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**"**
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Supplementary Figure 1

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

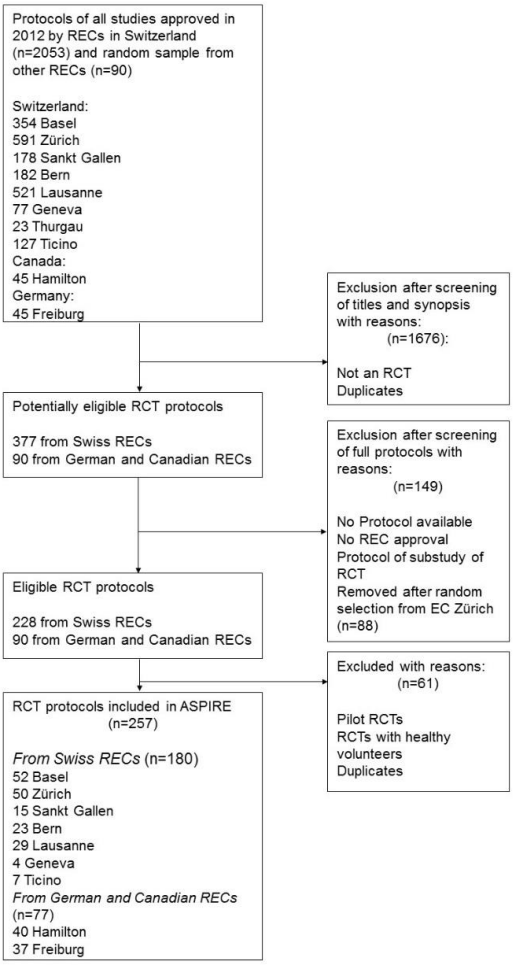
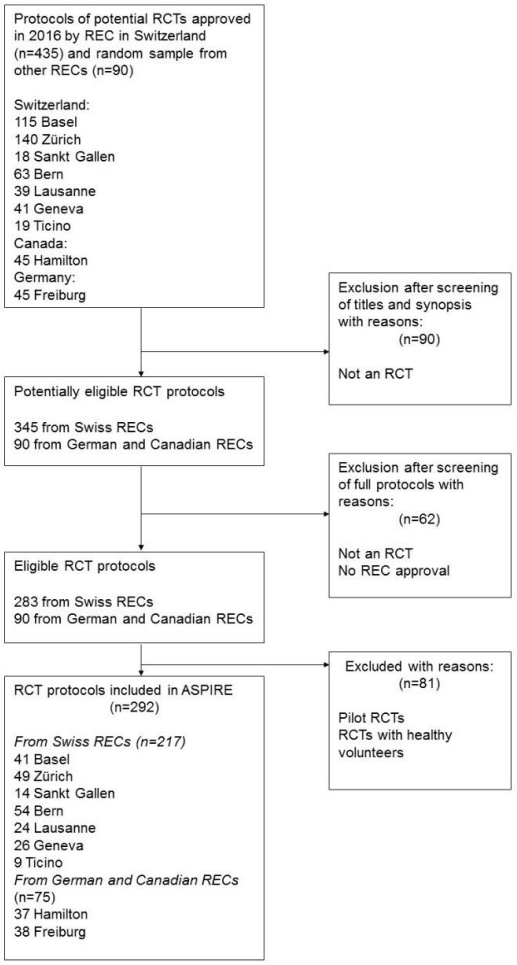


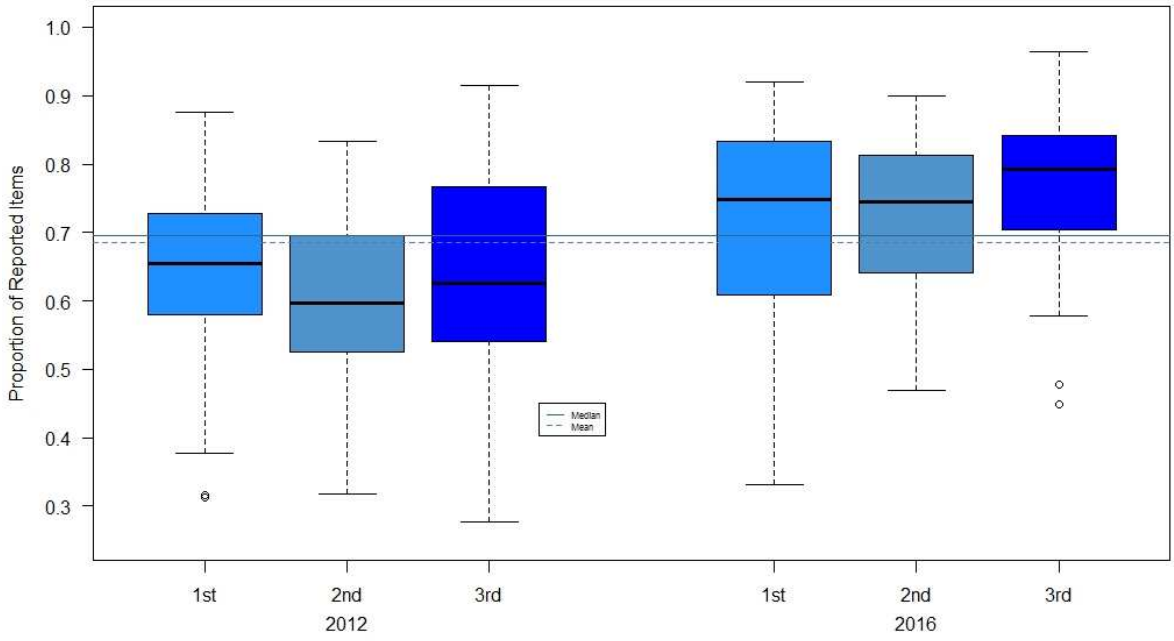
Figure 1B: Flow diagram for included randomized clinical trial protocols in ASPIRE with ethics approval in 2016



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%)