



ORIGINAL ARTICLE

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

Szimonetta Lohner^{a,b,*}, Dmitry Gryaznov^c, Belinda von Niederhäusern^{d,e}, Benjamin Speich^{c,f}, Benjamin Kasenda^{c,g,h}, Elena Ojeda-Ruiz^{c,i}, Stefan Schandelmaier^{c,j}, Dominik Mertz^j, Ayodele Odutayo^{f,k}, Yuki Tomonaga^l, Alain Amstutz^{c,m,n}, Christiane Pauli-Magnus^d, Viktoria Gloy^c, Karin Bischoff^{o,p}, Katharina Wollmann^{o,p}, Laura Rehner^{o,q}, Joerg J Meerpohl^{o,p}, Alain Nordmann^c, Katharina Klatte^d, Nilabh Ghosh^r, Ala Taji Heravi^c, Jacqueline Wong^j, Ngai Chow^j, Patrick Jiho Hong^{j,s}, Kimberly McCord^c, Sirintip Sricharoenchai^c, Jason W. Busse^{j,t}, Arnav Agarwal^{u,j}, Ramon Saccilotto^c, Matthias Schwenkglenks^{l,v}, Giusi Moffa^{c,w}, Lars G. Hemkens^{c,x,y}, Sally Hopewell^f, Erik von Elm^z, Anette Blümle^{A,1}, Matthias Briel^{c,j,1}

^a *Cochrane Hungary, Clinical Centre of the University of Pécs, Medical School, University of Pécs, Pécs, Hungary*

^b *Department of Public Health Medicine, Medical School, University of Pécs, Pécs, Hungary*

^c *Department of Clinical Research, Basel Institute for Clinical Epidemiology and Biostatistics, University Hospital Basel and University of Basel, Basel, Switzerland*

^d *Department of Clinical Research, Clinical Trial Unit, University Hospital Basel and University of Basel, Basel, Switzerland*

^e *Roche Pharma AG, Grenzach-Wyhlen, Germany*

^f *Centre for Statistics in Medicine, Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, University of Oxford, Oxford, United Kingdom*

^g *Department of Medical Oncology, University Hospital Basel, Basel, Switzerland*

^h *iOMEDICO AG, Research & Development, Freiburg, Germany*

ⁱ *Infanta Elena University Hospital, Preventive Medicine Department, Madrid, Spain*

^j *Department of Health Research Methods, Evidence, and Impact, McMaster University, Hamilton, Canada*

^k *Applied Health Research Centre, Li Ka Shing Knowledge Institute of St Michael's Hospital, Toronto, Canada*

Competing interests: All authors have completed the [Unified Competing Interest form](#) (available on request from the corresponding author) and declare: BvN is currently employed by Roche Pharma AG, Grenzach-Wyhlen, Germany. BK is currently employed by iOMEDICO AG, Freiburg, Germany and reports personal fees from Roche, Riemser, and Astellas, outside the submitted work. 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.

Funding: The study was supported by the Swiss Federal Office of Public Health. The funder had no role in the study design, data collection and analysis, decision to publish, or preparation of this manuscript. BS was supported by an Advanced Postdoc. Mobility grant from the Swiss National Science Foundation (P300PB_177933). SL was supported by the Alexander von Humboldt Foundation, Germany during her research stay at the Institute for Evidence in Medicine, University of Freiburg, Germany and is currently supported by the János Bolyai Research Scholarship of the Hungarian Academy of Sciences for SL (BO/00498/17/5). AA receives his salary through a grant from the MD-PhD programme of the Swiss National Science Foundation (grant number 323530_177576).

Authors' contributions: AO, SH, EvE, BK, and MB designed the main study. SL designed the present substudy. RS developed the web-tool for data extractions. DG, BvN, BS, and MB coordinated data extraction from protocols. DG performed statistical analyses. SL and MB wrote the first draft of the manuscript. DG, BvN, BS, BK, EOR, AB, StS, DM, YT, AA, CPM, VG, KB, Kku, LR, SL, JJM, AN, KKI, 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.

Transparency declaration: MB as the the manuscript's guarantor affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as have been explained.

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

Patient and public involvement statement: It was not appropriate to involve patients or the public in the design, conduct, reporting, or dissemination plans of our research.

Dissemination declaration: Dissemination of results to patient organisations is not applicable.

¹ shared last authorship.

* Corresponding author. fax no. +36 72 536395; tel no. +36 72 501500

E-mail address: lohner.szimonetta@pte.hu (S. Lohner).

¹Epidemiology, Biostatistics and Prevention Institute, University of Zurich, Zurich, Switzerland^mSwiss Tropical and Public Health Institute, University of Basel, Basel, SwitzerlandⁿDepartment of Infectious Diseases and Hospital Epidemiology, University Hospital Basel, Basel, Switzerland^oInstitute for Evidence in Medicine, Medical Center – University of Freiburg, Faculty of Medicine, University of Freiburg, Freiburg, Germany^pCochrane Germany, Cochrane Germany Foundation, Freiburg, Germany^qDepartment of Epidemiology and Community Health, Institute for Community Medicine, University Medicine Greifswald, Greifswald, Germany^rDepartment of Neurosurgery and Department of Biomedicine, University Hospital Basel, University of Basel, Basel, Switzerland^sDepartment of Anesthesiology and Pain Medicine, University of Toronto, Toronto, Canada^tDepartment of Anesthesia, McMaster University, Hamilton, Canada^uDepartment of Medicine, University of Toronto, Toronto, ON, Canada^vInstitute of Pharmaceutical Medicine (ECPM), University of Basel, Basel, Switzerland^wDepartment of Mathematics and Computer Science, University of Basel, Basel, Switzerland^xMeta-Research Innovation Center at Stanford (METRICS), Stanford University, Stanford, USA^yMeta-Research Innovation Center Berlin (METRIC-B), Berlin Institute of Health, Berlin, Germany^xCochrane Switzerland, Centre for Primary Care and Public Health (Unisanté), University of Lausanne, Lausanne, Switzerland^AClinical Trials Unit, Medical Center – University of Freiburg, Faculty of Medicine, University of Freiburg, Freiburg, Germany

Received 10 February 2021; Received in revised form 6 May 2021; Accepted 12 May 2021; Available online xxx

Abstract

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

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

Results: Overall, 131 (24%) of trial protocols tested non-regulated interventions. In 2012, the median proportion of SPIRIT items reported in these protocols (59%, interquartile range [IQR], 53%-69%) was lower than in protocols with regulated interventions (median, 74%, IQR, 66%-80%). In 2016, the reporting quality of protocols with non-regulated interventions (median, 75%, IQR, 62%-83%) improved to the level of regulated intervention protocols, which had not changed on average.

Conclusions: Reporting of RCT protocols evaluating non-regulated interventions improved between 2012 and 2016, although remained suboptimal. SPIRIT recommendations need to be further endorsed by researchers, ethics committees, funding agencies, and journals to optimize reporting of RCT protocols. © 2021 The Author(s). Published by Elsevier Inc. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>)

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

What is new?

- There was an improvement in adherence of trial protocols of non-regulated intervention trials to the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) recommendations between 2012 and 2016; their reporting quality reached the level of regulated trials in 2016 but still remained suboptimal.
- A descriptive title identifying the study design, details on data collection, plans on a Data Monitoring Committee, access to data, and details on ancillary care were identified as the worst reported protocol elements in non-regulated trials in 2016.

- The improvements and remaining deficiencies of trial protocols of non-regulated interventions were similar across types of intervention (surgical, dietary, behavioural, exercise).

1. Introduction

Trials of regulated interventions, such as drugs, biologics, or medical devices, must adhere to regulations of responsible authorities (e.g. European Medicines Agency, Swissmedic) [1-4]. Regulators promote completeness and transparency of protocols and prospective registration in a trial register. However, trials assessing non-regulated interventions, such as dietary interventions, surgical proce-

dures, behavioural and lifestyle interventions, or exercise programmes, are not subject to oversight by regulatory agencies.

Although recommendations have been developed for the design, conduct and reporting of trials with non-regulated interventions [5, 6], study reports of these trials often lack important study information, such as final sample size [7], age [8], or health status of participants [8], and adherence to the CONSORT (Consolidated Standards of Reporting Trials) Statement is generally poor [8-12].

Careful writing of a clinical trial protocol is important for all involved stakeholders, i.e. researchers, ethics review boards, funders, journal editors and patients [13], because this document describes the planned research steps and methods in a comprehensive manner. The SPIRIT 2013 Statement (Standard Protocol Items: Recommendations for Interventional Trials), a checklist of a minimal set of items to be reported in a protocol, was developed to improve the reporting quality of study protocols [14]. Empirical evidence on the impact of the SPIRIT recommendations on the quality of trial protocols with non-regulated interventions is lacking.

The aim of the present study was to assess the extent to which RCT protocols with non-regulated interventions adhered to the SPIRIT recommendations in 2012 and 2016, that is, before and after the SPIRIT recommendations were published. Further, we compared adherence to the SPIRIT checklist [15] between trial protocols with non-regulated as compared to regulated interventions.

2. Methods

2.1. Protocol selection and inclusion criteria

The present study is one of the add-on projects of Adherence to SPIRIT Recommendations - Switzerland, Canada, and Germany (ASPIRE-SCAGE) Study. A detailed description of the methodology, including eligibility criteria, process of protocol selection, data extraction, and additional objectives addressed in add-on studies has previously been published [16]. In brief, the ASPIRE-SCAGE investigated adherence of protocols approved by research ethics committees in Switzerland, Germany, or Canada before (2012) and after (2016) the publication of the SPIRIT guidelines in 2013. Protocols were eligible if they described an RCT of a health care intervention in patients. We excluded pilot studies, trials enrolling healthy volunteers, animal studies, studies based on tissue samples, and studies with a quasi-random method of allocation. Results of ASPIRE-SCAGE will be published separately. Originally, we had planned to additionally include protocols from UK research ethics committees in this subproject, but delays in accessing protocols from 2016 rendered this not feasible [16].

In the present study we categorised the protocols included in ASPIRE-SCAGE as follows: 1) drug, 2) bio-

logical, 3) device, 4) dietary supplement, 5) surgery, 6) behavioural, 7) exercise, or 8) other non-regulated.

2.2. Data extraction

From each eligible trial protocol, we extracted main study characteristics and information on the adherence to the SPIRIT checklist [15]. Data extractors assessed whether each item and sub-item of the SPIRIT checklist was reported among eligible trials, either as ‘Yes’, ‘No’, or ‘Not applicable’.

Data were extracted by two independent extractors, using web-based software developed for data collection (www.squiekero.org). All extractors signed confidentiality agreements before starting data extraction. To reduce inter-extractor variability in interpreting individual questions, each of the extractors received personal training provided by one of the project leaders (DG, BvN, MB) and extracted the first protocols with a project leader as the second extractor. The software enabled comparison of extracted data from two extractors and the discussion of discrepancies before making a consensual final decision.

2.3. Data analysis

We expressed *adherence of trial protocols to SPIRIT* by allocating a score between zero and one to each of the 33 SPIRIT items and summing up these scores. Each protocol was able to reach a total score (hereafter referred to as *SPIRIT adherence score*) between zero and 33 points, with higher scores designating better SPIRIT adherence [16].

In case of SPIRIT items consisting of a single variable, we assigned one point if the answer to the question about the variable was “Yes” or “Not applicable” and zero points if the answer was “No” (dichotomization). In case of composite SPIRIT checklist items with two or more questions (sub-items), we applied an approach, which gave equal credit to all sub-items (with dichotomization on sub-item level). The ratio calculated by dividing the number of fulfilled sub-items and the total number of sub-items was allocated as a score to these composite SPIRIT items. This means, for example, that an item consisting of three sub-items received 0.66 points in case two sub-items were fulfilled, while one sub-item remained unfulfilled [16].

We calculated *overall trial adherence to SPIRIT* for different intervention categories (drugs, biologicals, devices, dietary supplements, surgical interventions, behavioural interventions and exercise) as the proportion of SPIRIT items adhered to per protocol. *Adherence to individual SPIRIT checklist items* was calculated as the proportion of trial protocols adhering to a given item. In case of composite items – to give equal credit to each of the sub-items – mean proportions were calculated.

We used descriptive statistical methods to compare characteristics of all intervention categories (drugs, biologicals, devices, dietary supplements, surgical interven-

tions, behavioural interventions and exercise). We conducted three multivariable analyses using a beta regression model [17] to examine whether and how the adherence of regulated and non-regulated trial protocols changed between 2012 and 2016. The proportion of SPIRIT items adhered to per protocol was the dependent variable in all three regression analyses. In the first analysis we used all trial protocols from 2012 and included the following independent variables: regulation status, planned sample size, centre status (single vs multiple), sponsorship, reported logistic or methodological support from a clinical trial unit (CTU) or contract research organisation (CRO). In the second analysis we used all protocols from 2016 with the same set of independent variables. In a third analysis we specifically investigated a potential interaction between year of approval (2012 or 2016) and regulation status, by including a corresponding interaction term in the regression model. An additional multivariable beta regression analysis was restricted to non-regulated trial protocols to reveal the factors that potentially influence the adherence of non-regulated intervention trial protocols to SPIRIT.

We used R version 3.6.1 for data analysis. We performed all statistical testing at the significance level of 0.05.

3. Results

We included 549 trial protocols in our analysis; 257 from 2012 and 292 from 2016. Out of these protocols, 418 (76%) described a trial with a regulated and 131 (24%) a trial with a non-regulated intervention. We summarized main characteristics of the included trial protocols in **Table 1**. Non-regulated intervention trials most often investigated surgical procedures (40.5%) or behavioural/lifestyle interventions (28.2%), while protocols with a dietary (12.2%) or exercise intervention (11.5%) were less common in our sample. As the comparator, non-regulated trial protocols most often had no treatment/standard care (47.3%) or another active treatment (35.9%) rather than placebo (16.8%). Most of the non-regulated trial protocols reported non-industry sponsorship (93.9%), and support from a CTU/CRO was less commonly mentioned than in protocols of regulated interventions (38.9% vs. 62.2%). Planned sample sizes were lower for non-regulated protocols than protocols of regulated intervention trials (median number of participants was 144 vs. 287).

Table 2 provides information on the adherence to the SPIRIT checklist for RCT protocols of both regulated and non-regulated interventions. The reporting quality of protocols with regulated interventions had, on average, not changed substantially from 2012 to 2016 (median of 74% versus 77% of the SPIRIT items were adhered to per protocol, respectively), while we observed for protocols with non-regulated interventions a substantial improvement (median of 59% versus 75% of the SPIRIT items were adhered to per protocol, in 2012 and 2016, respectively). We found

improvements from 2012 to 2016 in all non-regulated intervention subcategories with levels of SPIRIT adherence at baseline ranging from 53% to 65% (**Table 2**).

Non-regulated status was identified as an independent predictor of non-adherence in 2012 (odds ratio 1.25, 95% confidence interval 1.07 to 1.45), but not in 2016 (odds ratio 1.01, 95% confidence interval 0.86 to 1.19) (**Table 3**). This selective improvement of protocols with non-regulated interventions (subgroup effect) is also reflected in the significant interaction term between intervention regulation status and protocol approval year in the third regression model in **Table 3**.

The protocol elements with over 10% difference in the proportion of SPIRIT adherence between regulated and non-regulated trials in 2016 were: (1) details on study design in the title, (2) providing trial registration details, (3) description of trial design, (4) plans about a Data Monitoring Committee, (5) monitoring harms, (6) ways for auditing study conduct, (7) process for making protocol amendments, and (8) provisions for ancillary care. Details on study setting, recruitment, access to data, and dissemination policy were better reported for trials with non-regulated interventions than for the regulated ones (**Table 4**). Details on ancillary care, a descriptive title identifying study design, details on access to data, data collection methods, and plans on a Data Monitoring Committee were identified as the five least reported SPIRIT items in 2016 (**Table 4**).

Multivariable regression model in protocols evaluating non-regulated interventions showed that more recent approval (2016) and CTU/CRO support were independent predictors of better adherence to SPIRIT, while planned sample size, the type of non-regulated intervention (dietary, surgery, behaviour, exercise, other), and being a multicentre or single centre study were not (**Supplementary Table 1**).

4. Discussion

4.1. Summary of principal findings

We found an improvement in the completeness of reporting of protocols for trials evaluating non-regulated interventions between 2012 and 2016. Although reporting quality in 2016 remained suboptimal, it basically reached the level of protocols of regulated interventions, which did not change over time. We saw this improvement not only overall, but in all investigated subcategories of non-regulated interventions, with the smallest improvement for protocols evaluating dietary interventions, and the most pronounced improvement for protocols of exercise programmes. Specific SPIRIT items with particularly poor reporting (all <50% adherence) were description of study design in title, details on data collection, plans about having a Data Monitoring Committee, details on access to data after trial completion, and plans about ancillary care. Apart

Table 1. Characteristics of investigated randomized controlled trial protocols

Characteristics	Drug (n = 268)	Device (n = 79)	Biological (n = 71)	All regulated interventions (n = 418)	Diet (n = 16)	Surgery (n = 53)	Behaviour (n = 37)	Exercise (n = 15)	Other* (n = 10)	All non-regulated interventions (n = 131)
Country of Ethics Committee										
Switzerland	177 (66.1%)	71 (89.9%)	51 (71.8%)	299 (71.5%)	11 (68.8%)	38 (71.7%)	30 (81.1%)	12 (80.0%)	7 (70.0%)	98 (74.8%)
Germany	44 (16.4%)	5 (6.3%)	14 (19.7%)	63 (15.1%)	2 (12.5%)	2 (3.8%)	4 (10.8%)	3 (20.0%)	1 (10.0%)	12 (9.2%)
Canada	47 (17.5%)	3 (3.8%)	6 (8.5%)	56 (13.4%)	3 (18.8%)	13 (24.5%)	3 (8.1%)	0 (0.0%)	2 (20.0%)	21 (16.0%)
Approved in										
2012	118 (44.0%)	42 (53.2%)	45 (63.4%)	205 (49.0%)	9 (56.2%)	26 (49.1%)	9 (24.3%)	5 (33.3%)	3 (30.0%)	52 (39.7%)
2016	150 (56.0%)	37 (46.8%)	26 (36.6%)	213 (51.0%)	7 (43.8%)	27 (50.9%)	28 (75.7%)	10 (66.7%)	7 (70.0%)	79 (60.3%)
Sponsorship										
Industry	168 (62.7%)	31 (39.2%)	61 (85.9%)	260 (62.2%)	3 (18.8%)	4 (7.5%)	1 (2.7%)	0 (0.0%)	0 (0.0%)	8 (6.1%)
Investigator	100 (37.3%)	48 (60.8%)	10 (14.1%)	158 (37.8%)	13 (81.2%)	49 (92.5%)	36 (97.3%)	15 (100.0%)	10 (100.0%)	123 (93.9%)
CTU or CRO support										
	178 (66.4%)	34 (43.0%)	48 (67.6%)	260 (62.2%)	9 (56.2%)	24 (45.3%)	6 (16.2%)	7 (46.7%)	5 (50.0%)	51 (38.9%)
Study design										
Parallel	251 (93.7%)	74 (93.7%)	68 (95.8%)	393 (94.0%)	11 (68.8%)	49 (92.5%)	35 (94.6%)	15 (100.0%)	10 (100.0%)	120 (91.6%)
Crossover	10 (3.7%)	3 (3.8%)	1 (1.4%)	14 (3.3%)	4 (25.0%)	3 (5.7%)	2 (5.4%)	0 (0.0%)	0 (0.0%)	9 (6.9%)
Factorial	7 (2.6%)	2 (2.5%)	2 (2.8%)	11 (2.6%)	1 (6.2%)	1 (1.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.5%)
Comparator										
No treatment/Standard care	45 (16.8%)	30 (38.0%)	4 (5.6%)	79 (18.9%)	0 (0.0%)	21 (39.6%)	24 (64.9%)	11 (73.3%)	6 (60.0%)	62 (47.3%)
Another active treatment	85 (31.7%)	33 (41.8%)	17 (23.9%)	135 (32.3%)	2 (12.5%)	28 (52.8%)	10 (27.0%)	3 (20.0%)	4 (40.0%)	47 (35.9%)
Placebo/sham	138 (51.5%)	16 (20.3%)	50 (70.4%)	204 (48.8%)	14 (87.5%)	4 (7.5%)	3 (8.1%)	1 (6.7%)	0 (0.0%)	22 (16.8%)
Planned number of study centers and participating countries										
Single center	28 (10.4%)	30 (38.0%)	3 (4.2%)	61 (14.6%)	7 (43.8%)	22 (41.5%)	23 (62.2%)	8 (53.3%)	3 (30.0%)	63 (48.1%)
Multicenter, national	32 (11.9%)	11 (13.9%)	7 (9.9%)	50 (12.0%)	7 (43.8%)	10 (18.9%)	12 (32.4%)	5 (33.3%)	3 (30.0%)	37 (28.2%)
Multicenter, international	208 (77.6%)	38 (48.1%)	61 (85.9%)	307 (73.4%)	2 (12.5%)	21 (39.6%)	2 (5.4%)	2 (13.3%)	4 (40.0%)	31 (23.7%)
Number of participants (median, IQR)										
	320 (140-674)	102 (60-293)	444 (183-805)	287 (120-638)	60 (46-233)	150 (75-470)	128 (78-246)	90 (58-110)	310 (203-733)	144 (67-322)

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

When not indicated otherwise, data are expressed as total number (percentage within the corresponding group).

* Other trial protocols that included any type of non-regulated intervention, which we were not able to classify to the four pre-defined non-regulated categories (e.g. intervention with a geriatric evaluation tool; intermittent vs. continuous oxygen saturation monitoring; cold exposure vs. room temperature).

Table 2. Overall protocol adherence to SPIRIT according to intervention category

Year of approval		Drug (n = 268)	Device (n = 79)	Biological (n = 71)	All regulated interventions (n = 418)	Diet (n = 16)	Surgery (n = 53)	Behaviour (n = 37)	Exercise (n = 15)	Other [‡] (n = 10)	All non-regulated interventions (n = 131)
2012	SPIRIT adherence scores, median (IQR)*	24.5 (22.8-26.2)	21.83 (18.9-25.1)	25.2 (23.8-26.9)	24.4 (21.9-26.3)	21.5 (19.0-25.3)	19.6 (17.8-23.0)	18.8 (15.9-20.5)	18.3 (16.5-19.5)	17.3 (14.8-20.8)	19.4 (17.5-22.9)
	Median % (IQR) [†]	74 (69-79)	66 (57-76)	76 (72-82)	74 (66-80)	65 (58-77)	60 (54-70)	57 (48-62)	56 (50-59)	53 (45-63)	59 (53-69)
2016	SPIRIT adherence scores, median (IQR)	25.3 (23.4-27.1)	23.9 (21.2-26.3)	25.8 (23.6-26.6)	25.3 (23.0-27.0)	22.5 (15.5-26.1)	24.5 (20.2-26.8)	25.5 (22.3-27.5)	26.6 (22.3-27.1)	24.08 (21.8-28.5)	24.6 (20.5-27.3)
	Median % (IQR)	77 (71-82)	72 (64-80)	78 (72-81)	77 (70-82)	68 (47-79)	74 (61-81)	77 (68-84)	81 (68-83)	73 (66-87)	75 (62-83)

Abbreviation: IQR, interquartile range.

* Spirit adherence scores are expressed as median (IQR) for each intervention category. Each single protocol was able to reach a SPIRIT adherence score between zero and 33 points (i.e. we allocated a score between zero and one for each of the 33 SPIRIT checklist items), with higher scores indicating greater SPIRIT adherence.

[†] % means the median percent of SPIRIT items that were adhered to per protocol.

[‡] Other trial protocols that included any type of non-regulated intervention, which we were not able to classify to the four pre-defined non-regulated categories (e.g. intervention with a geriatric evaluation tool; intermittent vs. continuous oxygen saturation monitoring; cold exposure vs. room temperature).

Table 3. Multivariable regression analyses for the years 2012, 2016 and for all included study protocols for potential predictors of SPIRIT adherence

	2012 (n = 257)		2016 (n = 292)		All protocols (n = 549)	
	OR (95%CI)	P	OR (95%CI)	p	OR (95%CI)	P
Regulation status (regulated vs. non-regulated)	1.25 (1.07 – 1.45)	0.005	1.01 (0.86 – 1.19)	0.92	1.40 (1.20 – 1.63)	<0.001
Planned sample size (in 1000 increments)	1.01 (0.99 – 1.03)	0.32	0.96 (0.91 – 1.02)	0.24	1.01 (0.99 – 1.03)	0.52
Multicentre (vs. single centre)	1.23 (1.05 – 1.46)	0.01	1.20 (1.02 – 1.42)	0.03	1.20 (1.06 – 1.34)	0.003
CTU/CRO support (yes vs. no)	1.37 (1.21 – 1.54)	<0.001	1.44 (1.26 – 1.64)	<0.001	1.43 (1.31 – 1.56)	<0.001
Industry sponsorship (vs investigator)	1.41 (1.22 – 1.62)	<0.001	0.95 (0.81 – 1.11)	0.49	1.15 (1.03 – 1.28)	0.01
Approval year (2016 vs. 2012)	-	-	-	-	1.20 (1.08 – 1.32)	<0.001
Interaction non-regulated interventions – approval year	-	-	-	-	1.54 (1.263 – 1.88)	<0.001

Abbreviations: CI, confidence interval; CRO, contract research organisation; CTU, clinical trials unit; OR, odds ratio.

from the approval year, reported CTU/CRO support in the protocol was an independent predictor of better protocol reporting quality in trials with non-regulated interventions. Adherence was worse than in regulated trials for reporting the study design in the title, trial registration details, study design, plans about a Data Monitoring Committee, about collecting details on harms, about auditing, about the process for making protocol amendments, and about provide or pay for ancillary care. Reporting was better for details on study setting, recruitment, access to data, and dissemination policy.

4.2. Strengths and weaknesses of the study

Strengths of our study include full access to RCT protocols and their associated documents from research ethics

committees in three countries. Included RCTs consist of all or a random sample of approved protocols at a participating research ethics committee. During data extraction we followed a rigorous process with pilot-testing of extraction forms and calibration exercises among all data extractors participating in the project to minimize inter-extractor differences. More than 95% of included protocols approved in 2012 and over 80% of protocols approved in 2016 were extracted and assessed by two independent reviewers.

It was a limitation of our study that, whereas all research ethic committees from Switzerland participated, only a convenience sample of one ethics committee from Germany (Freiburg) and one from Canada (Hamilton) took part. Thereby, Swiss protocols are overrepresented in our sample and we could not conduct meaningful sub-group analyses according to country. Accordingly, we cannot be

Table 4. Adherence to individual SPIRIT checklist items in 2016

SPIRIT checklist items which had to be described in the protocol	Number of SPIRIT checklist sub-items*	Non-regulated interventions (n = 79) %	Regulated interventions (n = 213) %	Differences [†]	Worst reported items for non-regulated
1) Study design, population, and interventions identified in title	1	34.2	64.8	↓	Top 2 worst
2) Registry name and trial identifier	1	68.4	85.4	↓	
3) Protocol version number and date	1	92.4	98.1		
4) Sources of financial/non-financial support	1	77.2	85.0		
5) Roles of protocol contributors, sponsors, funders	4	56.3	56.5		
6) Research question, justification of comparator choice	3	57.6	53.3		
7) Specific objectives for each comparison	1	91.1	94.8		
8) Trial design	1	77.2	87.3	↓	
9) Study setting	1	87.3	44.1	↑	
10) Eligibility criteria for participants	2	79.3	72.8		
11) Intervention, in detail	6	82.8	89.7		
12) Primary outcome, in detail	3	88.2	95.5		
13) Time schedule of enrolment, interventions, assessments and visits for participants	1	91.1	99.5		
14) Sample size calculation, in detail	9	89.9	94.5		
15) Recruitment (location, responsible persons, expected recruitment rate, monitoring, financial and non-financial incentives)	8	56.1	26.9	↑	
16) Allocation methods, in detail	7	67.1	61.0		
17) Blinding of participants, investigators, and outcome assessors	4	83.5	87.8		
18) Data collection (responsible persons and strategies to promote participant retention)	2	47.5	53.1		Top 4 worst
19) Data management methods	1	72.2	76.1		
20) Statistical methods, in detail	6	75.9	85.3		
21) Plans about having a Data Monitoring Committee and to conduct interim analysis	6	48.1	74.2	↓	Top 5 worst
22) Plans for collecting, assessing, reporting, managing adverse events	1	77.2	95.8	↓	
23) Procedures of auditing/ external monitoring	1	63.3	80.3	↓	
24) Affected research ethics committee	1	100	100		
25) Process for making protocol amendments	1	67.1	80.3	↓	
26) Informed consent process described	2	90.5	86.4		
27) Confidentiality of data collection and secure keeping	1	84.8	89.7		
28) Competing interests	1	55.7	64.8		
29) Persons having access to data after trial completion	1	40.5	28.6	↑	Top 3 worst
30) Plans to provide or pay for ancillary care	1	21.5	36.2	↓	Top 1 worst
31) Dissemination policy	4	78.5	67.6	↑	
32) Model consent form	1	97.5	96.2		
33) Details of biological specimen collection	1	97.5	91.5		

* For items with more than one sub-item, the mean proportion of protocols adhering to the sub-items of the given SPIRIT item (%) was calculated

[†] ↓ indicates SPIRIT items where adherence was $\geq 10\%$ worse in case of non-regulated as compared to regulated interventions, while ↑ indicates that adherence for non-regulated intervention protocols was $\geq 10\%$ better than for regulated protocols; Top 1-5 worst indicate those five SPIRIT items, which non-regulated protocols were less likely to adhere to.

sure whether our findings are also externally valid in an international context. A further limitation is that since we included RCT protocols that had already been approved by ethic committees, two of the SPIRIT items (“research ethics approval” and “consent forms provided”) were always fulfilled which inflates our total adherence scores.

The category “dietary interventions” was defined as any alteration in the participant’s diet as part of a controlled clinical trial, including trials with dietary supplements. We did not evaluate whether a health claim was intended based on trial results, instead all dietary interventions were considered to be non-regulated, which may have affected our results. It is important to mention that lack of reporting in the study protocol does not necessarily mean poor study conduct or poor reporting in the subsequent publication. Some studies have found that methodological information missing from protocols may be reported in the final publication [18-20]. Finally, the observed changes in protocol quality for non-regulated interventions between 2012 and 2016 cannot be causally attributed to the publication of SPIRIT due to the observational nature of this study; however, other initiatives and changes that could have had an impact on protocol quality too (e.g. a new Swiss protocol template [21], the enactment of new Legislation on Human Research in Switzerland in 2014, a common protocol template from Transclerate in 2015 [22] might have been influenced by SPIRIT guidance.

4.3. Discussion of findings in light of other studies

To our knowledge, our study is the first that focused on the reporting quality of non-regulated intervention trial protocols, including trials with dietary interventions, surgical procedures, behavioural and lifestyle interventions or exercise programmes. Previous meta-research focused on registration and publication tendencies of non-regulated trials. Dal Ré et al. summarized evidence on low registration and publication tendencies of trials of non-regulated interventions compared with drug trials in 2015. [23] Poor prospective trial registration rate [24-26], incomplete registration data [24-26] and low publication rates [27] were also described in other studies, focusing on specific subgroups of non-regulated intervention trials.

4.4. Implications for practice and future research

As non-regulated trials make up a large proportion of RCTs (i.e. about 40% of RCTs published [23,28]), it is important to set the same expectations for them as for trials of regulated interventions. Independently of whether or not interventions fall under regulations of specific authorities, researchers and research ethics committees should consider recommendations for protocol reporting in the same way.

During trial implementation all researchers have to face several challenges, e.g. recruitment of participants [29], randomisation, blinding [30-32], and the choice of placebo

or sham control [33,34] might be difficult. In addition, there might be specific challenges for trials with non-regulated interventions. For dietary supplementation trials it might be difficult to ensure and control compliance of participants [35, 36]. In surgical trials, a large heterogeneity of surgical patients and procedures [37] and different skills of surgeons in performing a particular procedure [38] may cause difficulties in standardizing surgical interventions [39]. In behavioural clinical trials, standardized training or a comparable, agreed competence level of involved trial investigators is crucial, but not yet common practice [40,41].

Findings of the present study are important as they inform researchers and research ethics committees about protocol elements in non-regulated trials which are often not reported properly. Providing details about trial design and plans about registration in an openly accessible trial register are essential elements of high-quality trial conduct and transparency, and have to be improved in case of non-regulated trials. Having plans for a Data Monitoring Committee, about managing adverse events and procedures for auditing and external monitoring are all trial safeguard issues, which need to be assessed as part of the protocol also in case of non-regulated trials. When preparing or assessing a trial protocol for a non-regulated intervention, researchers and research ethics committees should pay particular attention to a sufficiently detailed description of these protocol elements, shown to be reported poorly.

A high-quality protocol not only facilitates the conduct of the trial as planned but study methods and results can be reported more reliably in a subsequent journal publication. Insufficient reporting quality or missing information in study protocols may subsequently increase the risk of selective reporting of study findings [42] or even lack of publication [43]. The extent to which protocol reporting quality is associated with subsequent study conduct and reporting quality of study reports needs further investigation.

5. Conclusion

To estimate the benefits and harms of non-regulated interventions, there is a need for high quality RCTs and complete and transparent study reports. One important step towards this goal are study protocols that adhere to high quality reporting standards. The reporting quality of protocols of non-regulated interventions improved between 2012 and 2016 in a sample of protocols from Switzerland, Germany, and Canada. The SPIRIT recommendations published in 2013 likely contributed to this development, but causality cannot be shown in an observational study. Further improvement of protocol adherence to SPIRIT recommendations, however, is needed.

Acknowledgments

We are grateful to Prof. Doug Altman (University of Oxford) who was instrumental in developing the initial concept of the Adherence to SPIrit REcommendations (ASPIRE) study and who sadly passed away before it came to fruition. We thank all participating research ethics committees from Germany (Freiburg), Switzerland (Basel, Bellinzona, Bern, Geneva, Lausanne, St. Gallen, Frauenfeld, Zurich), Canada (Hamilton), and the UK (National Health Service Health Research Authority) for their support and cooperation.

Data sharing: No additional data available.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:[10.1016/j.jclinepi.2021.05.011](https://doi.org/10.1016/j.jclinepi.2021.05.011).

References

- [1] European Parliament and Council of the European Union, Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC. OJ 2014 L158/1-75.
- [2] 110th United States Congress. Food and Drug Administration Amendments Act of 2007. Public Law 2007:110–85.
- [3] Zenger CA. Comparison between the Swiss federal human research act and implementing ordinances and the EU regulation of 16 April 2014 (CTR) on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC. Bern, 2014. Available at : <https://www.bag.admin.ch/bag/en/home/medizin-und-forschung/forschung-am-menschen/klinische-pruefungen-humanarzneimitteln-eu.html> (Accessed on 13 Aug 2020).
- [4] Federal Act on Research involving Human Beings (Human Research Act, HRA). 2011 Available at: <https://www.admin.ch/opc/en/classified-compilation/20061313/202001010000/810.30.pdf> (Accessed on 13 Aug 2020).
- [5] Welch RW, Antoine JM, Berta JL, Bub A, de Vries J, Guarner F, et al. Guidelines for the design, conduct and reporting of human intervention studies to evaluate the health benefits of foods. *Br. J. Nutr* 2011;106 Suppl 2:S3–15.
- [6] Woodside JV, Koletzko BV, Patterson CC, Welch RW. Scientific standards for human intervention trials evaluating health benefits of foods, and their application to infants, children and adolescents. *World Rev Nutr Diet* 2013;108:18–31.
- [7] Speich B. Adequate reporting of the sample size calculation in surgical randomized controlled trials. *Surgery* 2020;167(5):812–14.
- [8] Gibson CA, Kirk EP, LeCheminant JD, Bailey BW Jr, Huang G, Donnelly JE. Reporting quality of randomized trials in the diet and exercise literature for weight loss. *BMC medical research methodology* 2005;5:9.
- [9] Agha R, Cooper D, Muir G. The reporting quality of randomised controlled trials in surgery: a systematic review. *IJS (London, England)* 2007;5(6):413–22.
- [10] Agha RA, Camm CF, Doganay E, Edison E, Siddiqui MR, Orgill DP. Randomised controlled trials in plastic surgery: a systematic review of reporting quality. *European journal of plastic surgery* 2014;37:55–62.
- [11] Thompson E, Lai A, Morrey L, Borofsky MS, Dahm P. A Longitudinal Assessment of the Reporting Quality of Randomized Controlled Trials for Surgical Interventions to Treat Nephrolithiasis Over 16 Years (2002 to 2017). *J Endourol* 2020;34(4):502–8.
- [12] Milette K, Roseman M, Thombs BD. Transparency of outcome reporting and trial registration of randomized controlled trials in top psychosomatic and behavioral health journals: A systematic review. *J Psychosom Res* 2011;70(3):205–17.
- [13] Tetzlaff JM, Chan AW, Kitchen J, Sampson M, Tricco AC, Moher D. Guidelines for randomized clinical trial protocol content: a systematic review. *Systematic reviews* 2012;1:43.
- [14] Chan AW, Tetzlaff JM, Gotzsche PC, Altman DG, Mann H, Berlin JA, et al. SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. *BMJ (Clinical research ed)* 2013;346:e7586.
- [15] Chan AW, Tetzlaff JM, Altman DG, Laupacis A, Gotzsche PC, Krleza-Jeric K, et al. SPIRIT 2013 statement: defining standard protocol items for clinical trials. *Ann Intern Med* 2013;158(3):200–7.
- [16] 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.
- [17] Ferrari S, Cribari-Neto F. Beta Regression for Modelling Rates and Proportions. *J Appl Stat*. 2004;31(7):799–815.
- [18] Kasenda B, Schandelmaier S, Sun X, von Elm E, You J, Blümle A, et al. Subgroup analyses in randomised controlled trials: cohort study on trial protocols and journal publications. *BMJ (Clinical research ed)* 2014;349:g4539.
- [19] Chan AW, Hróbjartsson A, Jørgensen KJ, Gøtzsche PC, Altman DG. Discrepancies in sample size calculations and data analyses reported in randomised trials: comparison of publications with protocols. *BMJ (Clinical research ed)* 2008;337:a2299.
- [20] Pildal J, Chan AW, Hróbjartsson A, Forfang E, Altman DG, Gøtzsche PC. Comparison of descriptions of allocation concealment in trial protocols and the published reports: cohort study. *BMJ (Clinical research ed)* 2005;330(7499):1049.
- [21] Swiss Association of Research Ethics Committees. Study protocols. Available at: <https://swissethics.ch/en/templates/studienprotokollvorlagen>. (Accessed on 20 Apr 2021).
- [22] TransCelerate. Clinical Content & Reuse Initiative. Available at : <https://www.transceleratebiopharmainc.com/assets/clinical-content-reuse-solutions/>(Accessed on 20 Apr 2021).
- [23] Dal-Re R, Bracken MB, Ioannidis JP. Call to improve transparency of trials of non-regulated interventions. *BMJ (Clinical research ed)* 2015;350:h1323.
- [24] Rokhsfat S, Morra DE, Offringa M, Askie LM, Kelly LE. Trial registration in pediatric surgery trials. *J. Pediatr. Surg.* 2018;53(7):1273–9.
- [25] Hardt JL, Metzendorf MI, Meerpohl JJ. Surgical trials and trial registers: a cross-sectional study of randomized controlled trials published in journals requiring trial registration in the author instructions. *Trials* 2013;14:407.
- [26] Riehm KE, Azar M, Thombs BD. Transparency of outcome reporting and trial registration of randomized controlled trials in top psychosomatic and behavioral health journals: A 5-year follow-up. *J Psychosom Res* 2015;79(1):1–12.
- [27] Chapman SJ, Shelton B, Mahmood H, Fitzgerald JE, Harrison EM, Bhangu A. Discontinuation and non-publication of surgical randomised controlled trials: observational study. *BMJ (Clinical research ed)* 2014;349:g6870.
- [28] Hopewell S, Dutton S, Yu LM, Chan AW, Altman DG. The quality of reports of randomised trials in 2000 and 2006: comparative study of articles indexed in PubMed. *BMJ (Clinical research ed)* 2010;340:c723.
- [29] Robinson L, Adair P, Coffey M, Harris R, Burnside G. Identifying the participant characteristics that predict recruitment and retention of participants to randomised controlled trials involving children: a systematic review. *Trials* 2016;17(1):294.

- [30] Berger D. Double blinding requirement for validity claims in cognitive-behavioral therapy intervention trials for major depressive disorder. Analysis of Hollon S, et al., Effect of cognitive therapy with antidepressant medications vs antidepressants alone on the rate of recovery in major depressive disorder: a randomized clinical trial. *F1000Research* 2015;4:639.
- [31] Aycock DM, Hayat MJ, Helvig A, Dunbar SB, Clark PC. Essential considerations in developing attention control groups in behavioral research. *Research in nursing & health* 2018;41(3):320–8.
- [32] Friedberg JP, Lipsitz SR, Natarajan S. Challenges and recommendations for blinding in behavioral interventions illustrated using a case study of a behavioral intervention to lower blood pressure. *Patient education and counseling* 2010;78(1):5–11.
- [33] Staudacher HM, Irving PM, Lomer MCE, Whelan K. The challenges of control groups, placebos and blinding in clinical trials of dietary interventions. *The Proceedings of the Nutrition Society* 2017;76(3):203–12.
- [34] Liu JC, Raine A, Ang RP, Fung DS. An analysis of blinding success in a randomised controlled trial of fish oil omega-3 fatty acids. *Annals of the Academy of Medicine, Singapore* 2015;44(3):85–91.
- [35] van der Wurff ISM, Meyer BJ, de Groot RHM. A Review of Recruitment, Adherence and Drop-Out Rates in Omega-3 Polyunsaturated Fatty Acid Supplementation Trials in Children and Adolescents. *Nutrients* 2017;9(5).
- [36] Ioannidis JP. Implausible results in human nutrition research. *BMJ (Clinical research ed)* 2013;347:f6698.
- [37] Darrow JJ. Explaining the absence of surgical procedure regulation. *Cornell journal of law and public policy*. 2017;27(1):189–206.
- [38] Baum M. Reflections on randomised controlled trials in surgery. *Lancet (London, England)* 1999;353 Suppl 1 Si6-8.
- [39] Campbell B. Regulation and safe adoption of new medical devices and procedures. *British Medical Bulletin* 2013;107(1):5–18.
- [40] Murphy SL, Byks-Jazayeri C, Calvin-Naylor N, Divecha V, Anderson E, Eakin B, et al. Best practices in social and behavioral research: report from the Enhancing Clinical Research Professional's Training and Qualifications project. *Journal of clinical and translational science* 2017;1(1):26–32.
- [41] Arango J, Chuck T, Ellenberg SS, Foltz B, Gorman C, Hinrichs H, et al. Good Clinical Practice Training: Identifying Key Elements and Strategies for Increasing Training Efficiency. *Therapeutic innovation & regulatory science* 2016;50(4):480–6.
- [42] Odutayo A, Emdin CA, Hsiao AJ, Shakir M, Copsey B, Dutton S, et al. Association between trial registration and positive study findings: cross sectional study (Epidemiological Study of Randomized Trials-ESORT). *BMJ (Clinical research ed)* 2017;356:j917.
- [43] Magni P, Bier DM, Pecorelli S, Agostoni C, Astrup A, Brighenti F, et al. Perspective: Improving Nutritional Guidelines for Sustainable Health Policies: Current Status and Perspectives. *Advances in nutrition (Bethesda, Md)* 2017;8(4):532–45.