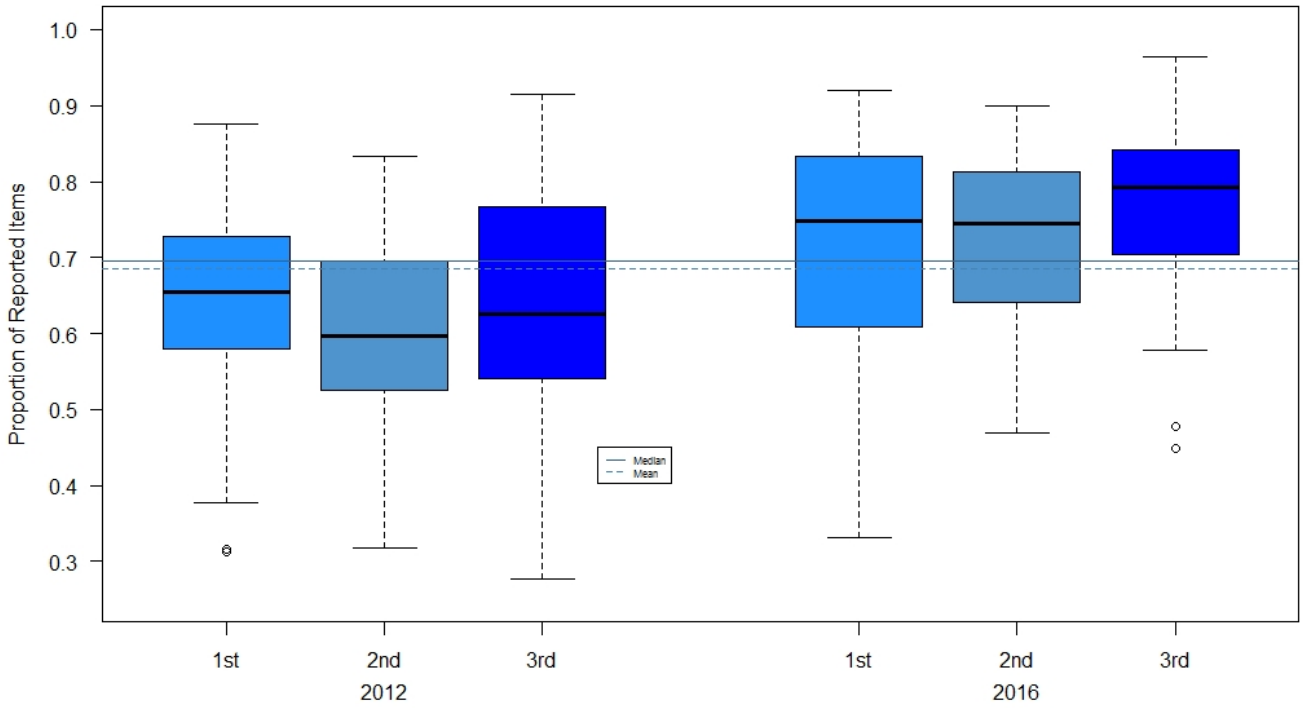
Figure 1B: Flow diagram for included randomized clinical trial protocols in ASPIRE with ethics approval in 2016



Abbreviations: REC: Research Ethic Committee; RCT: Randomised clinical trial

Legend Supplementary eFigure 1: Flow diagram for included randomised clinical trial protocols in ASPIRE with ethics approval in 2012 and 2016 from Switzerland, Germany, and Canada

Supplementary Figure 2



Legend Supplementary eFigure 2: Box-plots of proportions of reported SPIRIT items by year and tertile in investigator-sponsored protocols

Supplementary Table 1

Data Extraction Form

Label	Options
1. Country of Ethics Committee	
2. Name of Ethics Centre	
3. Local Ethics Identification Number	
4. Sponsor name (title, first name, surname, company if applicable)	
5. Sponsor email address	
6. Site/Location of overall study initiation (PI affiliation)	Switzerland
	Other
	Not reported
If site initiation in Switzerland, please provide name and location of institution:	
7. Study Acronym	
8. Study Title (Exact Quote)	
9. Date of Ethics Application	
9a. Date of first RESPONSE by Ethics Committee (does not need to be the same as approval date)	
9b. Response category (Switzerland specific, others select "not applicable")	A positiv
	B positiv mit Bemerkung
	C mit Auflage, Nachbegutachtung notwendig
	C mit Auflage, schriftliche Mitteilung ausreichend
	D negativ
	E Nicht-Eintreten
	Not applicable as Ethics Committee not in Switzerland
10. Date of first APPROVAL by Ethics Committee	
11. Clinical Area	Medical
	Surgical
	Paediatrics
	Other
If medical area, choose from list	Neurology
	Cardiovascular
	Respiratory
	Gastro/intestinal
	Nephrology
	Rheumatology
	Infectious Disease
	Oncology
	Intensive Care
	Hematology

	Endocrinology
	Dermatology
	Anaesthetics
	Psychiatry
	Other
If surgical area, choose from list	General Surgery
	Obstetrics/Gynecology
	Neurosurgery
	Ophthalmology
	Ear-nose-throat (ENT)
	Cardiothoracic
	Urology
	Orthopedics
	Plastic Surgery
	Other
If pediatrics area, choose from list	Neurology
	Cardiovascular
	Respiratory
	Gastro/intestinal
	Nephrology
	Rheumatology
	Infectious diseases
	Oncology
	Intensive care
	Hematology
	Endocrinology
	Dermatology
	Anaesthetics
	General surgery
	Neurosurgery
	Ophthalmology
	Ear-nose-throat (ENT)
	Cardiothoracic
	Urology
	Orthopedics
	Plastic Surgery
	Other
12. Trial Registration Number	
13. Trial Registry Name	Clinicaltrials.gov
	ISRCTN
	EudraCT
	ANZCTR
	Not reported
	Other (please specify)
14. Swiss Human Research Act Risk Category	A

	B
	C
	Not applicable
	Not reported
15. Is trial labelled as pilot or feasibility trial?	Yes
	No
16. Is it a dose finding trial?	Yes
	No
17. Hypothesis (check all that apply)	Superiority
	Non-inferiority / Equivalence
	Not labelled in this regard / unclear
18. Please copy the primary outcome(s) from the protocol	
19. Are any outcomes specifically labelled as “adverse events”, “adverse effects”, “side effects”, or "tolerability"?	Yes
	No
If yes, adverse events (or synonyms thereof) are...	not further specified (e.g. the term adverse events is just mentioned under outcome section)
	specifically defined (e.g. specific types of adverse events such as rash, itching, nausea etc. are mentioned)
20. Is a patient-reported outcome specified (an outcome that comprises information reported by a patient or a caregiver (parent or guardian))?	Yes
	No
If yes: the specified patient-reported outcome captures the following information (check all that apply):	Symptoms (pain, headaches, sleeplessness, etc.)
	Physical functioning
	Mental/emotional functioning
	Social functioning
	Disease-specific outcome measure (eg. Asthma QoL questionnaire, Beck Depression Inventory)
	Multidimensional health-related quality of life (HRQL; eg. SF-36)
	Overall sense of well-being in one question (holistic HRQL; eg. captured with a VAS)
	Satisfaction with treatment

	Utility (an individual's preferences/values for certain health states/outcomes)
	Other (please specify)
If yes: patient-reported outcome + measurement instrument	
If yes, patient-reported outcome used for sample size calculation?	Yes
	No
If yes, minimal important difference (MID) mentioned?	Yes
	No
If yes, reference for MID? (please enter full citation or if not reported, enter "NR")	
20a. Is routinely collected data used in the study?	Yes
	No
20b. If yes, routinely collected data is used:	For patient identification and/or recruitment?
	As part of the randomized intervention?
	For any of the planned outcomes?
	Other
21. Any planned collection of costs or cost-effectiveness analysis mentioned?	Yes
	No
22. The setting for the majority of recruited patients is (check all that apply)	Community
	Outpatient clinic
	Emergency department
	In-patients hospital care
	Intensive care unit
	Unclear
23. The age-group of patient population is (check all that apply)	Adults (>=16 years)
	Only elderly (>=60)
	Pediatric (<18)
24. Please specify the study population	
25. Estimated sample size/number of participants	
26. Number of overall study centres	
27. If multicentre, national or multinational	National
	International
	Not applicable
28. Number of study centres recruiting in Switzerland (or Canada/Germany if applicable)	
29. Trial Design (check all that apply)	Parallel
	Crossover
	Cluster
	Factorial
	Split Body
	Other

	Not applicable
30. Number of trial arms	
31. Presence of logistic/ methodological support/experience? (check all that apply)	Clinical trial unit (CTU)
	Contract Research Organization (CRO)
	Evidence for ample expertise of the PI/Institution
	Not reported
	Other
32. Please specify the intervention(s)	
33. Intervention category/ies	Drug
	Surgery / Invasive Procedure
	Device
	Vaccine
	Radiation
	Rehabilitation
	Behavioural / Lifestyle / Education / Counselling
	Dietary Supplement
	Other
34. Please specify the control(s)	
35. Type of control(s)	No treatment / Standard care
	Active (drug/other treatment)
	Placebo / Sham
36. Name of funder(s)	
37. Initiation/Sponsorship	Definitely industry initiated
	Probably industry initiated
	Probably investigator initiated
	Definitely investigator initiated
38. Title: Basic study design, patient population, and intervention provided in study title (if applicable trial acronym)? (reporting)	Yes
	No
39. Trial Registration: Registry name and trial identifier provided? (reporting)	Yes
	No
40. Protocol: Version Number and date provided? (reporting)	Yes
	No
41. Funding: Sources of financial and non-financial support declared? (reporting)	Yes
	No
42. Roles and Responsibilities: Names of protocol contributors/ authors provided? (reporting)	Yes
	No
	Yes

43. Roles and Responsibilities: Name and contact details of sponsor provided? (reporting)	No
44. Roles and Responsibilities: Role of sponsor and funder in trial described? (reporting)	Yes
	No
45. Roles and Responsibilities: Steering Committee General Membership and Role described? (reporting)	Yes
	No
	Not applicable
46. Background and rationale: Is research question described and justified? (as a minimum, we expect a systematic search, see info) (reporting)	Yes
	No
46a. Systematic review on PICO explicitly mentioned in background/introduction?	Yes
	No
47. Background and rationale: Comparator choice explained? (reporting)	Yes
	No
48. Objectives: Specific objectives described for each comparison (if multiple)? (reporting)	Yes
	No
49. Trial design: Trial design described? (trial type (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)) (reporting)	Yes
	No
50. Study Setting: Are countries where data will be collected listed? (reporting)	Yes
	No
51. Eligibility criteria: Inclusion and exclusion criteria for trial participants described? (reporting)	Yes
	No
52. Eligibility criteria: Inclusion and exclusion criteria for study centres and individuals who will perform the intervention described? (reporting)	Yes
	No
	Not applicable
53. Intervention(drug): Generic Name, Dose and Schedule of intervention described? (reporting)	Yes
	No
	Not applicable
54. Intervention(non-drug): Setting of intervention administration described? (reporting)	Yes
	No
	Not applicable
55. Intervention(non-drug): Individuals administering interventions (e.g. expertise) mentioned? (reporting)	Yes
	No
	Not applicable
56. Interventions - Modifications: Standard criteria for modifications of interventions described? (reporting)	Yes
	No
	Not applicable
57. Interventions - Adherence: Are strategies to improve adherence or any procedures for monitoring adherence described? (reporting)	Yes
	No
	Not applicable
58. Interventions - Concomitant care: Permitted care and interventions during trial described? (reporting)	Yes
	No
59. Primary Outcome: Specific measurement variable described? (reporting)	Yes
	No
	Not applicable
	Yes

60. Primary Outcome: Analysis metric (e.g. change from baseline) described? (reporting)	No
	Not applicable
61. Primary Outcomes: Is time point of measurement mentioned? (reporting)	Yes
	No
	Not applicable
62. Participant timeline: Timing of visit for participants described (e.g. schematic diagram)? (reporting)	Yes
	No
63. Sample size: Estimated number total or per group mentioned? (reporting)	Yes
	No
64. Sample size: Outcome used for samples size calculation described? (reporting)	Yes
	No
	Not applicable
65. Sample size: Assumed values for outcome in each study group provided? (reporting)	Yes
	No
	Not applicable
66. Sample size: Rationale or reference for assumed outcome values provided? (reporting)	Yes
	No
	Not applicable
67. Sample size: Type of statistical test provided? (reporting)	Yes
	No
	Not applicable
68. Sample size: Alpha value provided? (reporting)	Yes
	No
	Not applicable
69. Sample size: Statistical Power provided? (reporting)	Yes
	No
	Not applicable
70. Sample size: Adjustment for missing data, if relevant, described? (reporting)	Yes
	No
	Not applicable
71. Sample size: Rationale for intended sample size if not derived statistically provided? (reporting)	Yes
	No
	Not applicable
72. Recruitment: Location of participant recruitment described? (reporting)	Yes
	No
73. Recruitment: Person(s) who will recruit participants described? (reporting)	Yes
	No
74. Recruitment: Expected recruitment rate provided? (reporting)	Yes
	No
75. Recruitment: Estimated number or rate of eligible patients	
76. Recruitment: Estimated duration of the patient recruitment	
77. Recruitment: Monitoring of recruitment during trial mentioned? (reporting)	Yes
	No
78. Recruitment: Financial and non-financial incentives for participants described? (reporting)	Yes
	No

	Not applicable
79. Recruitment: Financial and non-financial incentives for investigators described? (reporting)	Yes
	No
80. Allocation: Method for generation of random sequence described? (e.g. computer-generated random numbers) (reporting)	Yes
	No
	Not applicable
81. Allocation: Ratio provided? (e.g. 1:1, 2:1) (reporting)	Yes
	No
	Not applicable
82. Allocation: Type of randomization described? (e.g. "simple", block, matched pair, etc.) (reporting)	Yes
	No
	Not applicable
83. Allocation: Non-random allocation-method described? (reporting)	Yes
	No
	Not applicable
84. Allocation: Rationale for non-random allocation provided? (reporting)	Yes
	No
	Not applicable
85. Allocation: Allocation concealment mechanism described? (reporting)	Yes
	No
	Not applicable
86. Allocation: Person who will enroll/assign participants described? (reporting)	Yes
	No
	Not applicable
87. Blinding: Status of participants described? (reporting)	Yes
	No
88. Blinding: Status of care providers described? (reporting)	Yes
	No
89. Blinding: Status of outcome assessors described? (reporting)	Yes
	No
90. Blinding: Conditions when unblinding is permissible mentioned? (reporting)	Yes
	No
	Not applicable
91. Data Collection: Personnel who will collect data specified? (reporting)	Yes
	No
92. Data collection: Strategies to promote participant retention and complete follow-up described? (reporting)	Yes
	No
93. Data Management: Data entry and coding processes described? (reporting)	Yes
	No
94. Statistical Methods: Main analysis for primary outcome including analysis methods for statistical comparisons described? (reporting)	Yes
	No
95. Statistical Methods: Handling of missing data defined? (reporting)	Yes
	No
	Not applicable
	Yes

96. Statistical Methods: Effect measure for primary analysis clearly specified? (e.g. risk ratio, odds ratio etc.) (reporting)	No
97. Statistical Methods: Significance level specified? (e.g. alpha of 5% or p<0.05) (reporting)	Yes
	No
98. Statistical Methods: Use of confidence intervals mentioned? (e.g. "results will be accompanied by a confidence interval") (reporting)	Yes
	No
99. Statistical Methods: Definition of subgroup categories provided? (reporting)	Yes
	No
	Not applicable
100. Any subgroup analysis mentioned (this question triggers a set of questions for a subproject independent of SPIRIT)?	Yes
	No
If yes, is it explicitly mentioned that subgroup analyses are exploratory?	Yes
	No
If yes, is a clear hypothesis for a subgroup effect pre-specified?	Yes
	No
If yes, is a clear hypothesis with a direction of subgroup effect pre-specified?	Yes
	No
If yes, use of interaction test for subgroup analysis mentioned?	Yes
	No
If yes, please list planned subgroup variables	
If yes, please list planned outcomes for subgroup analyses	
If yes, please specify number of subgroup analyses planned (=SG variables x outcomes)	
If yes, subgroup analysis considered in sample size calculation?	Yes
	No
101. Statistical Methods: Does the protocol define which participants will be included in the main analysis in terms of protocol adherence and missing data? (reporting)	Yes
	No
102. Data Monitoring Committee: Is a data monitoring committee planned for this study?	Yes
	No
103. Data Monitoring Committee: Is it explicitly reported whether a DMC is planned or why it is not planned? (reporting)	Yes
	No
104. Data Monitoring: Planned number of interim analyses	
105. Data Monitoring: Purpose of interim analyses (check all that apply)	Benefit
	Harm
	Futility
	Sample size recalculation
	No reason provided
	Not applicable
	Other
106. Data Monitoring: Reported who has ultimate authority to stop the trial? (reporting)	Yes
	No
107. Data Monitoring: Does the sponsor retain the right to stop the trial?	Yes
	No
	Not reported
If yes, explicitly at any time for any reason?	Yes
	No

108. Harms: Plans for collecting, assessing, reporting, managing anticipated/unanticipated adverse events provided? (reporting)	Yes
	No
109. Auditing: Procedures of audits and/or external monitoring described (e.g. clinical trial unit/CROs)? (reporting)	Yes
	No
	Not applicable
110. Research Ethics Approval: Where approval has been obtained, or plans for seeking approval, provided? (should always be yes in this study) (reporting)	Yes
	No
111. Protocol Amendments: Process for making amendments described? (reporting)	Yes
	No
112. Consent or Assent: Informed Consent process described? (reporting)	Yes
	No
113. Consent or Assent – Ancillary Studies: Process to obtain additional consent for collection and use of data and biological specimens described? (reporting)	Yes
	No
	Not applicable
114. Confidentiality: Described how data will be collected, kept secure, and maintained during the trial? (reporting)	Yes
	No
115. Declaration of Interests: Financial and other competing interests clearly stated? (reporting)	Yes
	No
116. Access to data: Is it clearly mentioned who will have access to full dataset after trial completion? (reporting)	Yes
	No
117. Ancillary and post-trial care: Any plans to provide or pay for ancillary care during the trial provided? (reporting)	Yes
	No
118. Dissemination Policy: Plans to disseminate trial results to key stakeholders/publication provided? (reporting)	Yes
	No
119. Dissemination Policy: Does the protocol mention any rules/regulations between the investigators and the sponsor with respect to the rights of publication of the trial results? (reporting)	Yes
	No
	Not applicable
If yes, please copy the corresponding statement from the protocol	
If yes, which statement suits best?	Only the sponsor retains the right to analyze and publish the data (no cooperation with investigators at all)
	The sponsor retains the right to approve any manuscript/abstract before publication (sponsor retains explicitly the right to reject submission for publication)
	The sponsor retains at least the right to review and comment on any manuscript/abstract before publication

	Free publication rights for the investigators, no constraints at all by the sponsor (sponsor has explicitly NOT the right to reject the submission for publication)
	Protocol refers to a separate publication agreement between sponsor and investigator
	Other (Please enter description for other)
120. Dissemination Policy: Authorship eligibility criteria described?	Yes
	No
121. Dissemination Policy: Plans for granting access to full trial protocol provided? (reporting)	Yes
	No
122. Informed Consent Materials: Model consent and/or assent forms provided (e.g in Appendix)? (reporting)	Yes
	No
123. Biological Specimens: Details of specimen collection provided? (reporting)	Yes
	No
	Not applicable
124. Any comments?	

Supplementary Table 2: Adherence to SPIRIT items in RCT protocols by approval year and median target sample size, multicentre vs single centre trials, and with vs without CTU or CRO support.

Characteristic	2012				2016			
	median (IQR)	mean (SD)	median (IQR)	mean (SD)	median (IQR)	mean (SD)	median (IQR)	mean (SD)
	Sample size <= 220 (n=117)		Sample size > 220 (n=140)		Sample size <= 220 (n=158)		Sample size > 220 (n=134)	
Frequency of items per protocol	21.75 (18.25, 24.79)	21.13 (4.85)	24.92 (22.81, 26.42)	24.33 (2.98)	25.04 (22.17, 27.06)	23.98 (4.38)	25.33 (23.06, 27.06)	24.88 (3.21)
Proportion of items per protocol	0.66 (0.55, 0.75)	0.64 (0.15)	0.76 (0.69, 0.80)	0.74 (0.09)	0.76 (0.67, 0.82)	0.73 (0.13)	0.77 (0.70, 0.82)	0.75 (0.10)
	Single centre trial (n=47)		Multicentre trial (n=210)		Single centre trial (n=77)		Multicentre trial (n=215)	
Frequency of items per protocol	18.79 (16.00, 22.67)	19.04 (5.03)	24.42 (21.75, 26.25)	23.73 (3.53)	24.67 (20.00, 27.17)	23.09 (5.08)	25.25 (23.29, 27.04)	24.87 (3.28)
Proportion of items per protocol	0.57 (0.48, 0.69)	0.58 (0.15)	0.74 (0.66, 0.80)	0.72 (0.11)	0.75 (0.61, 0.82)	0.70 (0.15)	0.77 (0.71, 0.82)	0.75 (0.10)
	No CTU or CRO support (n=108)		CTU or CRO support (n=149)		No CTU or CRO support (n=130)		CTU or CRO support (n=162)	
Frequency of items per protocol	21.71 (18.31, 24.19)	20.92 (4.71)	24.92 (22.58, 26.42)	24.29 (3.22)	24.08 (20.21, 26.25)	22.92 (4.33)	26.12 (23.92, 27.65)	25.59 (3.05)
Proportion of items per protocol	0.66 (0.55, 0.73)	0.63 (0.14)	0.76 (0.68, 0.80)	0.74 (0.10)	0.73 (0.61, 0.80)	0.69 (0.13)	0.79 (0.72, 0.84)	0.78 (0.09)

Abbreviations: SPIRIT, Standard Protocol Items: Recommendations for Interventional Trials; RCT, randomised clinical trial; CTU, clinical trials unit; CRO, contract research organization; IQR, interquartile range; SD, standard deviation

Supplementary Table 3: Adherence to SPIRIT items in RCT protocols by country and sponsorship

Characteristic	2012						2016					
	Sponsorship				Total 2012 (n=257)		Sponsorship				Total 2016 (n=292)	
	Industry (n=138)		Investigator (n=119)				Industry (n=130)		Investigator (n=162)			
	median (IQR)	mean (SD)	median (IQR)	mean (SD)	median (IQR)	mean (SD)	median (IQR)	mean (SD)	median (IQR)	mean (SD)	median (IQR)	mean (SD)
Switzerland	Industry (n=91)		Investigator (n=89)		Total 2012 (n=180)		Industry (n=86)		Investigator (n=131)		Total 2016 (n=217)	
Frequency of items per protocol	26.08 (24.71, 27.08)	25.52 (2.71)	21.42 (18.33, 24.25)	20.99 (4.61)	24.49 (21.15, 26.44)	23.28 (4.39)	25.98 (24.35, 27.08)	25.25 (3.05)	26.08 (22.50, 27.67)	24.81 (4.02)	26.04 (23.50, 27.33)	24.98 (3.67)
Proportion of items per protocol	0.79 (0.75, 0.82)	0.77 (0.08)	0.65 (0.56, 0.74)	0.64 (0.14)	0.74 (0.64, 0.80)	0.71 (0.13)	0.79 (0.74, 0.82)	0.77 (0.09)	0.79 (0.68, 0.84)	0.75 (0.12)	0.79 (0.71, 0.83)	0.76 (0.11)
Germany	Industry (n=26)		Investigator (n=11)		Total 2012 (n=37)		Industry (n=27)		Investigator (n=11)		Total 2016 (n=38)	
Frequency of items per protocol	24.58 (22.96, 25.75)	24.36 (1.88)	19.50 (17.17, 23.54)	19.28 (5.14)	24.17 (21.92, 25.08)	22.85 (3.92)	23.92 (22.38, 25.25)	22.74 (4.21)	22.42 (19.38, 24.63)	22.07 (3.76)	23.58 (21.09, 25.21)	22.55 (4.04)
Proportion of items per protocol	0.75 (0.70, 0.78)	0.74 (0.06)	0.59 (0.52, 0.71)	0.58 (0.16)	0.73 (0.66, 0.76)	0.69 (0.12)	0.73 (0.68, 0.77)	0.69 (0.13)	0.68 (0.59, 0.75)	0.67 (0.11)	0.72 (0.64, 0.76)	0.68 (0.12)
Canada	Industry (n=21)		Investigator (n=19)		Total 2012 (n=40)		Industry (n=17)		Investigator (n=20)		Total 2016 (n=37)	
Frequency of items per protocol	22.83 (21.42, 24.42)	22.56 (2.70)	19.42 (18.17, 22.29)	19.48 (3.45)	21.75 (19.22, 23.15)	21.10 (3.41)	25.92 (23.67, 27.08)	25.37 (1.93)	20.04 (17.98, 23.65)	20.71 (4.45)	23.67 (20.00, 26.00)	22.85 (4.20)
Proportion of items per protocol	0.69 (0.65, 0.74)	0.68 (0.08)	0.59 (0.55, 0.68)	0.59 (0.10)	0.66 (0.58, 0.70)	0.64 (0.10)	0.79 (0.72, 0.82)	0.77 (0.06)	0.61 (0.55, 0.72)	0.63 (0.14)	0.72 (0.61, 0.79)	0.69 (0.13)

Abbreviations: SPIRIT, Standard Protocol Items: Recommendations for Interventional Trials; RCT, randomised clinical trial; IQR, interquartile range; SD, standard deviation

Supplementary Table 4: Sensitivity analyses of calculating the adherence to SPIRIT items for RCT protocols by sponsorship

Characteristic	2012						2016					
	Industry-sponsored (n=138)		Investigator-sponsored (n=119)		Total 2012 (n=257)		Industry-sponsored (n=130)		Investigator-sponsored (n=162)		Total 2016 (n=292)	
	median (IQR)	mean (SD)	median (IQR)	mean (SD)	median (IQR)	mean (SD)	median (IQR)	mean (SD)	median (IQR)	mean (SD)	median (IQR)	mean (SD)
Major Item approach (simple) NA=0												
Frequency of items per protocol	18.00 (17.00, 20.00)	18.04 (2.99)	13.00 (11.00, 16.00)	13.48 (4.27)	17.00 (13.00, 19.00)	15.93 (4.29)	18.00 (16.00, 20.00)	18.12 (3.44)	17.00 (14.00, 19.00)	16.40 (4.08)	18.00 (15.00, 20.00)	17.16 (3.89)
Proportion of items per protocol	0.56 (0.52, 0.61)	0.55 (0.09)	0.42 (0.33, 0.50)	0.41 (0.13)	0.52 (0.41, 0.58)	0.49 (0.13)	0.56 (0.50, 0.62)	0.56 (0.10)	0.53 (0.42, 0.59)	0.51 (0.12)	0.55 (0.47, 0.61)	0.53 (0.12)
Major Item approach (simple) NA=1												
Frequency of items per protocol	22.00 (20.00, 23.00)	21.14 (3.20)	16.00 (14.00, 19.00)	16.39 (4.76)	20.00 (16.00, 22.00)	18.95 (4.64)	22.00 (20.00, 24.00)	21.25 (3.68)	21.00 (17.00, 24.00)	20.19 (4.73)	21.00 (18.00, 24.00)	20.66 (4.32)
Proportion of items per protocol	0.67 (0.61, 0.70)	0.64 (0.10)	0.48 (0.42, 0.58)	0.50 (0.14)	0.61 (0.48, 0.67)	0.57 (0.14)	0.67 (0.61, 0.73)	0.64 (0.11)	0.64 (0.52, 0.73)	0.61 (0.14)	0.64 (0.55, 0.73)	0.63 (0.13)
Major item approach (allowing for partial credit) NA=0												
Frequency of items per protocol	24.75 (22.75, 26.17)	24.22 (2.86)	19.47 (16.59, 22.27)	19.19 (4.91)	22.87 (19.29, 25.42)	21.88 (4.68)	24.50 (22.40, 26.21)	23.89 (3.64)	23.92 (19.85, 25.83)	22.72 (4.44)	24.25 (21.25, 26.08)	23.24 (4.14)

Proportion of items per protocol	0.76 (0.70, 0.80)	0.74 (0.08)	0.60 (0.51, 0.69)	0.59 (0.15)	0.71 (0.60, 0.78)	0.67 (0.14)	0.76 (0.69, 0.80)	0.73 (0.11)	0.74 (0.60, 0.80)	0.70 (0.14)	0.74 (0.66, 0.80)	0.72 (0.13)
Major item approach (allowing for partial credit) NA=1												
Frequency of items per protocol	25.46 (23.58, 26.50)	24.85 (2.77)	21.25 (18.25, 23.67)	20.59 (4.52)	23.67 (20.67, 26.17)	22.88 (4.25)	25.33 (23.67, 26.91)	24.75 (3.35)	25.00 (21.24, 27.31)	24.12 (4.29)	25.25 (22.50, 27.08)	24.40 (3.90)
Proportion of items per protocol	0.77 (0.71, 0.80)	0.75 (0.08)	0.64 (0.55, 0.72)	0.62 (0.14)	0.72 (0.63, 0.79)	0.69 (0.13)	0.77 (0.72, 0.82)	0.75 (0.10)	0.76 (0.64, 0.83)	0.73 (0.13)	0.77 (0.68, 0.82)	0.74 (0.12)
All item approach NA=0												
Frequency of items per protocol	43.00 (40.25, 46.00)	42.38 (5.26)	35.00 (30.00, 40.00)	34.57 (8.33)	41.00 (35.00, 44.00)	38.76 (7.87)	42.00 (40.00, 45.75)	41.65 (6.46)	41.00 (35.00, 45.00)	39.69 (7.91)	42.00 (37.75, 45.00)	40.57 (7.35)
Proportion of items per protocol	0.73 (0.69, 0.78)	0.73 (0.08)	0.62 (0.53, 0.70)	0.60 (0.14)	0.70 (0.61, 0.76)	0.67 (0.13)	0.73 (0.68, 0.78)	0.71 (0.11)	0.73 (0.62, 0.79)	0.70 (0.13)	0.73 (0.65, 0.78)	0.71 (0.12)
All item approach NA=1												
Frequency of items per protocol	49.00 (46.00, 51.75)	48.27 (4.71)	43.00 (37.00, 46.00)	41.42 (7.80)	46.00 (42.00, 50.00)	45.10 (7.18)	48.50 (45.00, 51.00)	47.45 (5.94)	49.00 (42.25, 52.00)	46.95 (7.42)	49.00 (44.00, 52.00)	47.17 (6.80)
Proportion of items per protocol	0.77 (0.72, 0.81)	0.75 (0.07)	0.67 (0.58, 0.72)	0.65 (0.12)	0.72 (0.66, 0.78)	0.70 (0.11)	0.76 (0.70, 0.80)	0.74 (0.09)	0.77 (0.66, 0.81)	0.73 (0.12)	0.77 (0.69, 0.81)	0.74 (0.11)

Abbreviations: IQR, interquartile range; NA, not applicable (SPIRIT items with rating “not applicable”); SD, standard deviation

Supplementary Table 5: Adherence to individual SPIRIT items by year and sponsorship

		2012			2016		
Variable	**Spirit Item Number**	**Industry sponsorship (n=138)**	**Investigator sponsorship (n=119)**	**Total 2012 (n=257)**	**Industry sponsorship (n=130)**	**Investigator sponsorship (n=162)**	**Total 2016 (n=292)**
Basic study design in Title	1	116 (84.1%)	47 (39.5%)	163 (63.4%)	108 (83.1%)	57 (35.2%)	165 (56.5%)
Trial registration	2	109 (79.0%)	43 (36.1%)	152 (59.1%)	111 (85.4%)	125 (77.2%)	236 (80.8%)
Protocol version, number and date	3	131 (94.9%)	100 (84.0%)	231 (89.9%)	127 (97.7%)	155 (95.7%)	282 (96.6%)
Funding sources	4	123 (89.1%)	70 (58.8%)	193 (75.1%)	122 (93.8%)	120 (74.1%)	242 (82.9%)
Names of protocol contributors/ authors	5a	30 (21.7%)	36 (30.3%)	66 (25.7%)	20 (15.4%)	30 (18.5%)	50 (17.1%)
Name and contact details of sponsor	5b	110 (79.7%)	82 (68.9%)	192 (74.7%)	91 (70.0%)	136 (84.0%)	227 (77.7%)
Role of sponsor and funder in trial	5c	112 (81.2%)	39 (32.8%)	151 (58.8%)	70 (53.8%)	43 (26.5%)	113 (38.7%)
Steering Committee General Membership and Role	5d	125 (90.6%)	107 (89.9)	232 (90.3%)	113 (86.9%)	156 (96.3%)	269 (92.1%)
Of which Not Applicable		94 (75.2%)	72 (67.3%)	164 (71.6%)	90 (79.6%)	109 (69.9%)	199 (74.0%)
Research question described and justified	6a	25 (18.1%)	31 (26.1%)	56 (21.8%)	22 (16.9%)	54 (33.3%)	76 (26.0%)
Comparator choice explained	6b	108 (78.3%)	88 (73.9%)	196 (76.3%)	105 (80.8%)	137 (84.6%)	242 (82.9%)
Specific objectives described	7	133 (96.4%)	107 (89.9%)	240 (93.4%)	125 (96.2%)	149 (92.0%)	274 (93.8%)
Trial design described	8	127 (92.0%)	80 (67.2%)	207 (80.5%)	115 (88.5%)	132 (81.5%)	247 (84.6%)
Countries where data will be collected listed	9	71 (51.4%)	94 (79.0%)	165 (64.2%)	19 (14.6%)	144 (88.9%)	163 (55.8%)
Eligibility criteria for trial participants	10	138 (100.0%)	116 (97.5%)	254 (98.8%)	130 (100.0%)	162 (100.0%)	292 (100.0%)
Eligibility criteria for study centres and who will perform the intervention	10	15 (10.9%)	58 (48.7%)	73 (28.4%)	12 (9.2%)	98 (60.5%)	110 (37.7%)

Of which Not Applicable		1 (6.7%)	39 (67.2%)	40 (54.8%)	2 (16.7%)	68 (69.4%)	70 (63.6%)
Individuals administering interventions (non-drug)	10	131 (94.9%)	93 (78.2%)	224 (87.2%)	120 (92.3%)	131 (80.9%)	251 (86.0%)
Of which Not Applicable		119 (90.8%)	49 (52.7%)	168 (75.0%)	106 (88.3%)	65 (49.6%)	171 (68.1%)
Generic Name, Dose and Schedule of intervention	11a	135 (97.8%)	118 (99.2%)	253 (98.4%)	130 (100%)	161 (99.4%)	291 (99.7%)
Of which Not Applicable		16 (11.9%)	63 (53.4%)	79 (31.2%)	19 (14.6%)	95 (59.0%)	114 (39.2%)
Setting of intervention administration	11a	129 (93.5%)	103 (86.6%)	232 (90.3%)	118 (90.8%)	147 (90.7%)	265 (90.8%)
Of which Not Applicable		118 (91.5%)	49 (47.6%)	167 (72.0%)	106 (89.8%)	62 (42.2%)	168 (63.4%)
Criteria for modifications of interventions	11b	114 (82.6%)	85 (71.4%)	199 (77.4%)	111 (85.4%)	128 (79.0%)	239 (81.8%)
Of which Not Applicable		13 (11.4%)	32 (37.7%)	45 (22.6%)	10 (9.0%)	35 (27.3%)	45 (18.8%)
Strategies to improve or monitoring of adherence	11c	123 (89.1%)	95 (79.8%)	218 (84.8%)	107 (82.3%)	144 (88.9%)	251 (86.0%)
Of which Not Applicable		44 (35.8%)	66 (69.5%)	110 (50.5%)	33 (30.8%)	78 (54.2%)	111 (44.2%)
Permitted concomitant care	11d	130 (94.2%)	61 (51.3%)	191 (74.3%)	124 (95.4%)	112 (69.1%)	236 (80.8%)
Primary Outcome: Specific measurement variable	12	138 (100%)	113 (95.0%)	251 (97.7%)	129 (99.2%)	153 (94.4%)	282 (96.6%)
Of which Not Applicable		1 (0.7%)	0 (0%)	1 (0.4%)	0 (0%)	0 (0%)	0 (0%)
Primary Outcome: Analysis metric	12	132 (95.7%)	101 (84.9%)	233 (90.7%)	124 (95.4%)	140 (86.4%)	264 (90.4%)
Of which Not Applicable		3 (2.3%)	0 (0%)	3 (1.3%)	1 (0.8%)	0 (0%)	1 (0.4%)
Primary Outcomes: time point of measurement	12	132 (95.7%)	105 (88.2%)	237 (92.2%)	124 (95.4%)	149 (92.0%)	273 (93.5%)
Of which Not Applicable		40 (30.3%)	20 (19.1%)	60 (25.3%)	26 (21.0%)	20 (13.4%)	46 (16.9%)
Participant timeline	13	136 (98.6%)	113 (95.0%)	249 (96.9%)	130 (100%)	154 (95.1%)	284 (97.3%)
Sample size: Estimated number	14	138 (100.0%)	116 (97.5%)	254 (98.8%)	128 (98.5%)	161 (99.4%)	289 (99.0%)
Sample size: Outcome used for samples size calculation	14	135 (97.8%)	107 (89.9%)	242 (94.2%)	127 (97.7%)	148 (91.4%)	275 (94.2%)
Of which Not Applicable		7 (5.2%)	3 (2.8%)	10 (4.1%)	4 (3.2%)	7 (4.7%)	11 (4.0%)

Sample size: Assumed values for outcome	14	122 (88.4%)	89 (74.8%)	211 (82.1%)	111 (85.4%)	116 (71.6%)	227 (77.7%)
Of which Not Applicable		6 (4.9%)	5 (5.6%)	11 (5.2%)	4 (3.6%)	7 (6.0%)	11 (4.9%)
Sample size: Alpha value	14	131 (94.9%)	106 (89.1%)	237 (92.2%)	126 (96.9%)	150 (92.6%)	276 (94.5%)
Of which Not Applicable		7 (5.3%)	3 (2.8%)	10 (4.2%)	4 (3.2%)	7 (4.7%)	11 (4.0%)
Sample size: Statistical Power	14	134 (97.1%)	111 (93.3%)	245 (95.3%)	128 (98.5%)	153 (94.4%)	281 (96.2%)
Of which Not Applicable		7 (5.2%)	3 (2.7%)	10 (4.1%)	4 (3.1%)	7 (4.6%)	11 (3.9%)
Sample size: Rationale sample size if not derived statistically	14	137 (99.3%)	110 (92.4%)	247 (96.1%)	127 (97.7%)	158 (97.5%)	285 (97.6%)
Of which Not Applicable		130 (94.9%)	110 (100%)	240 (97.2%)	123 (96.9%)	155 98.1%)	278 (97.5%)
Location of participant recruitment	15	24 (17.4%)	78 (65.5%)	102 (39.7%)	17 (13.1%)	112 (69.1%)	129 (44.2%)
Person(s) who will recruit participants	15	40 (29.0%)	52 (43.7%)	92 (35.8%)	33 (25.4%)	91 (56.2%)	124 (42.5%)
Expected recruitment rate	15	37 (26.8%)	52 (43.7%)	89 (34.6%)	13 (10.0%)	39 (24.1%)	52 (17.8%)
Method for generation of random sequence	16a	89 (64.5%)	63 (52.9%)	152 (59.1%)	68 (52.3%)	109 (67.3%)	177 (60.6%)
Allocation concealment mechanism	16b	126 (91.3%)	80 (67.2%)	206 (80.2%)	113 (86.9%)	130 (80.2%)	243 (83.2%)
Of which Not Applicable		8 (6.4%)	3 (3.8%)	11 (5.3%)	1 (0.9%)	3 (2.3%)	4 (1.7%)
Person who will enroll/assign participants	16c	59 (42.8%)	44 (37.0%)	103 (40.1%)	50 (38.5%)	79 (48.8%)	129 (44.2%)
Of which Not Applicable		0 (0%)	2 (4.6%)	2 (1.9%)	1 (2%)	1 (1.3%)	2 (1.6%)
Blinding status of participants	17a	133 (96.4%)	97 (81.5%)	230 (89.5%)	128 (98.5%)	148 (91.4%)	276 (94.5%)
Blinding status of care providers	17a	134 (97.1%)	97 (81.5%)	231 (89.9%)	127 (97.7%)	148 (91.4%)	275 (94.2%)
Blinding status of outcome assessors	17a	103 (74.6%)	71 (59.7%)	174 (67.7%)	94 (72.3%)	105 (64.8%)	199 (68.2%)
Conditions when unblinding is permissible	17b	127 (92.0%)	92 (77.3%)	219 (85.2%)	120 (82.3%)	142 (87.7%)	262 (89.7%)
Of which Not Applicable		34 (26.8%)	66 (71.7%)	100 (45.7%)	36 (30%)	91 (64.1%)	127 (48.5%)

Personnel who will collect data	18a	58 (42.0%)	52 (43.7%)	110 (42.8%)	61 (46.9%)	96 (59.3%)	157 (53.8%)
Strategies to promote participant retention and complete follow-up	18b	84 (60.9%)	34 (28.6%)	118 (45.9%)	80 (61.5%)	64 (39.5%)	144 (49.3%)
Data entry and coding	19	106 (76.8%)	64 (53.8%)	170 (66.1%)	102 (78.5%)	117 (72.2%)	219 (75.0%)
Main analysis for primary outcome	20a	131 (94.9%)	96 (80.7%)	227 (88.3%)	121 (93.1%)	132 (81.5%)	253 (86.6%)
Definition of subgroup categories	20b	117 (84.8%)	98 (82.4%)	215 (83.7%)	108 (83.1%)	148 (91.4%)	256 (87.7%)
Of which Not Applicable		60 (51.3%)	79 (80.6%)	139 (64.7%)	63 (58.3%)	116 (78.4%)	179 (69.9%)
Definition of analysis population	20c	125 (90.6%)	49 (41.2%)	174 (67.7%)	120 (92.3%)	96 (59.3%)	216 (74.0%)
DMC is planned or why it is not planned	21a	102 (73.9%)	49 (41.2%)	151 (58.8%)	97 (74.6%)	72 (44.4%)	169 (57.9%)
Who has authority to stop the trial	21b	111 (80.4%)	73 (61.3%)	184 (71.6%)	111 (85.4%)	112 (69.1%)	223 (76.4%)
Anticipated/unanticipated adverse events collection	22	136 (98.6%)	91 (76.5%)	227 (88.3%)	127 (97.7%)	138 (85.2%)	265 (90.8%)
Audits/external monitoring described	23	106 (76.8%)	49 (41.2%)	155 (60.3%)	109 (83.8%)	112 (69.1%)	221 (75.7%)
Of which Not Applicable		0 (0%)	3 (6.1%)	3 (1.9%)	3 (2.8%)	15 (13.4%)	18 (8.2%)
Research ethics approval	24	138 (100%)	118 (100%)	256 (100%)	130 (100%)	162 (100%)	292 (100%)
Process for making amendments described	25	106 (76.8%)	48 (40.3%)	154 (59.9%)	103 (79.2%)	121 (74.7%)	224 (76.7%)
Informed Consent process described	26a	119 (86.2%)	77 (64.7%)	196 (76.3%)	110 (84.6%)	139 (85.8%)	249 (85.3%)
Process to obtain additional consent for collection and use of data and biological specimens	26b	123 (89.1%)	103 (86.6%)	226 (87.9%)	111 (85.4%)	151 (93.2%)	262 (89.7%)
Of which Not Applicable		70 (56.9%)	87 (84.5%)	157 (69.5%)	65 (58.6%)	126 (83.4%)	191 (72.9%)
Confidentiality of data	27	125 (90.6%)	88 (73.9%)	213 (82.9%)	114 (87.7%)	144 (88.9%)	258 (88.4%)
Declaration of Interests	28	54 (39.1%)	27 (22.7%)	81 (31.5%)	94 (72.3%)	88 (54.3%)	182 (62.3%)
Who will have access to full dataset	29	29 (21.0%)	23 (19.3%)	52 (20.2%)	37 (28.5%)	56 (34.6%)	93 (31.8%)

Ancillary and post-trial care	30	61 (44.2%)	39 (32.8%)	100 (38.9%)	50 (38.5%)	44 (27.2%)	94 (32.2%)
Plans to disseminate trial results to key stakeholders/publication provided	31a	72 (52.2%)	51 (42.9%)	123 (47.9%)	77 (59.2%)	129 (79.6%)	206 (70.5%)
Authorship eligibility criteria	31b	50 (36.2%)	30 (25.2%)	80 (31.1%)	41 (31.5%)	57 (35.2%)	98 (33.6%)
Plans for granting access to full trial protocol	31c	7 (5.1%)	2 (1.7%)	9 (3.5%)	4 (3.1%)	13 (8.0%)	17 (5.8%)
Consent forms provided	32	133 (96.4%)	118 (99.2%)	251 (97.7%)	125 (96.2%)	157 (96.9%)	282 (96.6%)
Details of specimen collection	33	126 (91.3%)	99 (83.2)	225 (87.5%)	120 (92.3%)	152 (93.8%)	272 (93.2%)
Of which Not Applicable		35 (27.8%)	61 (61.6%)	96 (42.7%)	53 (44.2%)	109 (71.7%)	162 (59.6%)

Supplementary Table 6: Adherence to SPIRIT items in Investigator-sponsored protocols that improved by 10% or more

		2012	2016
Variable	**Spirit Item Number**	**Yes**	**Yes**
Trial registration	2	43 (36.1%)	125 (77.2%)
Protocol version, number and date	3	100 (84.0%)	155 (95.7%)
Funding sources	4	70 (58.8%)	120 (74.1%)
Name and contact details of sponsor	5b	82 (68.9%)	136 (84.0%)
Comparator choice explained	6b	88 (73.9%)	137 (84.6%)
Trial design described	8	80 (67.2%)	132 (81.5%)
Eligibility criteria for study centres and who will perform the intervention	10	58 (48.7%)	98 (60.5%)
Of which Not Applicable		39 (67.2%)	68 (69.4%)
Permitted concomitant care	11d	61 (51.3%)	112 (69.1%)
Person(s) who will recruit participants	15	52 (43.7%)	91 (56.2%)
Method for generation of random sequence	16a	63 (52.9%)	109 (67.3%)
Allocation concealment mechanism	16b	80 (67.2%)	130 (80.3%)
Of which Not Applicable		3 (3.8%)	3 (2.3%)
Person who will enroll/assign participants	16c	44 (37.0%)	79 (48.8%)
Of which Not Applicable		2 (1.4%)	1 (1.3%)
Personnel who will collect data	18a	52 (43.7%)	96 (59.3%)
Strategies to promote participant retention and complete follow-up	18b	34 (28.6%)	64 (39.5%)
Data entry and coding	19	64 (53.8%)	117 (72.2%)
Definition of analysis population	20c	49 (41.2%)	96 (59.3%)
Audits/external monitoring described	23	49 (41.2%)	112 (69.1%)
Of which Not Applicable		3 (6.1%)	15 (13.4%)
Process for making amendments described	25	48 (40.3%)	121 (74.7%)
Informed Consent process described	26a	77 (64.7%)	139 (85.8%)
Confidentiality of data	27	88 (73.9%)	144 (88.9%)
Declaration of Interests	28	27 (22.7%)	88 (54.3%)
Who will have access to full dataset	29	23 (19.3%)	56 (34.6%)
Plans to disseminate trial results to key stakeholders/publication provided	31a	51 (42.9%)	129 (79.6%)

Authorship eligibility criteria	31b	30 (25.2%)	57 (35.2%)
Details of specimen collection	33	99 (83.2%)	152 (93.8)
Of which Not Applicable		61 (61.6%)	109 (71.7%)

Supplementary Table 7: Results from multivariable Beta and Logistic regressions for all approaches

Approach	Independent Variable	Beta Regression			Likelyhood ratio		Logistic regression with Protocol as random effect			Likelyhood ratio	
		Odds Ratio	CI	p value	Chisq	p	Odds Ratio	CI	p value	Chisq	p
Major Item approach (simple) NA=0	Sample size in 1000 increments	1.01	0.99- 1.03	0.235	-	-	1.00	0.98 – 1.02	0.747	-	-
	Multicentre study	1.29	1.17- 1.43	<.001	-	-	1.21	1.08 – 1.36	0.001	-	-
	CTU or CRO support	1.35	1.25- 1.45	<.001	-	-	1.42	1.29 – 1.56	<.001	-	-
	Industry sponsorship	1.23	1.14- 1.34	<.001	-	-	1.36	1.23 – 1.51	<.001	-	-
	Year 2016	1.25	1.16- 1.35	<.001	-	-	1.26	1.15 – 1.38	<.001	-	-
Interaction term	Sponsorship:Year interaction	0.71	0.61- 0.81	<.001	22.24	<.001	0.69	0.58 – 0.83	<.001	16.21	<.001
	CTU/CRO support:Year interaction	0.91	0.78- 1.05	0.190	1.72	0.190	0.87	0.73 – 1.04	0.118	2.43	0.119
Major Item approach (simple) NA=1	Sample size in 1000 increments	1.01	0.99- 1.03	0.233	-	-	0.99	0.97 – 1.02	0.654	-	-
	Multicentre study	1.22	1.08- 1.37	0.001	-	-	1.16	1.02 – 1.31	0.022	-	-
	CTU or CRO support	1.42	1.30- 1.55	<.001	-	-	1.46	1.32 – 1.60	<.001	-	-
	Industry sponsorship	1.23	1.11- 1.35	<.001	-	-	1.34	1.21 – 1.50	<.001	-	-
	Year 2016	1.32	1.21- 1.43	<.001	-	-	1.34	1.22 – 1.48	<.001	-	-
Interaction term	Sponsorship:Year interaction	0.64	0.55- 0.76	<.001	26.27	<.001	0.67	0.55 – 0.81	<.001	17.322	<.001
	CTU/CRO support:Year interaction	0.99	0.83- 1.17	0.881	0.02	0.881	0.90	0.75 – 1.09	0.292	1.10	0.294

Major item approach (allowing for partial credit) NA=0	Sample size in 1000 increments	1.01	0.99- 1.03	0.290	-	-	-	-	-	-	-	
	Multicentre study	1.22	1.08- 1.38	0.001	-	-	-	-	-	-	-	
	CTU or CRO support	1.43	1.31- 1.57	<.001	-	-	-	-	-	-	-	
	Industry sponsorship	1.25	1.13- 1.38	<.001	-	-	-	-	-	-	-	
	Year 2016	1.33	1.21- 1.46	<.001	-	-	-	-	-	-	-	
Interaction term	Sponsorship:Year interaction	0.60	0.50- 0.71	<.001	31.48	<.001	-	-	-	-	-	
	CTU/CRO support:Year interaction	0.94	0.79- 1.13	0.515	0.42	0.515	-	-	-			
Major item approach (allowing for partial credit) NA=1	Sample size in 1000 increments	1.01	0.99- 1.03	0.389	-	-	-	-	-	-	-	
	Multicentre study	1.18	1.05- 1.33	0.006	-	-	-	-	-	-	-	
	CTU or CRO support	1.44	1.31- 1.57	<.001	-	-	-	-	-	-	-	
	Industry sponsorship	1.20	1.09- 1.33	<.001	-	-	-	-	-	-	-	
	Year 2016	1.33	1.22- 1.45	<.001	-	-	-	-	-	-	-	
Interaction term	Sponsorship:Year interaction	0.61	0.52- 0.73	<.001	30.01	<.001	-	-	-	-	-	
	CTU/CRO support:Year interaction	0.98	0.82- 1.16	0.790	0.07	0.790	-	-	-			
All item approach NA=0	Sample size in 1000 increments	1.02	1.00- 1.04	0.095	-	-	1.02	1.00 – 1.04	0.027	-	-	
	Multicentre study	1.27	1.14- 1.43	<.001	-	-	1.37	1.24 – 1.52	<.001	-	-	
	CTU or CRO support	1.39	1.28- 1.52	<.001	-	-	1.33	1.23 – 1.44	<.001	-	-	
	Industry sponsorship	1.14	1.03- 1.25	0.010	-	-	1.15	1.05 – 1.25	0.001	-	-	
	Year 2016	1.25	1.15- 1.36	<.001	-	-	1.20	1.11 – 1.29	<.001	-	-	
Interaction term	Sponsorship:Year interaction	0.63	0.53- 0.74	<.001	29.29	<.001	0.69	0.59 – 0.80	<.001	24.20	<.001	

	CTU/CRO support:Year interaction	1.02	0.86- 1.21	0.841	0.04	0.842	0.97	0.83 – 1.12	0.643	0.22	0.643
All item approach NA=1	Sample size in 1000 increments	1.02	1.00- 1.04	0.131	-	-	1.02	1.00 – 1.04	0.118	-	-
	Multicentre study	1.18	1.06- 1.31	0.003	-	-	1.20	1.07 – 1.35	0.002	-	-
	CTU or CRO support	1.36	1.26- 1.48	<.001	-	-	1.39	1.27 – 1.51	<.001	-	-
	Industry sponsorship	1.13	1.03- 1.23	0.010	-	-	1.14	1.04 – 1.25	0.006	-	-
	Year 2016	1.23	1.14- 1.34	<.001	-	-	1.23	1.14 – 1.34	<.001	-	-
Interaction term	Sponsorship:Year interaction	0.64	0.55- 0.75	<.001	31.18	<.001	0.63	0.54 – 0.74	<.001	30.67	<.001
	CTU/CRO support:Year interaction	1.05	0.90- 1.23	0.564	0.33	0.5643	1.05	0.89 – 1.24	0.594	0.28	0.594

Abbreviations: CI, confidence interval

Supplementary Table 8: Results from multivariable Beta regression, subset of Investigator-sponsored protocols

Approach	Independent Variable	Beta Regression			Likelyhood ratio	
		Odds Ratio	CI	p value	Chisq	p
Major item approach (allowing for partial credit) NA=0	Sample size/1000	1.01	0.95- 1.07	0.803	-	-
	Multicentre	1.21	1.05- 1.40	0.008	-	-
	CTU or CRO support	1.55	1.35- 1.77	<.001	-	-
	Year	1.61	1.42- 1.84	<.001	-	-
	Swiss cohort	1.48	1.27- 1.74	<.001	-	-
Interaction term	CTU/CRO support:Year	1.02	0.79- 1.33	0.869	0.03	0.869
	Swiss trials:Year	1.39	1.03- 1.88	0.034	4.42	0.036
Major item approach (allowing for partial credit) NA=1	Sample size/1000	1.00	0.95- 1.06	0.891	-	-
	Multicentre	1.19	1.03- 1.37	0.016	-	-
	CTU or CRO support	1.53	1.34- 1.75	<.001	-	-
	Year	1.60	1.41- 1.82	<.001	-	-
	Swiss cohort	1.46	1.25- 1.70	<.001	-	-
Interaction term	CTU/CRO support:Year	1.08	0.83- 1.39	0.568	0.33	0.568
	Swiss trials:Year	1.39	1.03- 1.87	0.031	4.57	0.032

Abbreviations: CI, confidence interval

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

The methods used to conduct the present study have previously been published:

Gryaznov D, Odutayo A, von Niederhäusern B, Speich B, Kasenda B, Ojeda-Ruiz E, et al. Rationale and design of repeated cross-sectional studies to evaluate the reporting quality of trial protocols: the Adherence to SPIrit REcommendations (ASPIRE) study and associated projects. Trials. 2020;21(1):896.
Link: https://trialsjournal.biomedcentral.com/articles/10.1186/s13063-020-04808-y

	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 (Section: Abstract, Design section)	4
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found (Section: Abstract, Results section)	5
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported (Section: Introduction, all paragraphs)	6
Objectives	3	State specific objectives, including any prespecified hypotheses (Section: Introduction, last paragraph)	6
Methods			
Study design	4	Present key elements of study design early in the paper (Section: Methods 1st paragraph (Published))	7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection (Section: Methods, Identification of included trial protocols; Supplementary Figure 1)	7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants (Section: Methods, Identification of included trial protocols)	7
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable (Section: Methods, Data Analysis, paragraphs 1 and 2)	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 (Section: Methods, Data extraction)	*7*
Bias	9	Describe any efforts to address potential sources of bias (Section: Methods, Data extraction)	7
Study size	10	Explain how the study size was arrived at (Section: Methods 1st paragraph (Published))	7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why (Section: Methods, Data Analysis, paragraph 1)	8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding (Section: Methods, Data Analysis, paragraph 2)	8
		(*b*) Describe any methods used to examine subgroups and interactions (Section: Methods, Data Analysis, paragraph 1)	8

		(*c*) Explain how missing data were addressed (na)	
		(*d*) If applicable, describe analytical methods taking account of sampling strategy (na)	
		(*e*) Describe any sensitivity analyses (Section: Methods, Data Analysis, paragraph 1)	8
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 (Supplementary Figure 1)	
		(b) Give reasons for non-participation at each stage (na)	
		(c) Consider use of a flow diagram (Supplementary Figure 1)	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (Section: Results, Characteristics of included trial protocols, paragraph 1 and 2. Table 1)	9
		(b) Indicate number of participants with missing data for each variable of interest (na)	
Outcome data	15*	Report numbers of outcome events or summary measures (Section: Results, Adherence to SPIRIT in protocols from 2012 and 2016. Table 2, Figure 1)	9,10
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 (Section: Results, Multivariable regression analysis. Figure 2, Supplementary Table 7)	10,11
		(*b*) Report category boundaries when continuous variables were categorized (Section: Methods, Data Analysis, paragraph 2. Figure 2)	8
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period (na)	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses (Section: Results, Multivariable regression analysis. Supplementary Table 7)	10,11
Discussion			
Key results	18	Summarise key results with reference to study objectives (Section: Discussion, Main findings and interpretation)	11,12
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 (Section: Discussion, Strengths and limitations, all paragraphs)	12, 13
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence (Section: Discussion, Comparison with other studies, Implications, all paragraphs)	13, 14
Generalisability	21	Discuss the generalisability (external validity) of the study results (Section: Discussion, Strengths and limitations, paragraphs 1 and 2)	12, 13
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 (Section: Declarations, Funding)	16

*Give information separately for exposed and unexposed groups.

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.

BMJ Open

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

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

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ABSTRACT

Objectives

Comprehensive protocols are key for the planning and conduct of randomized 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.

Participants

RCT protocols approved by research ethics committees 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% (interquartile range [IQR], 63%-79%) in 2012 to 77% (IQR, 68%-82%) in 2016. However, in a pre-planned 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 organization, and investigator-sponsorship.

Conclusions

In 2012, 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.

Strengths and limitations of the study:

- We had full access to randomised clinical trial protocols from all research ethics committees in Switzerland and a convenience sample of one ethics committee in Germany and one in Canada approved in 2012 and 2016.
- The sample of trial protocols from Switzerland (n=397) was much larger than the sample from Germany (n=75) or Canada (n=77).
- The results from multivariable beta regression and logistic regression models were robust in sensitivity analyses using methods outlined *a priori* in a previously published protocol.
- All analyses were observational and any causal effect of the published SPIRIT checklist cannot be inferred.
- Included trial protocols came all from three high-income countries limiting the generalisability of the results.

Key words: Randomised clinical trials, trial protocol, reporting quality, reporting guideline adherence, meta-research

INTRODUCTION

Randomised clinical trials (RCTs) are directed by their protocol, which documents the rationale, design, and planned reporting of a trial.[1] Funding agencies, research ethics committees (RECs), regulatory agencies, medical journals, systematic reviewers and other groups rely on protocols to appraise the quality of a proposed trial.[2] With incomplete protocols reviewers typically cannot distinguish between the use of inappropriate methodology and the non-reporting of appropriate methodology. In addition, if details about the application of the trial intervention or situations with un-blinding of trial participants are lacking, the resulting uncertainty with treating clinicians may compromise the safety of trial participants. Empirical evidence from meta-research suggested numerous limitations in the reporting of RCT protocols including insufficient descriptions of treatment allocation methods, primary outcomes, sample size calculations, data analysis, and the roles of sponsors in trial design or access to data.[3-9] About half of protocols approved by French RECs, for instance, were estimated to have subsequent amendments to address deficiencies,[10] and a third of amendments submitted to RECs for industry-sponsored trial protocols could have been avoided by preparing more comprehensive protocols.[11 12]

In response, a minimum set of items to be addressed in trial protocols was developed by the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) Initiative, and published in January 2013.[13 14] Subsequently, a number of journals publishing trial protocols, funding agencies, and RECs endorsed the use of SPIRIT or related recommendations (e.g., www.swissethics.ch).[15] Researchers have applied the SPIRIT checklist to assess the quality of trial protocols with respect to patient reported outcomes,[16] statistical analyses,[17] and cluster-randomised trials with stepped wedge design.[18] However, there is no large-scale empirical study that has longitudinally evaluated the impact of the SPIRIT recommendations on the quality of reporting among RCT protocols.

The Adherence to SPIrit REcommendations (ASPIRE) study group is an international collaboration of researchers with a mandate to (i) evaluate the completeness of RCT

protocols before and after publication of the SPIRIT statement, (ii) determine trial characteristics associated with non-adherence to SPIRIT checklist items, and (iii) investigate whether the comprehensiveness of RCT protocols varies across countries.[19] In the present paper we report the results from our investigation of RCT protocols from Switzerland, CAnada, and GErmany (ASPIRE-SCAGE).

METHODS

The methods used to conduct the present study have previously been published.[19]

Identification of included trial protocols

We included trial protocols approved by RECs in 2012 or 2016 that assigned patients or groups of patients at random to one or more interventions to evaluate their effect on health outcomes. We excluded RCTs enrolling healthy volunteers, economic evaluations, animal studies, studies based on tissue samples, observational studies, studies involving only qualitative methods, and studies with a quasi-random method of allocation. The participating RECs in Switzerland (Basel, Bern, Geneva, Lausanne, St. Gallen, Thurgau, Ticino, Zurich), Germany (Freiburg) and Canada (Hamilton) approved this study or explicitly stated that no ethical approval was required. Details of the identification of included RCT protocols are presented in **Supplementary Figure 1**. The eligibility of RCT protocols was assessed independently and in duplicate. Any disagreements were resolved by discussion and consensus.

Data extraction

We used a web-based, password protected data extraction tool (http://squiekero.ch) for data collection and storage.[19 20] Researchers trained in trial methodology completed a calibration process to improve reliability, and then extracted relevant data from RCT protocols independently and in duplicate, including whether individual SPIRIT items were reported.[19] Disagreements were resolved by discussion. Due to limited resources 15% of included protocols were extracted by a single researcher (having extracted at least 100 RCT protocols

in duplicate). All researchers extracting data from RCT protocols signed confidentiality agreements and the final database contained only coded data. Our data extraction forms are provided as **Supplementary Table 1**.

Data Analysis

The outcomes of interest were the proportion of SPIRIT checklist items that were reported among our cohorts of study protocols, and the proportion of RCT protocols addressing each SPIRIT checklist item. Our primary analysis was based on a rating approach that allowed for partial credit of individually met sub-items or components of major SPIRIT items, because it keeps the hierarchical structure of the SPIRIT checklist and it independently considers all components and sub-items of all individual SPIRIT items.[19] Other rating approaches that consider major SPIRIT items only or equally consider items and sub-items, were used in sensitivity analyses. We provided descriptive statistics as frequencies and proportions for binary data and median (interquartile range, IQR) for continuous data.

To investigate whether the reporting quality of RCT protocols (as defined by the proportion of reported SPIRIT checklist items) has increased from 2012 to 2016, we conducted multivariable beta regression analysis[21] with the proportion of SPIRIT items adhered to per protocol as dependent variable and the following predefined independent variables: (i) approval year (2012 *versus* 2016), (ii) investigator sponsorship *versus* industry sponsorship, (iii) planned sample size (in increments of 1000), (iv) single centre *versus* multicentre RCTs, and (v) reported methodological support from a CRO or CTU *versus* no reported support. We included interaction terms in our model to investigate potential interactions of year of approval (2012 or 2016) with either sponsorship of protocols or reported methodological support. We performed a likelihood ratio test to check if the interaction terms improved the goodness of fit of the models. To examine in a sensitivity analysis whether the comprehensiveness of RCT protocols varied across countries we stratified the median proportion of addressed SPIRIT items per protocol by country (Switzerland, Canada, Germany), by year of approval (2012 versus 2016), and by sponsorship (investigator versus

industry), and added a country variable to the regression model. In further sensitivity analyses, we used hierarchical logistic regression (response is a binary variable indicating adherence to each SPIRIT item with clustering by protocol; i.e. independent variables were included in the model as fixed effects and the protocol as a random effect) instead of beta regression.[19] Beta regression allowed us to directly model the proportion of SPIRIT items adhered to per protocol[21], while hierarchical logistic regression allowed us to capture the variability within protocols. For all types of regression analyses we reported coefficients or odds ratios (ORs) accompanied by 95% confidence intervals (CIs). We used the statistical software R version 3.6.1 for all data analysis. All statistical tests were performed using a significance level of p=0.05.

Patient and public Involvement

No patients were involved in the study.

RESULTS

Characteristics of included trial protocols

We included 549 RCT protocols in our study; 257 from 2012 and 292 from 2016 (**Table 1**). The majority of which were individually randomised, multicentre, parallel-group, superiority trials in oncology or cardiovascular medicine, and approved by a Swiss REC. Seventy-seven RCT protocols were from Canada, and 75 from Germany. About half of the protocols were investigator-sponsored and half were industry-sponsored. In 2016 there were more investigator-sponsored protocols (162/292, 55.5%) included than in 2012 (119/257, 46.3%). In 2016 the median planned sample size was lower (199; IQR, 100-490) than in 2012 (300; IQR, 100-720). Otherwise, trial characteristics were similar between cohorts. Protocols of industry-sponsored RCTs had, on average, a larger sample size, were predominantly multinational, and more frequently placebo-controlled than those of investigator-sponsored RCTs (**Table 1**).

Table 1: Characteristics of included randomised trial protocols

Characteristics	2012			2016			Overall
	Sponsorship		Total (n=257)	Sponsorship		Total (N=292)	Total (N=549)
	Industry (N=138)	Investigator (N=119)		Industry (N=130)	Investigator (N=162)		
Planned target sample size, median (IQR)	450 (184.5, 800)	150 (63, 516)	300 (100, 720)	306.5 (150,621)	141 (70, 300)	199 (100, 490)	220 (100, 597)
Planned centres							
Single centre, No. (%)	2 (1.4%)	45 (37.8%)	47 (18.3%)	4 (3.1%)	73 (45.1%)	77 (26.4%)	124 (22.6%)
Multicentre, national, No. (%)	10 (7.2%)	30 (25.2%)	40 (15.6%)	6 (4.6%)	41 (25.3%)	47 (16.1%)	87 (15.8%)
Multicentre, multinational, No. (%)	126 (91.3%)	44 (37.0%)	170 (66.1%)	120 (92.3%)	48 (29.6%)	168 (57.5%)	338 (61.6%)
Unit of randomisation							
Individuals	137 (99.3%)	113 (95.0%)	250 (97.3%)	127 (97.7%)	158 (97.5%)	285 (97.6%)	535 (97.4%)
Clusters	0 (0.0%)	4 (3.4%)	4 (1.6%)	1 (0.8%)	3 (1.9%)	4 (1.4%)	8 (1.5%)
Body parts	1 (0.7%)	2 (1.7%)	3 (1.2%)	2 (1.5%)	1 (0.6%)	3 (1.0%)	6 (1.1%)
Study design							
Parallel	135 (97.8%)	104 (87.4%)	239 (93.0%)	127 (97.7%)	147 (90.7%)	274 (93.8%)	513 (93.4%)
Crossover	2 (1.4%)	9 (7.6%)	11 (4.3%)	2 (1.5%)	10 (6.2%)	12 (4.1%)	23 (4.2%)
Factorial	1 (0.7%)	6 (5.0%)	7 (2.7%)	1 (0.8%)	5 (3.1%)	6 (2.1%)	13 (2.4%)
Study purpose							
Superiority	110 (79.7%)	93 (78.2%)	203 (79.0%)	107 (82.3%)	132 (81.5%)	239 (81.8%)	442 (80.5%)
Non-inferiority	23 (16.7%)	19 (16.0%)	42 (16.3%)	20 (15.4%)	24 (14.8%)	44 (15.1%)	86 (15.7%)
Unclear	5 (3.6%)	7 (5.9%)	12 (4.7%)	3 (2.3%)	6 (3.7%)	9 (3.1%)	21 (3.8%)
Placebo used	77 (55.8%)	30 (25.2%)	107 (41.6%)	78 (60.0%)	41 (25.3%)	119 (40.8%)	226 (41.2%)
CTU or CRO support	93 (67.4%)	56 (47.1%)	149 (58.0%)	79 (60.8%)	83 (51.2%)	162 (55.5%)	311 (56.6%)
Country							
Switzerland	91 (66.0%)	89 (74.8%)	180 (70.0%)	86 (66.2%)	131 (80.9%)	217 (74.3%)	397 (72.3%)
Canada	21 (15.2%)	19 (16.0%)	40 (15.6%)	17 (13.1%)	20 (12.3%)	37 (12.7%)	77 (14.0%)

Germany	26 (18.8%)	11 (9.2%)	37 (14.4%)	27 (20.8%)	11 (6.8%)	38 (13.0%)	75 (13.7%)

Abbreviations: CRO, contract research organization; CTU, clinical trials unit; IQR, interquartile range.

Adherence to SPIRIT in protocols from 2012 and 2016

Overall, the median proportion of reported SPIRIT items increased from 72% (IQR, 63%-79%) in 2012 to 77% (IQR, 68%-82%) in 2016 (**Table 2, Figure 1**).

Table 2: Adherence to SPIRIT items in RCT protocols

Characteristic	2012			2016		
	Sponsorship		Total 2012 (n=257)	Sponsorship		Total 2016 (n=292)
	Industry (n=138)	Investigator (n=119)		Industry (n=130)	Investigator (n=162)	
	median (IQR)	median (IQR)	median (IQR)	median (IQR)	median (IQR)	median (IQR)
Absolute number of SPIRIT items reported per protocol (out of 33)	25.5 (23.6-26.5)	21.3 (18.3, 23.7)	23.7 (20.7, 26.2)	25.3 (23.7%-26.9)	25.0 (21.3-27.3)	25.3 (22.5-27.1)
Proportion of SPIRIT items reported per protocol	77% (72%-80%)	64% (55%-72%)	72% (63%-79%)	77% (72%-82%)	76% (64%-83%)	77% (68%-82%)

Abbreviations: IQR, interquartile range

Stratifying by sponsorship, we found that the comprehensiveness increased only in investigator-sponsored RCT protocols (adherence stratified by other study characteristics can be found in **Supplementary Table 2**). The median proportion of reported SPIRIT items in investigator-sponsored protocols increased from 64% (IQR, 55%-72%) in 2012 to 76% (IQR, 64%-83%) in 2016, while it remained unchanged at 77% for both years among industry-sponsored protocols (77%, IQR 72%-80% in 2012, and 77%, IQR 72%-82% in 2016). This pattern was consistent across countries (**Supplementary Table 3**). Sensitivity analyses using different approaches to calculate the proportion of reported SPIRIT items provided similar results (**Supplementary Table 4**).

Regarding individual SPIRIT items, we found that the improvement in investigator-sponsored RCT protocols was due to an improvement in a broad range of SPIRIT items (**Supplementary Table 5**); for 25 individual items the proportion of adherent protocols improved in investigator-sponsored RCTs by 10% or more (**Supplementary Table 6**). These 25 items included descriptive (e.g. information on study registration, protocol version & date, name & contact details of sponsor) as well as methodological aspects (e.g. comparator choice explained, or allocation concealment mechanism). The largest improvements occurred with “trial registration” (SPIRIT item 2, +41.1%), “plans to disseminate trial results to key stakeholders/publication provided” (SPIRIT item 31a, +36.7%), “description of process for making amendments” (SPIRIT item 25, +34.4%), and “declaration of interests” (SPIRIT item 28, +31.6%). In industry-sponsored protocols, adherence to individual SPIRIT items remained practically stable from 2012 to 2016, i.e. items with low adherence in 2012 remained low in 2016. SPIRIT items with particularly low adherence (< 30%) in both industry- and investigator-sponsored protocols were “names of protocol contributors/authors” (SPIRT item 5a), “research question described and justified” (SPIRIT item 6a), “eligibility criteria for study centres” (SPIRIT item 10) in applicable RCTs, “location of participant recruitment” and “estimated recruitment rate” (SPIRIT item 15), “information about who will have access to the full dataset” (SPIRIT item 29), and “description of plans for granting access to full trial protocol” (SPIRIT item 31c), (**Supplementary Table 5**).

Multivariable regression analysis

Using multivariable beta regression, we found that four characteristics were independently associated with greater reporting of SPIRIT items: multicentre RCTs (OR, 1.18; 95% CI, 1.05-1.33; p=0.006), RCTs with reported methodological support from CTUs or CROs (OR, 1.44; 95% CI, 1.31-1.57; p<0.001), industry-sponsored RCTs (OR, 1.20; 95% CI, 1.09-1.33; p<0.001), and RCTs approved in 2016 (OR, 1.33; 95% CI, 1.22-1.45; p<0.001) (**Supplementary Table 7, Figure 2**).

Adding the interaction term of year of approval and sponsorship to the model, improved the model fit (likelihood ratio test, Chisq =30.01, p<0.01) and provided evidence for a differential improvement in the adherence to SPIRIT over time (2012 vs 2016) for industry-sponsored and investigator-sponsored protocols suggesting that there was an improvement in investigator-sponsored protocols but not in industry-sponsored protocols (interaction p<0.001). We did not find evidence for an interaction between year of approval and CTU/CRO support (interaction p=0.79), i.e. protocols with or without reported support from CTUs or CROs improved to a similar extent from 2012 to 2016. Limiting our multivariable regression to investigator-sponsored protocols in an exploratory analysis, we found a notable interaction suggesting a more pronounced improvement in Swiss protocols compared with protocols from Canada or Germany (interaction p=0.032; **Supplementary Table 8**). Sensitivity analyses using hierarchical logistic regression instead of beta regression confirmed all results.

DISCUSSION

Main findings and interpretation

This study of 549 RCT protocols approved by RECs in Switzerland, Canada, and Germany before (2012) and after (2016) the publication of the SPIRIT recommendations suggested a small overall improvement in reporting comprehensiveness. This change was driven by an increase in the median proportion of reported SPIRIT items in investigator-sponsored RCTs

from 64% in 2012 to 76% in 2016. Protocols of industry-sponsored RCTs remained, on average, unchanged (median of 77% SPIRIT items reported in both years). The reporting of investigator-sponsored protocols improved for the majority of individual SPIRIT items, and was independent of the planned sample size, reported support from a CTU or CRO, and centre status (single- vs multicentre) of RCTs. Single centre status, no reported support from a CTU or CRO, investigator sponsorship, and approval in 2012 were independently associated with lower adherence to the SPIRIT checklist. These results were similar across countries, but the improvement in investigator-sponsored RCT protocols appeared more pronounced among Swiss protocols compared with protocols approved in Canada or Germany. SPIRIT items with particularly low adherence in investigator- and industry sponsored protocols concerned the names of protocol contributors/authors, the justification of the research question, details about the planned participant recruitment, information about who will have access to the full dataset, and plans for granting access to the full trial protocol.

Our findings suggest an international improvement in the comprehensiveness of investigator-sponsored RCT protocols probably due to a combination of reasons including the publication of the SPIRIT checklist and its implementation by research institutions, funding agencies, and medical journals; the ongoing discussion about the importance of protocol publication, thoughtful planning of RCTs, and minimising reporting biases in the scientific community; and efforts to teach RCT methodology to clinician scientists in under- and postgraduate courses. The more pronounced improvement of Swiss investigator-sponsored protocols could be related to a SPIRIT-based protocol template and guidance provided by swissethics [22] that were particularly welcomed by academic researchers or other changes in the context of the new Swiss legislation on human research from 2014.

Strengths and limitations

Strengths of our study include full access to RCT protocols and associated documents from RECs in three countries. We used standardized methods and procedures for data extraction and protocol assessment at all RECs and involved only trained methodologists in this

process. This included use of piloted extraction forms with detailed written instructions as well as calibration exercises with all data extractors. More than 95% of included protocols approved in 2012 and over 80% of protocols approved in 2016 were extracted independently and in duplicate. To minimise chance associations, we considered only a limited number of variables in our statistical models.[23] Our results proved robust in sensitivity analyses applying alternative assumptions and statistical approaches. The fact that all Swiss RECs participated in this study strengthens the representativeness of our data for Switzerland and the additional inclusion of a German and a Canadian REC allowed for an international comparison to some extent.

Our study has several limitations. First, we used a convenience sample of two RECs outside of Switzerland (Freiburg in Germany, Hamilton in Canada) but we cannot be certain if they are representative of other RECs in these or other countries. Second, we used RCT protocols that had already been approved by RECs, therefore SPIRIT items such as "research ethics approval" and "consent forms provided" were always fulfilled and could not discriminate more comprehensive from less comprehensive protocols. Third, although we had adequate statistical power to detect even interactions within the subgroup of investigator-sponsored protocols, the number of included protocols approved outside of Switzerland was relatively small (28%; 152/549), limiting the precision of estimates for German and Canadian protocols. Fourth, 15% of included protocols were not evaluated in duplicate which could have increased the risk of bias in our study. However, these protocols were from different RECs in Switzerland and they were handled by one of the two most experienced data extractors only, so we feel that a relevant increase in the risk of bias is unlikely. Fifth, we are not aware of the fact that any of the participating RECs explicitly endorsed SPIRIT guidance, however, in Switzerland a new protocol template provided by swissethics became available which was influenced by SPIRIT impacting the generalisability of our results. In addition, it remains unclear to what extent our findings can be extrapolated to trial protocols from middle- or low-income countries and to protocols from medical disciplines underrepresented in our sample (e.g. dentistry or geriatrics; **Supplementary**

Table 9). Finally, our findings are not proof of causality due to the observational nature of this study, however, it is plausible that the publication of the SPIRIT statement at least contributed to an increase in the comprehensiveness of investigator-sponsored protocols. Investigations of a potential time trend with gradually increasing comprehensiveness of investigator-sponsored protocols by year tertiles did not suggest a continuous development, but rather a one-step-effect (**Supplementary Figure 2**).

Comparison with other studies

Few studies in the literature have used[16] or planned to use[17 18 24] the SPIRIT checklist as a tool to assess the comprehensiveness of trial protocols. One study investigated 75 RCT protocols from the UK National Institute for Health Research (NIHR) Health Technology Assessment (HTA) programme on the reporting of patient-reported outcomes and the association with general protocol completeness according to SPIRIT.[16] They found that these investigator-sponsored UK RCT protocols from 2012 and 2013 reported, on average, 63% of SPIRIT checklist items, which is very similar to our findings for investigator-sponsored RCT protocols from 2012. Apart from the ongoing study using protocols from UK RECs (ASPIRE-UK[19]), we are not aware of any other study evaluating the comprehensiveness of RCT protocols before and after the publication of the SPIRIT statement in industry- and investigator-sponsored protocols.

There are studies assessing the quality of RCT protocols using measures other than the SPIRIT checklist. An analysis of drug trial protocols submitted to three Dutch RECs in 2010/11 focused on critical comments by RECs.[25] They found that applicants of investigator-sponsored trials received more critical comments on participant selection, methodology, and statistical analysis than applicants of industry-sponsored trials, resonating with our findings of less comprehensive investigator-sponsored protocols compared with industry protocols in 2012. Similarly, studies by Getz et al. used the proportion of protocols with substantial amendments as a measure of RCT protocol quality in the industry setting showing that more comprehensive protocols could have prevented amendments.[11 12] Finally, a study of 596

published RCT protocols from 2001 to 2011 assessed protocol quality (high versus low) based on reporting of the allocation method, allocation concealment, and intention-to-treat analysis.[26] This study found a substantial improvement in some methodological aspects of protocols (e.g. allocation concealment), but acknowledged the overall low proportion of high quality protocols with 24% in 2001-2004, 31% in 2005-2008, and 37% in 2008-2011.

Implications

Incomplete protocols may jeopardize the clinical research process at all stages with potentially harmful consequences for patients, decision-makers in health care, the scientific community, and society as a whole. Whether there is indeed an association between better reported or more comprehensive RCT protocols and better methodology, successful trial conduct, and/or publication of RCTs remains to be established. Based on the RCT sample of this study, we will examine the relationship between completeness of RCT protocols and risks for premature discontinuation or non-publication of RCTs as well as potential improvements between 2012 and 2016 in terms of fewer trial discontinuations and non-publications particularly for investigator-sponsored RCTs in subsequent investigations [19].

Our results show improvement in the reporting quality of investigator-sponsored trial protocols such that they became consistent with industry protocols. About why industry protocols have not improved according to SPIRIT between 2012 and 2016, we can only speculate. It might be that routines and processes for writing trial protocols have been well established at companies earlier explaining our finding of consistently low adherence to specific SPIRIT items in 2012 and 2016 in industry-sponsored protocols. So, as long as regulators do not make specific protocol templates mandatory for all applicants, industry may not adapt routines and templates according to SPIRIT.

Our finding of insufficient reporting of names of protocol contributors/authors, the justification of the research question, details about the planned participant recruitment, information about who will have access to the full dataset, and plans for granting access to the full trial protocol guides involved stakeholders with respect to further needs for protocol improvement. The

identified items constitute important pieces of information to enable a valid assessment of the relevance, feasibility, and transparency of planned clinical trials.

Conclusions

This before-and-after study suggests that the comprehensiveness of investigator-sponsored RCT protocols from Switzerland, Canada, and Germany improved after publication of the SPIRIT checklist, achieving a similar reporting quality as industry-sponsored protocols. Single centre status, no reported support from a CTU or CRO, investigator sponsorship, and approval in 2012 were independently associated with lower adherence to SPIRIT. Further means are needed to improve the reporting of RCT protocols particularly with respect to protocol authorship, justification of the research question, participant recruitment, access to the full dataset, and plans for granting access to the full trial protocol. Future research should clarify the relationship between protocol quality and success of subsequent trial conduct and publication.

DECLARATIONS

Ethics approval and consent to participate: All participating ethics committees are project partners.

Consent for publication: Not applicable.

Availability of data and material: Data underlying this article will be shared on reasonable request to the corresponding author

Data access, responsibility, and analysis: DG had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Competing interests: BvN is currently employed by Roche Pharma AG, Grenzach-Wyhlen, Germany. BK is currently employed by iOMEDICO AG, Freiburg, Germany. All other authors declare no financial relationships with any organization that might have an interest in the

submitted work and no other relationships or activities that could appear to have influenced the submitted work.

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Authors' contributions: AO, SH, EvE, BK, and MB conceived of the study. EvE and MB acquired funding. RS developed the web-tool for data extractions. DG, BvN, BS, and MB coordinated data extraction from protocols. DG, GM and MB developed the data analysis plan and interpreted the data. DG performed the data analysis. MB and DG wrote the first draft of the manuscript. DG, BvN, BS, BK, EOR, AB, StS, DM, YT, AA, CPM, VG, KB, KKu, LR, SIL, JM, AN, KKl, NG, ATH, JW, NC, PJHH, KMC, SiS, JWB, ArA, MS, LH, SH, KW, EvE and MB were involved in data collection and critically revised the manuscript. All authors approved the final version before submission.

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Authors' information (optional): Not applicable

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Figure Legends

Figure 1: Proportion of reported SPIRIT items by year and trial sponsorship

Figure 2: Association between comprehensiveness of trial protocols and trial characteristics, accessed by multivariable beta regression

Abbreviations: CTU, Clinical Trials Unit; CRO, Contract Research Organization; CI, confidence interval. * Interaction terms were added to the multivariable model one at a time.

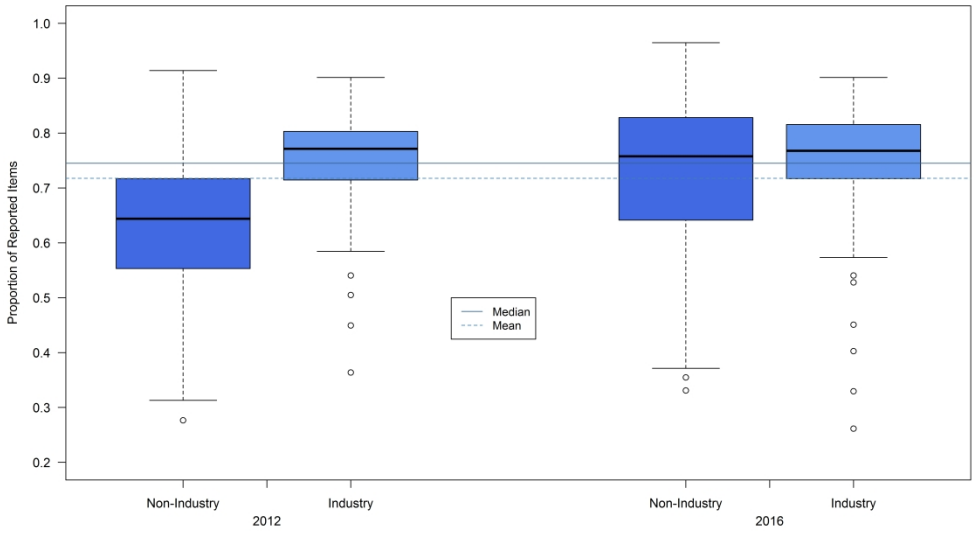
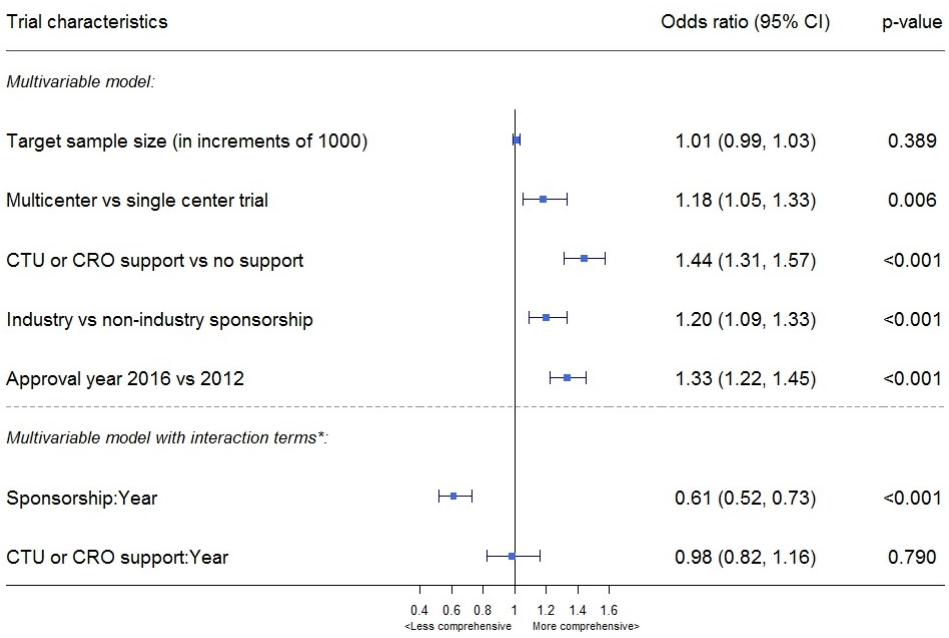


Figure 1: Proportion of reported SPIRIT items by year and study sponsorship

330x203mm (500 x 500 DPI)



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

Supplementary material

1. **Supplementary Figure 1: "**Flow diagram for included randomised clinical trial protocols in ASPIRE with ethics approval in 2012 and 2016 from Switzerland, Germany, and Canada**"**
2. **Supplementary Figure 2:** Box-plots of proportions of reported SPIRIT items by year and tertile in investigator-sponsored protocols
3. **Supplementary Table 1:** Data Extraction Form
4. **Supplementary Table 2:** Adherence to SPIRIT items in RCT protocols by approval year and median target sample size, multicentre vs single centre trials, and with vs without CTU or CRO support
5. **Supplementary Table 3:** Adherence to SPIRIT items in RCT protocols by country and sponsorship
6. **Supplementary Table 4:** Sensitivity analyses of calculating the adherence to SPIRIT items for RCT protocols by sponsorship
7. **Supplementary Table 5:** Adherence to individual SPIRIT items by year and sponsorship
8. **Supplementary Table 6:** Adherence to SPIRIT items in Investigator-sponsored protocols that improved by 10% or more
9. **Supplementary Table 7:** Results from multivariable Beta and Logistic regressions for all approaches
10. **Supplementary Table 8:** Results from multivariable Beta regression, subset of Investigator-sponsored protocols
11. **Supplementary Table 9:** Medical disciplines of included RCTs

Supplementary Figure 1

Figure 1A: Flow diagram for included randomized clinical trial protocols in ASPIRE with ethics approval in 2012

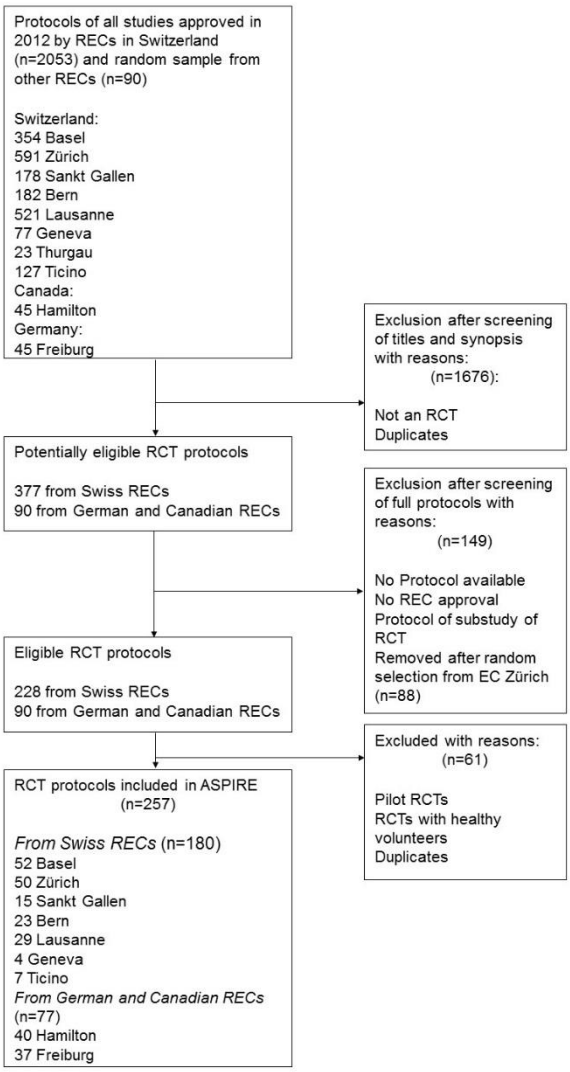
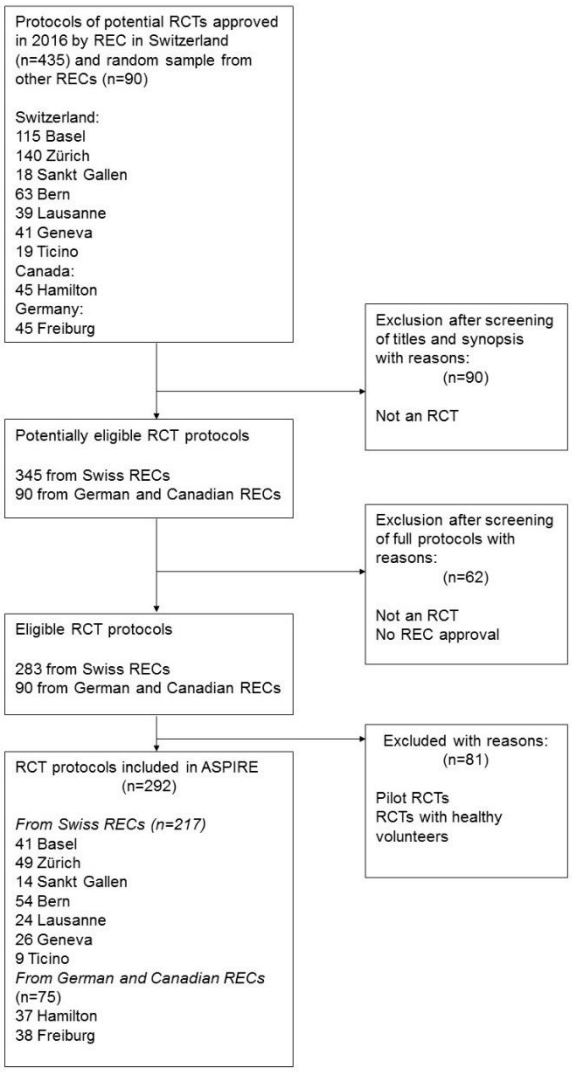


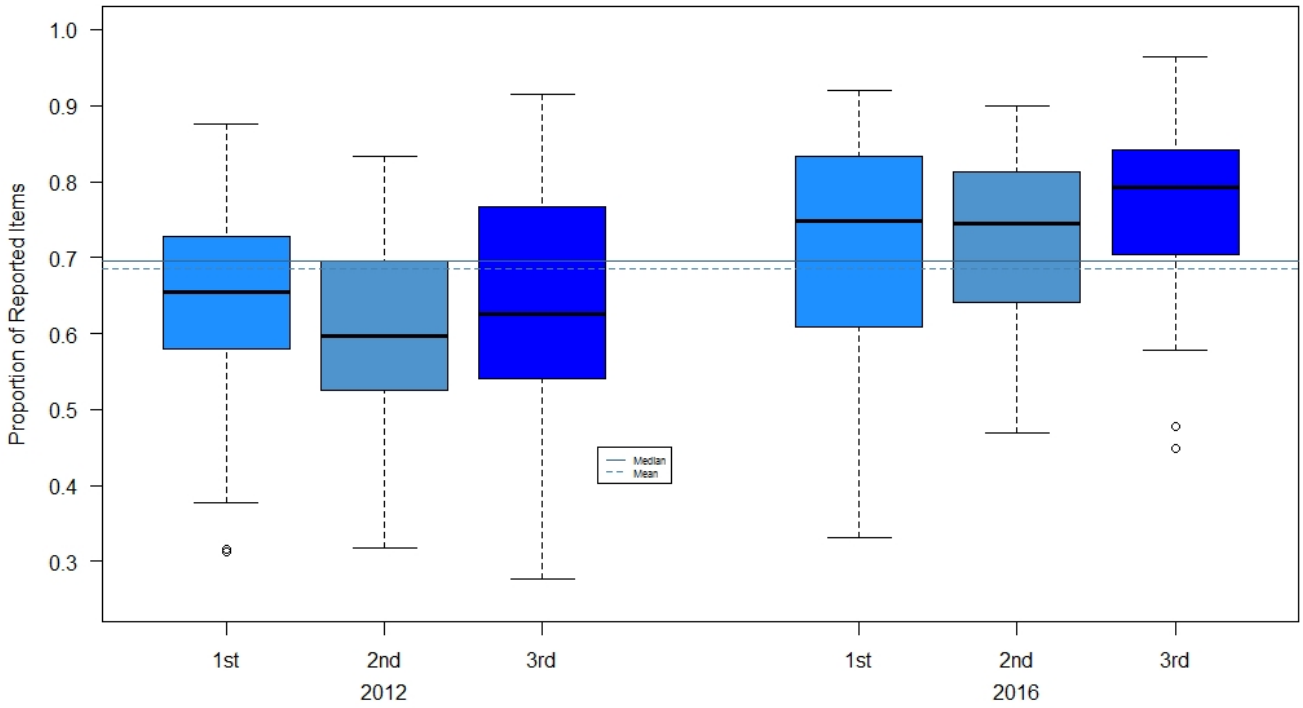
Figure 1B: Flow diagram for included randomized clinical trial protocols in ASPIRE with ethics approval in 2016



Abbreviations: REC: Research Ethic Committee; RCT: Randomised clinical trial

Legend Supplementary eFigure 1: Flow diagram for included randomised clinical trial protocols in ASPIRE with ethics approval in 2012 and 2016 from Switzerland, Germany, and Canada

Supplementary Figure 2



Legend Supplementary eFigure 2: Box-plots of proportions of reported SPIRIT items by year and tertile in investigator-sponsored protocols

Supplementary Table 1

Data Extraction Form

Label	Options
1. Country of Ethics Committee	
2. Name of Ethics Centre	
3. Local Ethics Identification Number	
4. Sponsor name (title, first name, surname, company if applicable)	
5. Sponsor email address	
6. Site/Location of overall study initiation (PI affiliation)	Switzerland
	Other
	Not reported
If site initiation in Switzerland, please provide name and location of institution:	
7. Study Acronym	
8. Study Title (Exact Quote)	
9. Date of Ethics Application	
9a. Date of first RESPONSE by Ethics Committee (does not need to be the same as approval date)	
9b. Response category (Switzerland specific, others select "not applicable")	A positiv
	B positiv mit Bemerkung
	C mit Auflage, Nachbegutachtung notwendig
	C mit Auflage, schriftliche Mitteilung ausreichend
	D negativ
	E Nicht-Eintreten
	Not applicable as Ethics Committee not in Switzerland
10. Date of first APPROVAL by Ethics Committee	
11. Clinical Area	Medical
	Surgical
	Paediatrics
	Other
If medical area, choose from list	Neurology
	Cardiovascular
	Respiratory
	Gastro/intestinal
	Nephrology
	Rheumatology
	Infectious Disease
	Oncology
	Intensive Care
	Hematology

	Endocrinology
	Dermatology
	Anaesthetics
	Psychiatry
	Other
If surgical area, choose from list	General Surgery
	Obstetrics/Gynecology
	Neurosurgery
	Ophthalmology
	Ear-nose-throat (ENT)
	Cardiothoracic
	Urology
	Orthopedics
	Plastic Surgery
	Other
If pediatrics area, choose from list	Neurology
	Cardiovascular
	Respiratory
	Gastro/intestinal
	Nephrology
	Rheumatology
	Infectious diseases
	Oncology
	Intensive care
	Hematology
	Endocrinology
	Dermatology
	Anaesthetics
	General surgery
	Neurosurgery
	Ophthalmology
	Ear-nose-throat (ENT)
	Cardiothoracic
	Urology
	Orthopedics
	Plastic Surgery
	Other
12. Trial Registration Number	
13. Trial Registry Name	Clinicaltrials.gov
	ISRCTN
	EudraCT
	ANZCTR
	Not reported
	Other (please specify)
14. Swiss Human Research Act Risk Category	A

	B
	C
	Not applicable
	Not reported
15. Is trial labelled as pilot or feasibility trial?	Yes
	No
16. Is it a dose finding trial?	Yes
	No
17. Hypothesis (check all that apply)	Superiority
	Non-inferiority / Equivalence
	Not labelled in this regard / unclear
18. Please copy the primary outcome(s) from the protocol	
19. Are any outcomes specifically labelled as “adverse events”, “adverse effects”, “side effects”, or "tolerability"?	Yes
	No
If yes, adverse events (or synonyms thereof) are...	not further specified (e.g. the term adverse events is just mentioned under outcome section)
	specifically defined (e.g. specific types of adverse events such as rash, itching, nausea etc. are mentioned)
20. Is a patient-reported outcome specified (an outcome that comprises information reported by a patient or a caregiver (parent or guardian))?	Yes
	No
If yes: the specified patient-reported outcome captures the following information (check all that apply):	Symptoms (pain, headaches, sleeplessness, etc.)
	Physical functioning
	Mental/emotional functioning
	Social functioning
	Disease-specific outcome measure (eg. Asthma QoL questionnaire, Beck Depression Inventory)
	Multidimensional health-related quality of life (HRQL; eg. SF-36)
	Overall sense of well-being in one question (holistic HRQL; eg. captured with a VAS)
	Satisfaction with treatment

	Utility (an individual's preferences/values for certain health states/outcomes)
	Other (please specify)
If yes: patient-reported outcome + measurement instrument	
If yes, patient-reported outcome used for sample size calculation?	Yes
	No
If yes, minimal important difference (MID) mentioned?	Yes
	No
If yes, reference for MID? (please enter full citation or if not reported, enter "NR")	
20a. Is routinely collected data used in the study?	Yes
	No
20b. If yes, routinely collected data is used:	For patient identification and/or recruitment?
	As part of the randomized intervention?
	For any of the planned outcomes?
	Other
21. Any planned collection of costs or cost-effectiveness analysis mentioned?	Yes
	No
22. The setting for the majority of recruited patients is (check all that apply)	Community
	Outpatient clinic
	Emergency department
	In-patients hospital care
	Intensive care unit
	Unclear
23. The age-group of patient population is (check all that apply)	Adults (>=16 years)
	Only elderly (>=60)
	Pediatric (<18)
24. Please specify the study population	
25. Estimated sample size/number of participants	
26. Number of overall study centres	
27. If multicentre, national or multinational	National
	International
	Not applicable
28. Number of study centres recruiting in Switzerland (or Canada/Germany if applicable)	
29. Trial Design (check all that apply)	Parallel
	Crossover
	Cluster
	Factorial
	Split Body
	Other

	Not applicable
30. Number of trial arms	
31. Presence of logistic/ methodological support/experience? (check all that apply)	Clinical trial unit (CTU)
	Contract Research Organization (CRO)
	Evidence for ample expertise of the PI/Institution
	Not reported
	Other
32. Please specify the intervention(s)	
33. Intervention category/ies	Drug
	Surgery / Invasive Procedure
	Device
	Vaccine
	Radiation
	Rehabilitation
	Behavioural / Lifestyle / Education / Counselling
	Dietary Supplement
	Other
34. Please specify the control(s)	
35. Type of control(s)	No treatment / Standard care
	Active (drug/other treatment)
	Placebo / Sham
36. Name of funder(s)	
37. Initiation/Sponsorship	Definitely industry initiated
	Probably industry initiated
	Probably investigator initiated
	Definitely investigator initiated
38. Title: Basic study design, patient population, and intervention provided in study title (if applicable trial acronym)? (reporting)	Yes
	No
39. Trial Registration: Registry name and trial identifier provided? (reporting)	Yes
	No
40. Protocol: Version Number and date provided? (reporting)	Yes
	No
41. Funding: Sources of financial and non-financial support declared? (reporting)	Yes
	No
42. Roles and Responsibilities: Names of protocol contributors/ authors provided? (reporting)	Yes
	No
	Yes

43. Roles and Responsibilities: Name and contact details of sponsor provided? (reporting)	No
44. Roles and Responsibilities: Role of sponsor and funder in trial described? (reporting)	Yes
	No
45. Roles and Responsibilities: Steering Committee General Membership and Role described? (reporting)	Yes
	No
	Not applicable
46. Background and rationale: Is research question described and justified? (as a minimum, we expect a systematic search, see info) (reporting)	Yes
	No
46a. Systematic review on PICO explicitly mentioned in background/introduction?	Yes
	No
47. Background and rationale: Comparator choice explained? (reporting)	Yes
	No
48. Objectives: Specific objectives described for each comparison (if multiple)? (reporting)	Yes
	No
49. Trial design: Trial design described? (trial type (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)) (reporting)	Yes
	No
50. Study Setting: Are countries where data will be collected listed? (reporting)	Yes
	No
51. Eligibility criteria: Inclusion and exclusion criteria for trial participants described? (reporting)	Yes
	No
52. Eligibility criteria: Inclusion and exclusion criteria for study centres and individuals who will perform the intervention described? (reporting)	Yes
	No
	Not applicable
53. Intervention(drug): Generic Name, Dose and Schedule of intervention described? (reporting)	Yes
	No
	Not applicable
54. Intervention(non-drug): Setting of intervention administration described? (reporting)	Yes
	No
	Not applicable
55. Intervention(non-drug): Individuals administering interventions (e.g. expertise) mentioned? (reporting)	Yes
	No
	Not applicable
56. Interventions - Modifications: Standard criteria for modifications of interventions described? (reporting)	Yes
	No
	Not applicable
57. Interventions - Adherence: Are strategies to improve adherence or any procedures for monitoring adherence described? (reporting)	Yes
	No
	Not applicable
58. Interventions - Concomitant care: Permitted care and interventions during trial described? (reporting)	Yes
	No
59. Primary Outcome: Specific measurement variable described? (reporting)	Yes
	No
	Not applicable
	Yes

60. Primary Outcome: Analysis metric (e.g. change from baseline) described? (reporting)	No
	Not applicable
61. Primary Outcomes: Is time point of measurement mentioned? (reporting)	Yes
	No
	Not applicable
62. Participant timeline: Timing of visit for participants described (e.g. schematic diagram)? (reporting)	Yes
	No
63. Sample size: Estimated number total or per group mentioned? (reporting)	Yes
	No
64. Sample size: Outcome used for samples size calculation described? (reporting)	Yes
	No
	Not applicable
65. Sample size: Assumed values for outcome in each study group provided? (reporting)	Yes
	No
	Not applicable
66. Sample size: Rationale or reference for assumed outcome values provided? (reporting)	Yes
	No
	Not applicable
67. Sample size: Type of statistical test provided? (reporting)	Yes
	No
	Not applicable
68. Sample size: Alpha value provided? (reporting)	Yes
	No
	Not applicable
69. Sample size: Statistical Power provided? (reporting)	Yes
	No
	Not applicable
70. Sample size: Adjustment for missing data, if relevant, described? (reporting)	Yes
	No
	Not applicable
71. Sample size: Rationale for intended sample size if not derived statistically provided? (reporting)	Yes
	No
	Not applicable
72. Recruitment: Location of participant recruitment described? (reporting)	Yes
	No
73. Recruitment: Person(s) who will recruit participants described? (reporting)	Yes
	No
74. Recruitment: Expected recruitment rate provided? (reporting)	Yes
	No
75. Recruitment: Estimated number or rate of eligible patients	
76. Recruitment: Estimated duration of the patient recruitment	
77. Recruitment: Monitoring of recruitment during trial mentioned? (reporting)	Yes
	No
78. Recruitment: Financial and non-financial incentives for participants described? (reporting)	Yes
	No

	Not applicable
79. Recruitment: Financial and non-financial incentives for investigators described? (reporting)	Yes
	No
80. Allocation: Method for generation of random sequence described? (e.g. computer-generated random numbers) (reporting)	Yes
	No
	Not applicable
81. Allocation: Ratio provided? (e.g. 1:1, 2:1) (reporting)	Yes
	No
	Not applicable
82. Allocation: Type of randomization described? (e.g. "simple", block, matched pair, etc.) (reporting)	Yes
	No
	Not applicable
83. Allocation: Non-random allocation-method described? (reporting)	Yes
	No
	Not applicable
84. Allocation: Rationale for non-random allocation provided? (reporting)	Yes
	No
	Not applicable
85. Allocation: Allocation concealment mechanism described? (reporting)	Yes
	No
	Not applicable
86. Allocation: Person who will enroll/assign participants described? (reporting)	Yes
	No
	Not applicable
87. Blinding: Status of participants described? (reporting)	Yes
	No
88. Blinding: Status of care providers described? (reporting)	Yes
	No
89. Blinding: Status of outcome assessors described? (reporting)	Yes
	No
90. Blinding: Conditions when unblinding is permissible mentioned? (reporting)	Yes
	No
	Not applicable
91. Data Collection: Personnel who will collect data specified? (reporting)	Yes
	No
92. Data collection: Strategies to promote participant retention and complete follow-up described? (reporting)	Yes
	No
93. Data Management: Data entry and coding processes described? (reporting)	Yes
	No
94. Statistical Methods: Main analysis for primary outcome including analysis methods for statistical comparisons described? (reporting)	Yes
	No
95. Statistical Methods: Handling of missing data defined? (reporting)	Yes
	No
	Not applicable
	Yes

96. Statistical Methods: Effect measure for primary analysis clearly specified? (e.g. risk ratio, odds ratio etc.) (reporting)	No
97. Statistical Methods: Significance level specified? (e.g. alpha of 5% or p<0.05) (reporting)	Yes
	No
98. Statistical Methods: Use of confidence intervals mentioned? (e.g. "results will be accompanied by a confidence interval") (reporting)	Yes
	No
99. Statistical Methods: Definition of subgroup categories provided? (reporting)	Yes
	No
	Not applicable
100. Any subgroup analysis mentioned (this question triggers a set of questions for a subproject independent of SPIRIT)?	Yes
	No
If yes, is it explicitly mentioned that subgroup analyses are exploratory?	Yes
	No
If yes, is a clear hypothesis for a subgroup effect pre-specified?	Yes
	No
If yes, is a clear hypothesis with a direction of subgroup effect pre-specified?	Yes
	No
If yes, use of interaction test for subgroup analysis mentioned?	Yes
	No
If yes, please list planned subgroup variables	
If yes, please list planned outcomes for subgroup analyses	
If yes, please specify number of subgroup analyses planned (=SG variables x outcomes)	
If yes, subgroup analysis considered in sample size calculation?	Yes
	No
101. Statistical Methods: Does the protocol define which participants will be included in the main analysis in terms of protocol adherence and missing data? (reporting)	Yes
	No
102. Data Monitoring Committee: Is a data monitoring committee planned for this study?	Yes
	No
103. Data Monitoring Committee: Is it explicitly reported whether a DMC is planned or why it is not planned? (reporting)	Yes
	No
104. Data Monitoring: Planned number of interim analyses	
105. Data Monitoring: Purpose of interim analyses (check all that apply)	Benefit
	Harm
	Futility
	Sample size recalculation
	No reason provided
	Not applicable
	Other
106. Data Monitoring: Reported who has ultimate authority to stop the trial? (reporting)	Yes
	No
107. Data Monitoring: Does the sponsor retain the right to stop the trial?	Yes
	No
	Not reported
If yes, explicitly at any time for any reason?	Yes
	No

108. Harms: Plans for collecting, assessing, reporting, managing anticipated/unanticipated adverse events provided? (reporting)	Yes
	No
109. Auditing: Procedures of audits and/or external monitoring described (e.g. clinical trial unit/CROs)? (reporting)	Yes
	No
	Not applicable
110. Research Ethics Approval: Where approval has been obtained, or plans for seeking approval, provided? (should always be yes in this study) (reporting)	Yes
	No
111. Protocol Amendments: Process for making amendments described? (reporting)	Yes
	No
112. Consent or Assent: Informed Consent process described? (reporting)	Yes
	No
113. Consent or Assent – Ancillary Studies: Process to obtain additional consent for collection and use of data and biological specimens described? (reporting)	Yes
	No
	Not applicable
114. Confidentiality: Described how data will be collected, kept secure, and maintained during the trial? (reporting)	Yes
	No
115. Declaration of Interests: Financial and other competing interests clearly stated? (reporting)	Yes
	No
116. Access to data: Is it clearly mentioned who will have access to full dataset after trial completion? (reporting)	Yes
	No
117. Ancillary and post-trial care: Any plans to provide or pay for ancillary care during the trial provided? (reporting)	Yes
	No
118. Dissemination Policy: Plans to disseminate trial results to key stakeholders/publication provided? (reporting)	Yes
	No
119. Dissemination Policy: Does the protocol mention any rules/regulations between the investigators and the sponsor with respect to the rights of publication of the trial results? (reporting)	Yes
	No
	Not applicable
If yes, please copy the corresponding statement from the protocol	
If yes, which statement suits best?	Only the sponsor retains the right to analyze and publish the data (no cooperation with investigators at all)
	The sponsor retains the right to approve any manuscript/abstract before publication (sponsor retains explicitly the right to reject submission for publication)
	The sponsor retains at least the right to review and comment on any manuscript/abstract before publication

	Free publication rights for the investigators, no constraints at all by the sponsor (sponsor has explicitly NOT the right to reject the submission for publication)
	Protocol refers to a separate publication agreement between sponsor and investigator
	Other (Please enter description for other)
120. Dissemination Policy: Authorship eligibility criteria described?	Yes
	No
121. Dissemination Policy: Plans for granting access to full trial protocol provided? (reporting)	Yes
	No
122. Informed Consent Materials: Model consent and/or assent forms provided (e.g in Appendix)? (reporting)	Yes
	No
123. Biological Specimens: Details of specimen collection provided? (reporting)	Yes
	No
	Not applicable
124. Any comments?	

Supplementary Table 2: Adherence to SPIRIT items in RCT protocols by approval year and median target sample size, multicentre vs single centre trials, and with vs without CTU or CRO support.

Characteristic	2012				2016			
	median (IQR)	mean (SD)	median (IQR)	mean (SD)	median (IQR)	mean (SD)	median (IQR)	mean (SD)
	Sample size <= 220 (n=117)		Sample size > 220 (n=140)		Sample size <= 220 (n=158)		Sample size > 220 (n=134)	
Frequency of items per protocol	21.75 (18.25, 24.79)	21.13 (4.85)	24.92 (22.81, 26.42)	24.33 (2.98)	25.04 (22.17, 27.06)	23.98 (4.38)	25.33 (23.06, 27.06)	24.88 (3.21)
Proportion of items per protocol	0.66 (0.55, 0.75)	0.64 (0.15)	0.76 (0.69, 0.80)	0.74 (0.09)	0.76 (0.67, 0.82)	0.73 (0.13)	0.77 (0.70, 0.82)	0.75 (0.10)
	Single centre trial (n=47)		Multicentre trial (n=210)		Single centre trial (n=77)		Multicentre trial (n=215)	
Frequency of items per protocol	18.79 (16.00, 22.67)	19.04 (5.03)	24.42 (21.75, 26.25)	23.73 (3.53)	24.67 (20.00, 27.17)	23.09 (5.08)	25.25 (23.29, 27.04)	24.87 (3.28)
Proportion of items per protocol	0.57 (0.48, 0.69)	0.58 (0.15)	0.74 (0.66, 0.80)	0.72 (0.11)	0.75 (0.61, 0.82)	0.70 (0.15)	0.77 (0.71, 0.82)	0.75 (0.10)
	No CTU or CRO support (n=108)		CTU or CRO support (n=149)		No CTU or CRO support (n=130)		CTU or CRO support (n=162)	
Frequency of items per protocol	21.71 (18.31, 24.19)	20.92 (4.71)	24.92 (22.58, 26.42)	24.29 (3.22)	24.08 (20.21, 26.25)	22.92 (4.33)	26.12 (23.92, 27.65)	25.59 (3.05)
Proportion of items per protocol	0.66 (0.55, 0.73)	0.63 (0.14)	0.76 (0.68, 0.80)	0.74 (0.10)	0.73 (0.61, 0.80)	0.69 (0.13)	0.79 (0.72, 0.84)	0.78 (0.09)

Abbreviations: SPIRIT, Standard Protocol Items: Recommendations for Interventional Trials; RCT, randomised clinical trial; CTU, clinical trials unit; CRO, contract research organization; IQR, interquartile range; SD, standard deviation

Supplementary Table 3: Adherence to SPIRIT items in RCT protocols by country and sponsorship

Characteristic	2012						2016					
	Sponsorship				Total 2012 (n=257)		Sponsorship				Total 2016 (n=292)	
	Industry (n=138)		Investigator (n=119)				Industry (n=130)		Investigator (n=162)			
	median (IQR)	mean (SD)	median (IQR)	mean (SD)	median (IQR)	mean (SD)	median (IQR)	mean (SD)	median (IQR)	mean (SD)	median (IQR)	mean (SD)
Switzerland	Industry (n=91)		Investigator (n=89)		Total 2012 (n=180)		Industry (n=86)		Investigator (n=131)		Total 2016 (n=217)	
Frequency of items per protocol	26.08 (24.71, 27.08)	25.52 (2.71)	21.42 (18.33, 24.25)	20.99 (4.61)	24.49 (21.15, 26.44)	23.28 (4.39)	25.98 (24.35, 27.08)	25.25 (3.05)	26.08 (22.50, 27.67)	24.81 (4.02)	26.04 (23.50, 27.33)	24.98 (3.67)
Proportion of items per protocol	0.79 (0.75, 0.82)	0.77 (0.08)	0.65 (0.56, 0.74)	0.64 (0.14)	0.74 (0.64, 0.80)	0.71 (0.13)	0.79 (0.74, 0.82)	0.77 (0.09)	0.79 (0.68, 0.84)	0.75 (0.12)	0.79 (0.71, 0.83)	0.76 (0.11)
Germany	Industry (n=26)		Investigator (n=11)		Total 2012 (n=37)		Industry (n=27)		Investigator (n=11)		Total 2016 (n=38)	
Frequency of items per protocol	24.58 (22.96, 25.75)	24.36 (1.88)	19.50 (17.17, 23.54)	19.28 (5.14)	24.17 (21.92, 25.08)	22.85 (3.92)	23.92 (22.38, 25.25)	22.74 (4.21)	22.42 (19.38, 24.63)	22.07 (3.76)	23.58 (21.09, 25.21)	22.55 (4.04)
Proportion of items per protocol	0.75 (0.70, 0.78)	0.74 (0.06)	0.59 (0.52, 0.71)	0.58 (0.16)	0.73 (0.66, 0.76)	0.69 (0.12)	0.73 (0.68, 0.77)	0.69 (0.13)	0.68 (0.59, 0.75)	0.67 (0.11)	0.72 (0.64, 0.76)	0.68 (0.12)
Canada	Industry (n=21)		Investigator (n=19)		Total 2012 (n=40)		Industry (n=17)		Investigator (n=20)		Total 2016 (n=37)	
Frequency of items per protocol	22.83 (21.42, 24.42)	22.56 (2.70)	19.42 (18.17, 22.29)	19.48 (3.45)	21.75 (19.22, 23.15)	21.10 (3.41)	25.92 (23.67, 27.08)	25.37 (1.93)	20.04 (17.98, 23.65)	20.71 (4.45)	23.67 (20.00, 26.00)	22.85 (4.20)
Proportion of items per protocol	0.69 (0.65, 0.74)	0.68 (0.08)	0.59 (0.55, 0.68)	0.59 (0.10)	0.66 (0.58, 0.70)	0.64 (0.10)	0.79 (0.72, 0.82)	0.77 (0.06)	0.61 (0.55, 0.72)	0.63 (0.14)	0.72 (0.61, 0.79)	0.69 (0.13)

Abbreviations: SPIRIT, Standard Protocol Items: Recommendations for Interventional Trials; RCT, randomised clinical trial; IQR, interquartile range; SD, standard deviation

Supplementary Table 4: Sensitivity analyses of calculating the adherence to SPIRIT items for RCT protocols by sponsorship

Characteristic	2012						2016					
	Industry-sponsored (n=138)		Investigator-sponsored (n=119)		Total 2012 (n=257)		Industry-sponsored (n=130)		Investigator-sponsored (n=162)		Total 2016 (n=292)	
	median (IQR)	mean (SD)	median (IQR)	mean (SD)	median (IQR)	mean (SD)	median (IQR)	mean (SD)	median (IQR)	mean (SD)	median (IQR)	mean (SD)
Major Item approach (simple) NA=0												
Frequency of items per protocol	18.00 (17.00, 20.00)	18.04 (2.99)	13.00 (11.00, 16.00)	13.48 (4.27)	17.00 (13.00, 19.00)	15.93 (4.29)	18.00 (16.00, 20.00)	18.12 (3.44)	17.00 (14.00, 19.00)	16.40 (4.08)	18.00 (15.00, 20.00)	17.16 (3.89)
Proportion of items per protocol	0.56 (0.52, 0.61)	0.55 (0.09)	0.42 (0.33, 0.50)	0.41 (0.13)	0.52 (0.41, 0.58)	0.49 (0.13)	0.56 (0.50, 0.62)	0.56 (0.10)	0.53 (0.42, 0.59)	0.51 (0.12)	0.55 (0.47, 0.61)	0.53 (0.12)
Major Item approach (simple) NA=1												
Frequency of items per protocol	22.00 (20.00, 23.00)	21.14 (3.20)	16.00 (14.00, 19.00)	16.39 (4.76)	20.00 (16.00, 22.00)	18.95 (4.64)	22.00 (20.00, 24.00)	21.25 (3.68)	21.00 (17.00, 24.00)	20.19 (4.73)	21.00 (18.00, 24.00)	20.66 (4.32)
Proportion of items per protocol	0.67 (0.61, 0.70)	0.64 (0.10)	0.48 (0.42, 0.58)	0.50 (0.14)	0.61 (0.48, 0.67)	0.57 (0.14)	0.67 (0.61, 0.73)	0.64 (0.11)	0.64 (0.52, 0.73)	0.61 (0.14)	0.64 (0.55, 0.73)	0.63 (0.13)
Major item approach (allowing for partial credit) NA=0												
Frequency of items per protocol	24.75 (22.75, 26.17)	24.22 (2.86)	19.47 (16.59, 22.27)	19.19 (4.91)	22.87 (19.29, 25.42)	21.88 (4.68)	24.50 (22.40, 26.21)	23.89 (3.64)	23.92 (19.85, 25.83)	22.72 (4.44)	24.25 (21.25, 26.08)	23.24 (4.14)

Proportion of items per protocol	0.76 (0.70, 0.80)	0.74 (0.08)	0.60 (0.51, 0.69)	0.59 (0.15)	0.71 (0.60, 0.78)	0.67 (0.14)	0.76 (0.69, 0.80)	0.73 (0.11)	0.74 (0.60, 0.80)	0.70 (0.14)	0.74 (0.66, 0.80)	0.72 (0.13)
Major item approach (allowing for partial credit) NA=1												
Frequency of items per protocol	25.46 (23.58, 26.50)	24.85 (2.77)	21.25 (18.25, 23.67)	20.59 (4.52)	23.67 (20.67, 26.17)	22.88 (4.25)	25.33 (23.67, 26.91)	24.75 (3.35)	25.00 (21.24, 27.31)	24.12 (4.29)	25.25 (22.50, 27.08)	24.40 (3.90)
Proportion of items per protocol	0.77 (0.71, 0.80)	0.75 (0.08)	0.64 (0.55, 0.72)	0.62 (0.14)	0.72 (0.63, 0.79)	0.69 (0.13)	0.77 (0.72, 0.82)	0.75 (0.10)	0.76 (0.64, 0.83)	0.73 (0.13)	0.77 (0.68, 0.82)	0.74 (0.12)
All item approach NA=0												
Frequency of items per protocol	43.00 (40.25, 46.00)	42.38 (5.26)	35.00 (30.00, 40.00)	34.57 (8.33)	41.00 (35.00, 44.00)	38.76 (7.87)	42.00 (40.00, 45.75)	41.65 (6.46)	41.00 (35.00, 45.00)	39.69 (7.91)	42.00 (37.75, 45.00)	40.57 (7.35)
Proportion of items per protocol	0.73 (0.69, 0.78)	0.73 (0.08)	0.62 (0.53, 0.70)	0.60 (0.14)	0.70 (0.61, 0.76)	0.67 (0.13)	0.73 (0.68, 0.78)	0.71 (0.11)	0.73 (0.62, 0.79)	0.70 (0.13)	0.73 (0.65, 0.78)	0.71 (0.12)
All item approach NA=1												
Frequency of items per protocol	49.00 (46.00, 51.75)	48.27 (4.71)	43.00 (37.00, 46.00)	41.42 (7.80)	46.00 (42.00, 50.00)	45.10 (7.18)	48.50 (45.00, 51.00)	47.45 (5.94)	49.00 (42.25, 52.00)	46.95 (7.42)	49.00 (44.00, 52.00)	47.17 (6.80)
Proportion of items per protocol	0.77 (0.72, 0.81)	0.75 (0.07)	0.67 (0.58, 0.72)	0.65 (0.12)	0.72 (0.66, 0.78)	0.70 (0.11)	0.76 (0.70, 0.80)	0.74 (0.09)	0.77 (0.66, 0.81)	0.73 (0.12)	0.77 (0.69, 0.81)	0.74 (0.11)

Abbreviations: IQR, interquartile range; NA, not applicable (SPIRIT items with rating “not applicable”); SD, standard deviation

Supplementary Table 5: Adherence to individual SPIRIT items by year and sponsorship

		2012			2016		
Variable	**Spirit Item Number**	**Industry sponsorship (n=138)**	**Investigator sponsorship (n=119)**	**Total 2012 (n=257)**	**Industry sponsorship (n=130)**	**Investigator sponsorship (n=162)**	**Total 2016 (n=292)**
Basic study design in Title	1	116 (84.1%)	47 (39.5%)	163 (63.4%)	108 (83.1%)	57 (35.2%)	165 (56.5%)
Trial registration	2	109 (79.0%)	43 (36.1%)	152 (59.1%)	111 (85.4%)	125 (77.2%)	236 (80.8%)
Protocol version, number and date	3	131 (94.9%)	100 (84.0%)	231 (89.9%)	127 (97.7%)	155 (95.7%)	282 (96.6%)
Funding sources	4	123 (89.1%)	70 (58.8%)	193 (75.1%)	122 (93.8%)	120 (74.1%)	242 (82.9%)
Names of protocol contributors/ authors	5a	30 (21.7%)	36 (30.3%)	66 (25.7%)	20 (15.4%)	30 (18.5%)	50 (17.1%)
Name and contact details of sponsor	5b	110 (79.7%)	82 (68.9%)	192 (74.7%)	91 (70.0%)	136 (84.0%)	227 (77.7%)
Role of sponsor and funder in trial	5c	112 (81.2%)	39 (32.8%)	151 (58.8%)	70 (53.8%)	43 (26.5%)	113 (38.7%)
Steering Committee General Membership and Role	5d	125 (90.6%)	107 (89.9)	232 (90.3%)	113 (86.9%)	156 (96.3%)	269 (92.1%)
Of which Not Applicable		94 (75.2%)	72 (67.3%)	164 (71.6%)	90 (79.6%)	109 (69.9%)	199 (74.0%)
Research question described and justified	6a	25 (18.1%)	31 (26.1%)	56 (21.8%)	22 (16.9%)	54 (33.3%)	76 (26.0%)
Comparator choice explained	6b	108 (78.3%)	88 (73.9%)	196 (76.3%)	105 (80.8%)	137 (84.6%)	242 (82.9%)
Specific objectives described	7	133 (96.4%)	107 (89.9%)	240 (93.4%)	125 (96.2%)	149 (92.0%)	274 (93.8%)
Trial design described	8	127 (92.0%)	80 (67.2%)	207 (80.5%)	115 (88.5%)	132 (81.5%)	247 (84.6%)
Countries where data will be collected listed	9	71 (51.4%)	94 (79.0%)	165 (64.2%)	19 (14.6%)	144 (88.9%)	163 (55.8%)
Eligibility criteria for trial participants	10	138 (100.0%)	116 (97.5%)	254 (98.8%)	130 (100.0%)	162 (100.0%)	292 (100.0%)
Eligibility criteria for study centres and who will perform the intervention	10	15 (10.9%)	58 (48.7%)	73 (28.4%)	12 (9.2%)	98 (60.5%)	110 (37.7%)

Of which Not Applicable		1 (6.7%)	39 (67.2%)	40 (54.8%)	2 (16.7%)	68 (69.4%)	70 (63.6%)
Individuals administering interventions (non-drug)	10	131 (94.9%)	93 (78.2%)	224 (87.2%)	120 (92.3%)	131 (80.9%)	251 (86.0%)
Of which Not Applicable		119 (90.8%)	49 (52.7%)	168 (75.0%)	106 (88.3%)	65 (49.6%)	171 (68.1%)
Generic Name, Dose and Schedule of intervention	11a	135 (97.8%)	118 (99.2%)	253 (98.4%)	130 (100%)	161 (99.4%)	291 (99.7%)
Of which Not Applicable		16 (11.9%)	63 (53.4%)	79 (31.2%)	19 (14.6%)	95 (59.0%)	114 (39.2%)
Setting of intervention administration	11a	129 (93.5%)	103 (86.6%)	232 (90.3%)	118 (90.8%)	147 (90.7%)	265 (90.8%)
Of which Not Applicable		118 (91.5%)	49 (47.6%)	167 (72.0%)	106 (89.8%)	62 (42.2%)	168 (63.4%)
Criteria for modifications of interventions	11b	114 (82.6%)	85 (71.4%)	199 (77.4%)	111 (85.4%)	128 (79.0%)	239 (81.8%)
Of which Not Applicable		13 (11.4%)	32 (37.7%)	45 (22.6%)	10 (9.0%)	35 (27.3%)	45 (18.8%)
Strategies to improve or monitoring of adherence	11c	123 (89.1%)	95 (79.8%)	218 (84.8%)	107 (82.3%)	144 (88.9%)	251 (86.0%)
Of which Not Applicable		44 (35.8%)	66 (69.5%)	110 (50.5%)	33 (30.8%)	78 (54.2%)	111 (44.2%)
Permitted concomitant care	11d	130 (94.2%)	61 (51.3%)	191 (74.3%)	124 (95.4%)	112 (69.1%)	236 (80.8%)
Primary Outcome: Specific measurement variable	12	138 (100%)	113 (95.0%)	251 (97.7%)	129 (99.2%)	153 (94.4%)	282 (96.6%)
Of which Not Applicable		1 (0.7%)	0 (0%)	1 (0.4%)	0 (0%)	0 (0%)	0 (0%)
Primary Outcome: Analysis metric	12	132 (95.7%)	101 (84.9%)	233 (90.7%)	124 (95.4%)	140 (86.4%)	264 (90.4%)
Of which Not Applicable		3 (2.3%)	0 (0%)	3 (1.3%)	1 (0.8%)	0 (0%)	1 (0.4%)
Primary Outcomes: time point of measurement	12	132 (95.7%)	105 (88.2%)	237 (92.2%)	124 (95.4%)	149 (92.0%)	273 (93.5%)
Of which Not Applicable		40 (30.3%)	20 (19.1%)	60 (25.3%)	26 (21.0%)	20 (13.4%)	46 (16.9%)
Participant timeline	13	136 (98.6%)	113 (95.0%)	249 (96.9%)	130 (100%)	154 (95.1%)	284 (97.3%)
Sample size: Estimated number	14	138 (100.0%)	116 (97.5%)	254 (98.8%)	128 (98.5%)	161 (99.4%)	289 (99.0%)
Sample size: Outcome used for samples size calculation	14	135 (97.8%)	107 (89.9%)	242 (94.2%)	127 (97.7%)	148 (91.4%)	275 (94.2%)
Of which Not Applicable		7 (5.2%)	3 (2.8%)	10 (4.1%)	4 (3.2%)	7 (4.7%)	11 (4.0%)

Sample size: Assumed values for outcome	14	122 (88.4%)	89 (74.8%)	211 (82.1%)	111 (85.4%)	116 (71.6%)	227 (77.7%)
Of which Not Applicable		6 (4.9%)	5 (5.6%)	11 (5.2%)	4 (3.6%)	7 (6.0%)	11 (4.9%)
Sample size: Alpha value	14	131 (94.9%)	106 (89.1%)	237 (92.2%)	126 (96.9%)	150 (92.6%)	276 (94.5%)
Of which Not Applicable		7 (5.3%)	3 (2.8%)	10 (4.2%)	4 (3.2%)	7 (4.7%)	11 (4.0%)
Sample size: Statistical Power	14	134 (97.1%)	111 (93.3%)	245 (95.3%)	128 (98.5%)	153 (94.4%)	281 (96.2%)
Of which Not Applicable		7 (5.2%)	3 (2.7%)	10 (4.1%)	4 (3.1%)	7 (4.6%)	11 (3.9%)
Sample size: Rationale sample size if not derived statistically	14	137 (99.3%)	110 (92.4%)	247 (96.1%)	127 (97.7%)	158 (97.5%)	285 (97.6%)
Of which Not Applicable		130 (94.9%)	110 (100%)	240 (97.2%)	123 (96.9%)	155 98.1%)	278 (97.5%)
Location of participant recruitment	15	24 (17.4%)	78 (65.5%)	102 (39.7%)	17 (13.1%)	112 (69.1%)	129 (44.2%)
Person(s) who will recruit participants	15	40 (29.0%)	52 (43.7%)	92 (35.8%)	33 (25.4%)	91 (56.2%)	124 (42.5%)
Expected recruitment rate	15	37 (26.8%)	52 (43.7%)	89 (34.6%)	13 (10.0%)	39 (24.1%)	52 (17.8%)
Method for generation of random sequence	16a	89 (64.5%)	63 (52.9%)	152 (59.1%)	68 (52.3%)	109 (67.3%)	177 (60.6%)
Allocation concealment mechanism	16b	126 (91.3%)	80 (67.2%)	206 (80.2%)	113 (86.9%)	130 (80.2%)	243 (83.2%)
Of which Not Applicable		8 (6.4%)	3 (3.8%)	11 (5.3%)	1 (0.9%)	3 (2.3%)	4 (1.7%)
Person who will enroll/assign participants	16c	59 (42.8%)	44 (37.0%)	103 (40.1%)	50 (38.5%)	79 (48.8%)	129 (44.2%)
Of which Not Applicable		0 (0%)	2 (4.6%)	2 (1.9%)	1 (2%)	1 (1.3%)	2 (1.6%)
Blinding status of participants	17a	133 (96.4%)	97 (81.5%)	230 (89.5%)	128 (98.5%)	148 (91.4%)	276 (94.5%)
Blinding status of care providers	17a	134 (97.1%)	97 (81.5%)	231 (89.9%)	127 (97.7%)	148 (91.4%)	275 (94.2%)
Blinding status of outcome assessors	17a	103 (74.6%)	71 (59.7%)	174 (67.7%)	94 (72.3%)	105 (64.8%)	199 (68.2%)
Conditions when unblinding is permissible	17b	127 (92.0%)	92 (77.3%)	219 (85.2%)	120 (82.3%)	142 (87.7%)	262 (89.7%)
Of which Not Applicable		34 (26.8%)	66 (71.7%)	100 (45.7%)	36 (30%)	91 (64.1%)	127 (48.5%)

Personnel who will collect data	18a	58 (42.0%)	52 (43.7%)	110 (42.8%)	61 (46.9%)	96 (59.3%)	157 (53.8%)
Strategies to promote participant retention and complete follow-up	18b	84 (60.9%)	34 (28.6%)	118 (45.9%)	80 (61.5%)	64 (39.5%)	144 (49.3%)
Data entry and coding	19	106 (76.8%)	64 (53.8%)	170 (66.1%)	102 (78.5%)	117 (72.2%)	219 (75.0%)
Main analysis for primary outcome	20a	131 (94.9%)	96 (80.7%)	227 (88.3%)	121 (93.1%)	132 (81.5%)	253 (86.6%)
Definition of subgroup categories	20b	117 (84.8%)	98 (82.4%)	215 (83.7%)	108 (83.1%)	148 (91.4%)	256 (87.7%)
Of which Not Applicable		60 (51.3%)	79 (80.6%)	139 (64.7%)	63 (58.3%)	116 (78.4%)	179 (69.9%)
Definition of analysis population	20c	125 (90.6%)	49 (41.2%)	174 (67.7%)	120 (92.3%)	96 (59.3%)	216 (74.0%)
DMC is planned or why it is not planned	21a	102 (73.9%)	49 (41.2%)	151 (58.8%)	97 (74.6%)	72 (44.4%)	169 (57.9%)
Who has authority to stop the trial	21b	111 (80.4%)	73 (61.3%)	184 (71.6%)	111 (85.4%)	112 (69.1%)	223 (76.4%)
Anticipated/unanticipated adverse events collection	22	136 (98.6%)	91 (76.5%)	227 (88.3%)	127 (97.7%)	138 (85.2%)	265 (90.8%)
Audits/external monitoring described	23	106 (76.8%)	49 (41.2%)	155 (60.3%)	109 (83.8%)	112 (69.1%)	221 (75.7%)
Of which Not Applicable		0 (0%)	3 (6.1%)	3 (1.9%)	3 (2.8%)	15 (13.4%)	18 (8.2%)
Research ethics approval	24	138 (100%)	118 (100%)	256 (100%)	130 (100%)	162 (100%)	292 (100%)
Process for making amendments described	25	106 (76.8%)	48 (40.3%)	154 (59.9%)	103 (79.2%)	121 (74.7%)	224 (76.7%)
Informed Consent process described	26a	119 (86.2%)	77 (64.7%)	196 (76.3%)	110 (84.6%)	139 (85.8%)	249 (85.3%)
Process to obtain additional consent for collection and use of data and biological specimens	26b	123 (89.1%)	103 (86.6%)	226 (87.9%)	111 (85.4%)	151 (93.2%)	262 (89.7%)
Of which Not Applicable		70 (56.9%)	87 (84.5%)	157 (69.5%)	65 (58.6%)	126 (83.4%)	191 (72.9%)
Confidentiality of data	27	125 (90.6%)	88 (73.9%)	213 (82.9%)	114 (87.7%)	144 (88.9%)	258 (88.4%)
Declaration of Interests	28	54 (39.1%)	27 (22.7%)	81 (31.5%)	94 (72.3%)	88 (54.3%)	182 (62.3%)
Who will have access to full dataset	29	29 (21.0%)	23 (19.3%)	52 (20.2%)	37 (28.5%)	56 (34.6%)	93 (31.8%)

Ancillary and post-trial care	30	61 (44.2%)	39 (32.8%)	100 (38.9%)	50 (38.5%)	44 (27.2%)	94 (32.2%)
Plans to disseminate trial results to key stakeholders/publication provided	31a	72 (52.2%)	51 (42.9%)	123 (47.9%)	77 (59.2%)	129 (79.6%)	206 (70.5%)
Authorship eligibility criteria	31b	50 (36.2%)	30 (25.2%)	80 (31.1%)	41 (31.5%)	57 (35.2%)	98 (33.6%)
Plans for granting access to full trial protocol	31c	7 (5.1%)	2 (1.7%)	9 (3.5%)	4 (3.1%)	13 (8.0%)	17 (5.8%)
Consent forms provided	32	133 (96.4%)	118 (99.2%)	251 (97.7%)	125 (96.2%)	157 (96.9%)	282 (96.6%)
Details of specimen collection	33	126 (91.3%)	99 (83.2)	225 (87.5%)	120 (92.3%)	152 (93.8%)	272 (93.2%)
Of which Not Applicable		35 (27.8%)	61 (61.6%)	96 (42.7%)	53 (44.2%)	109 (71.7%)	162 (59.6%)

Supplementary Table 6: Adherence to SPIRIT items in Investigator-sponsored protocols that improved by 10% or more

		2012	2016
Variable	**Spirit Item Number**	**Yes**	**Yes**
Trial registration	2	43 (36.1%)	125 (77.2%)
Protocol version, number and date	3	100 (84.0%)	155 (95.7%)
Funding sources	4	70 (58.8%)	120 (74.1%)
Name and contact details of sponsor	5b	82 (68.9%)	136 (84.0%)
Comparator choice explained	6b	88 (73.9%)	137 (84.6%)
Trial design described	8	80 (67.2%)	132 (81.5%)
Eligibility criteria for study centres and who will perform the intervention	10	58 (48.7%)	98 (60.5%)
Of which Not Applicable		39 (67.2%)	68 (69.4%)
Permitted concomitant care	11d	61 (51.3%)	112 (69.1%)
Person(s) who will recruit participants	15	52 (43.7%)	91 (56.2%)
Method for generation of random sequence	16a	63 (52.9%)	109 (67.3%)
Allocation concealment mechanism	16b	80 (67.2%)	130 (80.3%)
Of which Not Applicable		3 (3.8%)	3 (2.3%)
Person who will enroll/assign participants	16c	44 (37.0%)	79 (48.8%)
Of which Not Applicable		2 (1.4%)	1 (1.3%)
Personnel who will collect data	18a	52 (43.7%)	96 (59.3%)
Strategies to promote participant retention and complete follow-up	18b	34 (28.6%)	64 (39.5%)
Data entry and coding	19	64 (53.8%)	117 (72.2%)
Definition of analysis population	20c	49 (41.2%)	96 (59.3%)
Audits/external monitoring described	23	49 (41.2%)	112 (69.1%)
Of which Not Applicable		3 (6.1%)	15 (13.4%)
Process for making amendments described	25	48 (40.3%)	121 (74.7%)
Informed Consent process described	26a	77 (64.7%)	139 (85.8%)
Confidentiality of data	27	88 (73.9%)	144 (88.9%)
Declaration of Interests	28	27 (22.7%)	88 (54.3%)
Who will have access to full dataset	29	23 (19.3%)	56 (34.6%)
Plans to disseminate trial results to key stakeholders/publication provided	31a	51 (42.9%)	129 (79.6%)

Authorship eligibility criteria	31b	30 (25.2%)	57 (35.2%)
Details of specimen collection	33	99 (83.2%)	152 (93.8)
Of which Not Applicable		61 (61.6%)	109 (71.7%)

Supplementary Table 7: Results from multivariable Beta and Logistic regressions for all approaches

Approach	Independent Variable	Beta Regression			Likelyhood ratio		Logistic regression with Protocol as random effect			Likelyhood ratio	
		Odds Ratio	CI	p value	Chisq	p	Odds Ratio	CI	p value	Chisq	p
Major Item approach (simple) NA=0	Sample size in 1000 increments	1.01	0.99- 1.03	0.235	-	-	1.00	0.98 – 1.02	0.747	-	-
	Multicentre study	1.29	1.17- 1.43	<.001	-	-	1.21	1.08 – 1.36	0.001	-	-
	CTU or CRO support	1.35	1.25- 1.45	<.001	-	-	1.42	1.29 – 1.56	<.001	-	-
	Industry sponsorship	1.23	1.14- 1.34	<.001	-	-	1.36	1.23 – 1.51	<.001	-	-
	Year 2016	1.25	1.16- 1.35	<.001	-	-	1.26	1.15 – 1.38	<.001	-	-
Interaction term	Sponsorship:Year interaction	0.71	0.61- 0.81	<.001	22.24	<.001	0.69	0.58 – 0.83	<.001	16.21	<.001
	CTU/CRO support:Year interaction	0.91	0.78- 1.05	0.190	1.72	0.190	0.87	0.73 – 1.04	0.118	2.43	0.119
Major Item approach (simple) NA=1	Sample size in 1000 increments	1.01	0.99- 1.03	0.233	-	-	0.99	0.97 – 1.02	0.654	-	-
	Multicentre study	1.22	1.08- 1.37	0.001	-	-	1.16	1.02 – 1.31	0.022	-	-
	CTU or CRO support	1.42	1.30- 1.55	<.001	-	-	1.46	1.32 – 1.60	<.001	-	-
	Industry sponsorship	1.23	1.11- 1.35	<.001	-	-	1.34	1.21 – 1.50	<.001	-	-
	Year 2016	1.32	1.21- 1.43	<.001	-	-	1.34	1.22 – 1.48	<.001	-	-
Interaction term	Sponsorship:Year interaction	0.64	0.55- 0.76	<.001	26.27	<.001	0.67	0.55 – 0.81	<.001	17.322	<.001
	CTU/CRO support:Year interaction	0.99	0.83- 1.17	0.881	0.02	0.881	0.90	0.75 – 1.09	0.292	1.10	0.294

Major item approach (allowing for partial credit) NA=0	Sample size in 1000 increments	1.01	0.99- 1.03	0.290	-	-	-	-	-	-	-	
	Multicentre study	1.22	1.08- 1.38	0.001	-	-	-	-	-	-	-	
	CTU or CRO support	1.43	1.31- 1.57	<.001	-	-	-	-	-	-	-	
	Industry sponsorship	1.25	1.13- 1.38	<.001	-	-	-	-	-	-	-	
	Year 2016	1.33	1.21- 1.46	<.001	-	-	-	-	-	-	-	
Interaction term	Sponsorship:Year interaction	0.60	0.50- 0.71	<.001	31.48	<.001	-	-	-	-	-	
	CTU/CRO support:Year interaction	0.94	0.79- 1.13	0.515	0.42	0.515	-	-	-			
Major item approach (allowing for partial credit) NA=1	Sample size in 1000 increments	1.01	0.99- 1.03	0.389	-	-	-	-	-	-	-	
	Multicentre study	1.18	1.05- 1.33	0.006	-	-	-	-	-	-	-	
	CTU or CRO support	1.44	1.31- 1.57	<.001	-	-	-	-	-	-	-	
	Industry sponsorship	1.20	1.09- 1.33	<.001	-	-	-	-	-	-	-	
	Year 2016	1.33	1.22- 1.45	<.001	-	-	-	-	-	-	-	
Interaction term	Sponsorship:Year interaction	0.61	0.52- 0.73	<.001	30.01	<.001	-	-	-	-	-	
	CTU/CRO support:Year interaction	0.98	0.82- 1.16	0.790	0.07	0.790	-	-	-			
All item approach NA=0	Sample size in 1000 increments	1.02	1.00- 1.04	0.095	-	-	1.02	1.00 – 1.04	0.027	-	-	
	Multicentre study	1.27	1.14- 1.43	<.001	-	-	1.37	1.24 – 1.52	<.001	-	-	
	CTU or CRO support	1.39	1.28- 1.52	<.001	-	-	1.33	1.23 – 1.44	<.001	-	-	
	Industry sponsorship	1.14	1.03- 1.25	0.010	-	-	1.15	1.05 – 1.25	0.001	-	-	
	Year 2016	1.25	1.15- 1.36	<.001	-	-	1.20	1.11 – 1.29	<.001	-	-	
Interaction term	Sponsorship:Year interaction	0.63	0.53- 0.74	<.001	29.29	<.001	0.69	0.59 – 0.80	<.001	24.20	<.001	

	CTU/CRO support:Year interaction	1.02	0.86- 1.21	0.841	0.04	0.842	0.97	0.83 – 1.12	0.643	0.22	0.643
All item approach NA=1	Sample size in 1000 increments	1.02	1.00- 1.04	0.131	-	-	1.02	1.00 – 1.04	0.118	-	-
	Multicentre study	1.18	1.06- 1.31	0.003	-	-	1.20	1.07 – 1.35	0.002	-	-
	CTU or CRO support	1.36	1.26- 1.48	<.001	-	-	1.39	1.27 – 1.51	<.001	-	-
	Industry sponsorship	1.13	1.03- 1.23	0.010	-	-	1.14	1.04 – 1.25	0.006	-	-
	Year 2016	1.23	1.14- 1.34	<.001	-	-	1.23	1.14 – 1.34	<.001	-	-
Interaction term	Sponsorship:Year interaction	0.64	0.55- 0.75	<.001	31.18	<.001	0.63	0.54 – 0.74	<.001	30.67	<.001
	CTU/CRO support:Year interaction	1.05	0.90- 1.23	0.564	0.33	0.5643	1.05	0.89 – 1.24	0.594	0.28	0.594

Abbreviations: CI, confidence interval

Supplementary Table 8: Results from multivariable Beta regression, subset of Investigator-sponsored protocols

Approach	Independent Variable	Beta Regression			Likelyhood ratio	
		Odds Ratio	CI	p value	Chisq	p
Major item approach (allowing for partial credit) NA=0	Sample size/1000	1.01	0.95- 1.07	0.803	-	-
	Multicentre	1.21	1.05- 1.40	0.008	-	-
	CTU or CRO support	1.55	1.35- 1.77	<.001	-	-
	Year	1.61	1.42- 1.84	<.001	-	-
	Swiss cohort	1.48	1.27- 1.74	<.001	-	-
Interaction term	CTU/CRO support:Year	1.02	0.79- 1.33	0.869	0.03	0.869
	Swiss trials:Year	1.39	1.03- 1.88	0.034	4.42	0.036
Major item approach (allowing for partial credit) NA=1	Sample size/1000	1.00	0.95- 1.06	0.891	-	-
	Multicentre	1.19	1.03- 1.37	0.016	-	-
	CTU or CRO support	1.53	1.34- 1.75	<.001	-	-
	Year	1.60	1.41- 1.82	<.001	-	-
	Swiss cohort	1.46	1.25- 1.70	<.001	-	-
Interaction term	CTU/CRO support:Year	1.08	0.83- 1.39	0.568	0.33	0.568
	Swiss trials:Year	1.39	1.03- 1.87	0.031	4.57	0.032

Abbreviations: CI, confidence interval

Supplementary Table 9: Medical disciplines of included RCTs

Medical disciplines	2012				2016		
	Sponsorship				Sponsorship		
	Industry (N=138)	Investigator (N=119)	Total (N=257)		Industry (N=130)	Investigator (N=162)	Total (N=292)
Oncology	30 (21.7%)	20 (16.8%)	50 (19.5%)	Oncology	30 (23.1%)	24 (14.8%)	54 (18.5%)
Surgery	11 (8.0%)	27 (22.7%)	38 (14.8%)	Cardiovascular	22 (16.9%)	14 (8.6%)	36 (12.3%)
Cardiovascular	19 (13.8%)	10 (8.4%)	29 (11.3%)	Surgery	6 (4.6%)	25 (15.4%)	31 (10.6%)
Neurology	15 (10.9%)	5 (4.2%)	20 (7.8%)	Neurology	11 (8.5%)	12 (7.4%)	23 (7.9%)
Respiratory	8 (5.8%)	6 (5.0%)	14 (5.4%)	Psychiatry	1 (0.8%)	20 (12.3%)	21 (7.2%)
Hematology	6 (4.3%)	6 (5.0%)	12 (4.7%)	Respiratory	9 (6.9%)	7 (4.3%)	16 (5.5%)
Infectious Disease	7 (5.1%)	4 (3.4%)	11 (4.3%)	Gastroenterology	13 (10.0%)	1 (0.6%)	14 (4.8%)
Anaesthetics	1 (0.7%)	9 (7.6%)	10 (3.9%)	Rheumatology	12 (9.2%)	1 (0.6%)	13 (4.5%)
Gastroenterology	8 (5.8%)	2 (1.7%)	10 (3.9%)	Anaesthetics	0 (0.0%)	11 (6.8%)	11 (3.8%)
Rheumatology	9 (6.5%)	1 (0.8%)	10 (3.9%)	Endocrinology	5 (3.8%)	5 (3.1%)	10 (3.4%)
Dermatology	8 (5.8%)	0 (0.0%)	8 (3.1%)	Dentistry	1 (0.8%)	6 (3.7%)	7 (2.4%)
Endocrinology	1 (0.7%)	5 (4.2%)	6 (2.3%)	Infectious Disease	4 (3.1%)	3 (1.9%)	7 (2.4%)
Obsterics and Gynecology	1 (0.7%)	5 (4.2%)	6 (2.3%)	Intensive care	0 (0.0%)	7 (4.3%)	7 (2.4%)
Ophthalmology	6 (4.3%)	0 (0.0%)	6 (2.3%)	Dermatology	4 (3.1%)	2 (1.2%)	6 (2.1%)
Psychiatry	1 (0.7%)	5 (4.2%)	6 (2.3%)	Nephrology	1 (0.8%)	4 (2.5%)	5 (1.7%)
Intensive care	0 (0.0%)	3 (2.5%)	3 (1.2%)	Obsterics and Gynecology	1 (0.8%)	4 (2.5%)	5 (1.7%)
Nephrology	2 (1.4%)	1 (0.8%)	3 (1.2%)	Other	2 (1.5%)	3 (1.9%)	5 (1.7%)
Rehabilitation	1 (0.7%)	2 (1.7%)	3 (1.2%)	Geriatrics	0 (0.0%)	4 (2.5%)	4 (1.4%)
Allergology	2 (1.4%)	0 (0.0%)	2 (0.8%)	Hematology	2 (1.5%)	2 (1.2%)	4 (1.4%)
Physiotherapy	0 (0.0%)	2 (1.7%)	2 (0.8%)	Ophthalmology	3 (2.3%)	1 (0.6%)	4 (1.4%)
Orthopedics	0 (0.0%)	2 (1.7%)	2 (0.8%)	Orthopedics	1 (0.8%)	2 (1.2%)	3 (1.0%)
Community Health	0 (0.0%)	1 (0.8%)	1 (0.4%)	Community Health	0 (0.0%)	3 (1.2%)	1 (0.3%)

Dentistry	1 (0.7%)	0 (0.0%)	1 (0.4%)	Emergency care	0 (0.0%)	5 (1.2%)	1 (0.3%)
Emergency care	0 (0.0%)	1 (0.8%)	1 (0.4%)	Neonatology	1 (0.8%)	6 (1.2%)	1 (0.3%)
Geriatrics	0 (0.0%)	1 (0.8%)	1 (0.4%)	Occupational Therapy	0 (0.0%)	7 (1.2%)	1 (0.3%)
Other	0 (0.0%)	1 (0.8%)	1 (0.4%)	Otorhinolaryngology	1 (0.8%)	8 (1.2%)	1 (0.3%)
Urology	1 (0.7%)	0 (0.0%)	1 (0.4%)	Rehabilitation	0 (0.0%)	9 (1.2%)	1 (0.3%)

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

The methods used to conduct the present study have previously been published:

Gryaznov D, Odutayo A, von Niederhäusern B, Speich B, Kasenda B, Ojeda-Ruiz E, et al. Rationale and design of repeated cross-sectional studies to evaluate the reporting quality of trial protocols: the Adherence to SPIrit REcommendations (ASPIRE) study and associated projects. Trials. 2020;21(1):896.
Link: https://trialsjournal.biomedcentral.com/articles/10.1186/s13063-020-04808-y

	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 (Section: Abstract, Design section)	4
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found (Section: Abstract, Results section)	5
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported (Section: Introduction, all paragraphs)	6
Objectives	3	State specific objectives, including any prespecified hypotheses (Section: Introduction, last paragraph)	6
Methods			
Study design	4	Present key elements of study design early in the paper (Section: Methods 1st paragraph (Published))	7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection (Section: Methods, Identification of included trial protocols; Supplementary Figure 1)	7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants (Section: Methods, Identification of included trial protocols)	7
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable (Section: Methods, Data Analysis, paragraphs 1 and 2)	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 (Section: Methods, Data extraction)	*7*
Bias	9	Describe any efforts to address potential sources of bias (Section: Methods, Data extraction)	7
Study size	10	Explain how the study size was arrived at (Section: Methods 1st paragraph (Published))	7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why (Section: Methods, Data Analysis, paragraph 1)	8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding (Section: Methods, Data Analysis, paragraph 2)	8
		(*b*) Describe any methods used to examine subgroups and interactions (Section: Methods, Data Analysis, paragraph 1)	8

		(*c*) Explain how missing data were addressed (na)	
		(*d*) If applicable, describe analytical methods taking account of sampling strategy (na)	
		(*e*) Describe any sensitivity analyses (Section: Methods, Data Analysis, paragraph 1)	8
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 (Supplementary Figure 1)	
		(b) Give reasons for non-participation at each stage (na)	
		(c) Consider use of a flow diagram (Supplementary Figure 1)	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (Section: Results, Characteristics of included trial protocols, paragraph 1 and 2. Table 1)	9
		(b) Indicate number of participants with missing data for each variable of interest (na)	
Outcome data	15*	Report numbers of outcome events or summary measures (Section: Results, Adherence to SPIRIT in protocols from 2012 and 2016. Table 2, Figure 1)	9,10
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 (Section: Results, Multivariable regression analysis. Figure 2, Supplementary Table 7)	10,11
		(*b*) Report category boundaries when continuous variables were categorized (Section: Methods, Data Analysis, paragraph 2. Figure 2)	8
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period (na)	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses (Section: Results, Multivariable regression analysis. Supplementary Table 7)	10,11
Discussion			
Key results	18	Summarise key results with reference to study objectives (Section: Discussion, Main findings and interpretation)	11,12
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 (Section: Discussion, Strengths and limitations, all paragraphs)	12, 13
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence (Section: Discussion, Comparison with other studies, Implications, all paragraphs)	13, 14
Generalisability	21	Discuss the generalisability (external validity) of the study results (Section: Discussion, Strengths and limitations, paragraphs 1 and 2)	12, 13
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 (Section: Declarations, Funding)	16

*Give information separately for exposed and unexposed groups.

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.