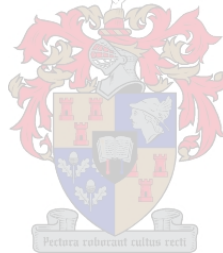


# Completeness of HIV intervention trial protocols: A systematic survey

by  
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Thesis presented in fulfilment of the requirements for the degree of Master of Science in Clinical Epidemiology in the Faculty of Medicine and Health Sciences at Stellenbosch University



Supervisor Dr Moleen Dzikiti

April 2019

## **Declaration**

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April 2019

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## **Abstract**

### **Introduction**

The Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT<sup>1</sup>) 2013 guideline provides guidance to improve the quality of protocols. The aim of this study was to determine the completeness of randomised controlled trial protocols evaluating the efficacy or effectiveness of HIV prevention, treatment and care strategies using the SPIRIT 2013 checklist, and to identify factors associated with completeness of trial protocols.

### **Methods**

We searched MEDLINE, EMBASE, LILACS, Africa-wide information (EBSCOhost), Web of Science, Clinicaltrials.gov and CENTRAL (Wiley Cochrane Library) for randomized controlled trial protocols in May and June 2018. We included protocols for interventions in the HIV prevention, treatment and care fields published between 2008 and 2018. Two individuals independently screened the titles and abstracts. The adapted SPIRIT checklist was pilot tested independently in duplicate on the first 4 (5%) protocols. The rest of the data was collected by a single individual and verified by second reviewer. Disagreements were resolved by consensus. We summarized categorical data using count (percent) and continuous variables using mean (standard deviation). Generalised estimation equations assuming a Poisson distribution were used to assess association of protocol factors with number of checklist items reported.

### **Results**

Seventy-nine protocols met the eligibility criteria and were included in the analysis. A mean of 32 (SD= 5) of the possible 51 SPIRIT checklist items were reported in the protocols. Detailed methodological aspects relating to intervention allocation, blinding, data management, study monitoring and dissemination policy information were often missing in the protocols. Intervention category, period of publication (before or after SPIRIT 2013 publication) and study setting were not significantly associated with protocol completeness.

### **Conclusion**

There is need for improvement in the reporting of recommended SPIRIT 2013 checklist items in HIV intervention protocols. We recommend active implementation

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<sup>1</sup> Abbreviation: SPIRIT- Standard Protocol Items: Recommendations for Interventional Trials

strategies of the SPIRIT guideline from publishing journals and HIV trialists to ensure more improvement in protocol quality.

## **Acknowledgements**

We thank Anel Schoonees for her input on the search strategy and implementing the search. Thanks to Prof. Lehana Thabane for advice on the scope of the search and statistical advice during the analysis. We wish to acknowledge the support and training Dr Moleen Dzikiti received from the University of California, San Francisco, International Traineeships in AIDS Prevention Studies (ITAPS), US NIMH, R25 MH064712.

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## Part A: Manuscript

Format follows the author guidelines of Contemporary Clinical Trials Communications journal.

# Completeness of HIV intervention trial protocols: A systematic survey

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## Keywords

HIV, randomized controlled trial, protocol, protocol quality, protocol completeness

## 1. Introduction

### 1.1 Background

Protocol publication is good practice as it increases transparency in research. The practice has evolved over the years from voluntary publication of links to full protocols in the results publications, to recommendations of prospective publication of protocols as pre-requisites for results publication by journals. The subsequent development of the EQUATOR network, which has guidelines and resources for writing and publishing protocols and clinical research is a great resource in this area [1, 2]. However, completeness and availability of protocols still remains poor [3, 4].

Published protocols should provide sufficient detail to enable understanding of the background, rationale, objectives, study population, interventions, methods, statistical analyses, ethical considerations, dissemination plans and administration of the trial, so as to enable replication of key aspects of trial methods and conduct [5]. Beyond trial conduct, the clarity of the protocol should facilitate proper appraisal of the scientific rigor by journal editors during peer review and systematic reviewers [6].

Empirical evidence comparing randomized controlled trial results publications and their corresponding protocols revealed unclear descriptions of allocation concealment in 83% of protocols reviewed, which potentially introduces selection bias during trial conduct [7]. Sample size and statistical plans were also found to be discrepant between protocol and final study publications in 82% of studies, which is associated with biased trial results and conclusions [3]. Biased results and conclusions may result in ill-informed policies to the detriment of human health. Poor reporting of methodological details may also necessitate protocol amendments which increases the costs of the research process and delay study conduct.

Empirical evidence of poor reporting in published protocols underscored the need for guidance to help improve the completeness and transparency of trial protocols. In 2013, a multiple stakeholder and evidence informed guidance document, the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) 2013

statement, was published [8]. It defined the minimum recommended standard items to be reported in interventional trial protocols [8].

A study evaluating reporting quality of protocols in the National Institute for Health Research Health Technology Assessment (NIHR-HTA<sup>2</sup>) database revealed that on average 63% of SPIRIT recommendations were reported [9]. However, this study was done seven months after the publication of the SPIRIT guideline, hence the impact of the guideline may not have been realised at that time.

HIV/AIDS is a public health priority and the field is fast evolving. Various interventions and strategies targeting prevention efforts, the care continuum from diagnosis, linkage to care, retention in care, with the desired outcome of viral suppression are under evaluation [10]. Given the pandemic nature of the disease, consequences of recommending inappropriate interventions caused by flawed study methodologies are significant at the individual and population level. It is therefore critical to investigate the status of protocol reporting in this field. There is no published study to our knowledge on the completeness of randomised controlled trial protocols in the HIV prevention, treatment and care field.

This manuscript was prepared following the PRISMA checklist, Appendix A. The protocol for the study is attached as Appendix B.

## **1.2 Study aim, objectives and hypotheses**

### **Study aim**

To assess the completeness of reporting of randomised controlled trial protocols evaluating the efficacy or effectiveness of HIV prevention, treatment and care interventions using the SPIRIT 2013 checklist.

### **Study objectives**

To determine how many items of SPIRIT guideline are documented in the trial protocols.

To determine study characteristics associated with completeness of reporting of trial protocols.

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<sup>2</sup> Abbreviation: NIHR-HTA -National Institute for Health Research Health Technology Assessment

## **Study hypotheses**

Hypothesis 1: SPIRIT endorsement of protocol publishing journal is associated with higher number of SPIRIT checklist items reported compared to non-endorsement by journals.

Hypothesis 2: SPIRIT checklist items reported in the different intervention categories HIV prevention alone; HIV treatment and prevention combined; HIV treatment and care are different.

Hypothesis 3: Multiple site studies are associated with higher number of SPIRIT checklist items reported compared to single site studies.

Hypothesis 4: Protocols published in post-SPIRIT 2013 publication are associated with higher number of SPIRIT checklist items reported compared to those published pre-SPIRIT 2013 publication.

## **2. Methods and materials**

### **2.1 Study design**

The study is a systematic survey of HIV intervention protocols published between 2008 and 2018.

### **2.2 Eligibility criteria**

Eligible articles were study protocols for randomised controlled trials (cluster, parallel, factorial or pragmatic design). Protocols investigating efficacy or effectiveness of pharmacological or non-pharmacological interventions, for HIV care, treatment and prevention. Protocols investigating efficacy or effectiveness of HIV related services or procedures for example counselling and testing services, linkage to care, adherence and retention. We included protocols published between 2008 and 2018 because we wanted to determine differences in protocol completeness 5 years prior to and 5 years post publication of the SPIRIT 2013 guidelines.

Ineligible articles were pilot or feasibility studies to determine feasibility of conducting a larger trial.

### **2.3 Study search**

Between 29 May and 01 June 2018, a researcher not involved in the survey conducted a database search for published randomised controlled trial protocols investigating HIV care, treatment and prevention interventions. We searched MEDLINE, EMBASE, LILACS, Africa-wide information (EBSCOhost), Web of

Science, Clinicaltrials.gov and CENTRAL (Wiley Cochrane Library) using medical subject headings (MESH) terms and search terms to identify the protocols. There was no language limitation in the search (see search strategy in Appendix C).

#### **2.4 Study selection**

Two reviewers (SS and MD) screened the titles and abstracts independently, using Covidence systematic reviews software (Veritas Health Innovation, Melbourne, Australia). Disagreements were resolved through discussion until consensus was reached. Following title and abstract screening, full texts of potentially eligible protocols were obtained and independently screened.

#### **2.5 Data extraction**

The SPIRIT checklist was adapted for this study. We also collected the following general information: year of publication, journal name, journal endorsement of SPIRIT statement (checked from SPIRIT website), whether it was a single or multiple site trial, study funding source and a brief description of the study intervention and intended outcomes to enable classification of the trials into different intervention categories. The adapted study checklist is attached as Appendix D. The first four (5%) protocols were reviewed and data extraction done independently by two individuals (SS and MD) in a pilot test of the checklist. Ratings were compared for all the items and conflicts resolved by discussion. The rest of the protocols were single extracted by SS and reviewed by MD. The reviewers were not blinded to the publishing journals.

Assessment of trial protocol completeness was done using the 33 items of the SPIRIT checklist which are recommended for inclusion in a trial protocol [5]. The individual recommendations of items with subcategories were retained to give a total of 51 items for which inclusion in the protocol was judged. Checklist items reported in the protocol were recorded as “yes” and unreported items as “no”. Items deemed as not applicable were checked as such. The number 1 was assigned to all “yes” responses and 0 to “no” responses. For an item with multiple components recommended, failure to satisfy all components would result in the item being assigned the number 2 and notes taken on the missing components. We summarized the information that was commonly missing on those items. However items rated 1 and 2 were combined during analysis. The data extracted for each

protocol is provided as supplementary file 1 in excel format together with the codebook to assist with review of the spreadsheet.

## **2.6 Data analysis**

We summarized categorical data using count (percent). We summarized the number of items in the SPIRIT guidelines that were reported in the study protocols using mean (standard deviation). Overall completeness of the protocol was calculated as the total number of the yes responses out of the total number of applicable items. We used generalized estimation equations (GEE<sup>3</sup>) assuming a Poisson distribution with an exchangeable correlation structure to determine factors associated with the number of SPIRIT guideline items reported. The GEE model accounted for within-journal clustering of the published protocols and we also adjusted for the number of items applicable for the specific protocol. The factors explored were: SPIRIT endorsement of protocol publishing journal; intervention category (HIV prevention alone; HIV treatment and prevention combined; HIV treatment and care); study setting (multiple or single site); and publication period (pre-SPIRIT 2008 to 2013 and post-SPIRIT 2014 to 2018). We hypothesised that these covariates would be associated with the number of checklist items reported. We required 37 protocols for the primary analysis (based on an estimated mean number of checklist items reported) , with an upward adjustment of 10 protocols for each factor we included in the GEE model to give a total of 87 protocols. Data analyses was performed using STATA 15 (Stata Corp., College Station, Texas, USA).

## **3. Results**

### **3.1 Results of the search**

The database search outputs yielded a total of 4871 references. After removing duplicates (n = 632) and non-eligible articles (n = 4119) articles after title and abstract screening, 120 protocols had full text screening with 79 protocols meeting the eligibility criteria (see Figure 1). A list of excluded protocols and reasons for exclusion is presented in Appendix E.

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<sup>3</sup> Abbreviation: GEE- Generalised estimation equations

### 3.2 Characteristics of included protocols

Characteristics of included protocols are summarized in Table 1. Characteristics of each protocol included and their references are presented in Appendix F. About three quarters (75%) of included studies were published after SPIRIT 2013 publication. Only 2 (3%) studies were industry funded. Over a third (35%) of the protocols were published in the *Trials* journal. About half (51%) of included studies were investigating behavioural intervention strategies. Most of the protocols (39%) were targeting a combination of HIV testing, linkage to and retention in care followed by HIV testing and risk reduction interventions in 22% of the protocols. Most studies (62%) were planned to be conducted in Africa.

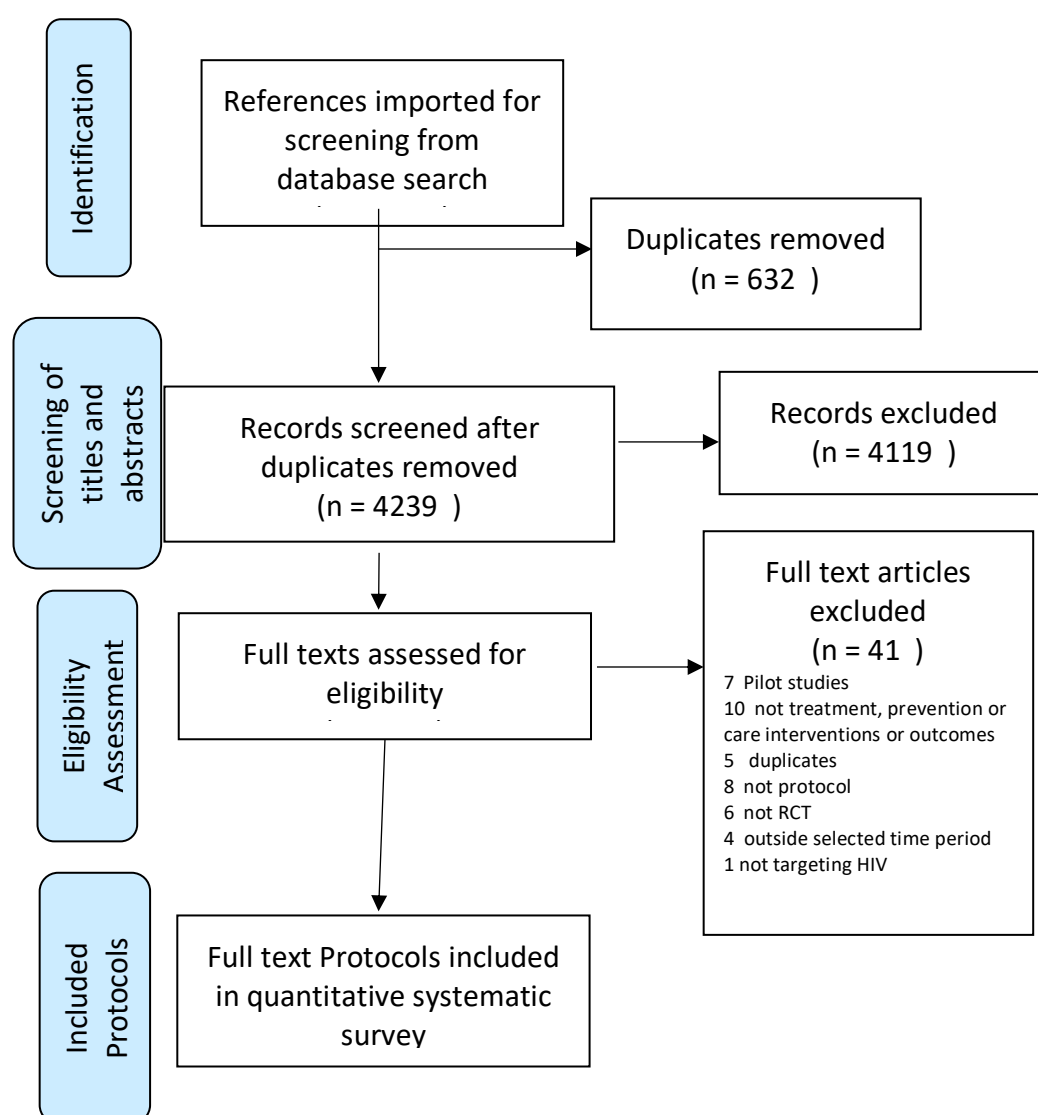


Figure 1 PRISMA flow diagram

### **3.3 Overall reporting of SPIRIT checklist recommendations**

The included protocols reported a mean of 32 (SD 5) checklist items. Study findings on SPIRIT items reported in included protocols are summarised below and presented in Figure 2.

#### **3.3.1 Administrative information**

All protocols reported a descriptive title as well as the roles of protocol contributors. Almost all protocols 75/79 (95% ) reported their trial registration number while none of the protocols included the WHO trial registration data set. The protocol version was reported in very few 5/79 (6%) protocols. The sources of funding were reported in almost all 76/79 (96%) protocols. However, only about half 36/79 (46%) of protocols reported on whether the study funders had any role or ultimate authority over any study activities. The least reported item was the study coordinating committees which was reported in a fifth 16/79 (20%) of the protocols.

#### **3.3.2 Introduction**

The introduction was generally well reported in all 79 protocols providing study justifications, objectives as well as the trial designs.

#### **3.3.3 Methods: Participants, interventions and outcomes**

Protocols routinely included participant, intervention and outcome information with all 79 of them reporting eligibility criteria, study setting, sufficiently detailed descriptions of interventions, study outcomes, participant schedules and study recruitment strategies. Sample size calculations were reported by almost all 76/79 (96%) protocols. Almost three quarters 56/79 (71%) of protocols reported on intervention adherence strategies. Concomitant care was reported by 33/79 (42%) of protocols, whilst only 9/79 (11%) protocols reported criteria for modifying or discontinuing interventions.

#### **3.3.4 Methods: Assignment of interventions**

With respect to allocation of interventions, detailed methods of allocation sequence generation and concealment of the sequence were reported in 57/79 (72%) and 46/79 (58%) of protocols respectively, with about 44/79 (56%) reporting on individuals involved in the randomization processes. Almost 48/79 (61%) reported on the blinding status of the trial, whilst only 5/59 (8%) of the blinded trials reported on circumstances when emergency unblinding would be permissible.

Table 1. Characteristics of included protocols (n = 79)

Characteristic		n (%)	
Period of protocol publication	Pre-SPIRIT 2008 - 2013	20 (25)	
	Post-SPIRIT 2014 - 2018	59 (75)	
Funding	Industry	2 (2)	
	Non-industry	74 (94)	
	Not reported	3 (4)	
Study setting	Single-site	16 (20)	
	Multi-site	63 (80)	
Geographical region	Africa	49 (62)	
	Asia	10 (13)	
	N. America	17 (21)	
	Europe	2 (3)	
	Middle East	1 (1)	
Protocol intervention category	HIV prevention	25 (32)	
	HIV prevention and treatment	13 (16)	
	HIV treatment and care	41 (52)	
Protocol Intervention target	Adherence and retention in care	14 (18)	
	Risk reduction and Testing	17 (22)	
	Testing, linkage and retention in care	31 (39)	
	Retention in care	8 (10)	
	Therapy initiation, option and switch	5 (6)	
	Immune boost	2 (3)	
	Opportunistic infection prophylaxis	1 (1)	
	Palliative care	1 (1)	
	Publishing journal	BMC Health Services Research	3 (4)
		BMC Medical Informatics and Decision making	1 (1)
BMC Medical Research methodology		1 (1)	
BMC Public health		7 (9)	
BMC infectious diseases		9 (11)	
BMJ Open		5 (6)	
Contemporary clinical trials		3 (4)	
Implementation Science		6 (8)	
Iranian Journal of Psychiatry		1 (1)	
J Acquired Immune Defic. Syndr.		3 (4)	
JMIR		12 (15)	
Trials		28 (35)	
Publishing journal SPIRIT endorsement status	Yes	72 (91)	
	No	7 (9)	

Funding: main trial sponsor

SPIRIT endorsement: based on listing on SPIRIT endorsement website [11].



### **3.3.5 Methods: Data collection, management and analysis**

All 79 protocols reported plans for trial data collection but about two thirds 54/79 (68%) reported on their data management plans. Over half 44/78 (56%) of protocols reported their plans to promote participant retention and complete follow-up of participants. Almost all protocols reported the statistical methods for primary and secondary outcome analysis 78/79 (99%) and any planned additional analyses 77/79 (98%). However, 55/79 (70%) defined the analysis population relating to protocol non-adherence.

### **3.3.6 Methods: Monitoring**

Data monitoring plans were poorly reported with 31/79 (39%) reporting on Data Monitoring Committees (DMC), just under a third 22/75 (29%) reporting on planned interim analyses and trial stopping guidelines and only 12/79 (15%) reporting on periodic (non-routine) trial auditing procedures and frequency. Evaluation of solicited and spontaneously reported harms was reported in just under half 37/78 (47%) of study protocols.

### **3.3.7 Ethics and dissemination**

Ethics approvals and plans for seeking such approvals were reported in almost all 77/79 (97%) of protocols while almost a quarter 18/79 (23%) reported on plans for communicating important modifications to the trial protocol. All 76/76 (100%) protocols reported on general consent and assent. However, just under half 5/11 (45%) of the protocols which reported on planned ancillary studies provided additional consent provisions for the use of participant data and specimens in future studies. Conflicts of interest were highly declared 75/79 (95%) while protection of confidentiality was reported in about 70% (55/79) of protocols. Low reporting was observed on issues regarding access to final trial dataset 25/79 (32%), ancillary and post-trial care for participants 10/78 (13%), trials results dissemination plans 26/79 (33%), authorship guidelines 7/79 (9%) and plans for making trial dataset and full protocol available to the public 16/79 (20%).

### **3.3.8 Appendices**

A few 7/76 (9%) protocols included a model informed consent form as an appendix.

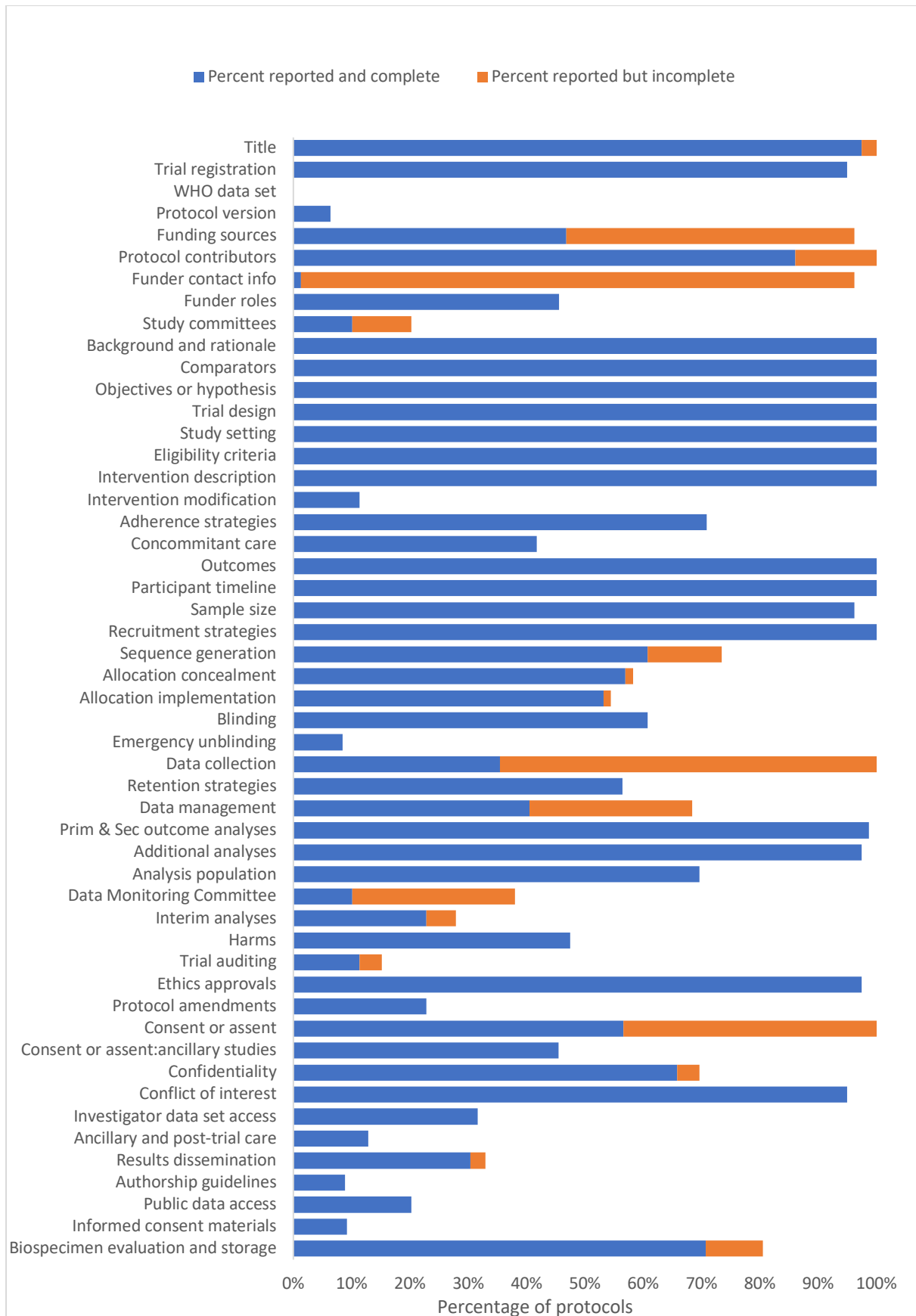


Figure 2 Percentage of protocols reporting individual items was calculated with adjusted denominators (n-x), x being the number of protocols for which that particular checklist item was judged to be inapplicable and n=79 protocols.

### 3.4 Factors associated with number of SPIRIT checklist items reported

Generalised estimation equations results for the protocol characteristics associated with number of reported items are presented in Table 2. We excluded the funding source from the multivariate model. This was because of significant imbalance in the numbers of protocols since almost all, 74/79 (94%) of included studies were non-industry funded, with only 2 studies that were industry funded. We also excluded SPIRIT endorsement because most protocols, 72/79 (91%) were published in journals which endorsed the guideline at the time this study was conducted. The full GEE model output is attached as Appendix G.

Table 2. Univariate and multivariate generalized estimation equations model results

Protocol characteristic	Unadjusted analysis			Adjusted analysis		
	Incidence Rate Ratio	95% CI	p-value	Incidence Rate Ratio	95% CI	p-value
Published 2014 - 2018 versus 2008 - 2013	1.05	0.98 to 1.13	0.15	1.05	0.98 to 1.12	0.20
Multi-site vs single-site trial	1.02	0.91 to 1.15	0.71	1.01	0.91 to 1.12	0.81
Intervention HIV prevention vs HIV prevention and treatment	1 (reference) 1.03	0.96 to 1.11	0.45	1 (reference) 1.03	0.93 to 1.14	0.58
HIV prevention vs HIV treatment and care	1 (reference) 1.00	0.95 to 1.05	1.00	1 (reference) 1.01	0.94 to 1.09	0.73

None of the covariates were associated with number of SPIRIT checklist items that were reported in the study protocol.

## 4. Discussion

### 4.1 Summary of findings

Overall, reporting of SPIRIT items in the included protocols was above average. A study conducted on the SPIRIT 2013 checklist by Kyte *et. al* produced similar results showing that about a third of checklist items were missing from protocols [9]. The administrative information and introduction sections were generally very well reported except for the WHO recommended trial registration data set, protocol version and roles of study committees and sponsors. Absence of information on

study coordinating committees results in reviewers being unable to appreciate the expertise of the individuals overseeing the safety of participants as well as other quality aspects of the study. The role of study sponsors could potentially be associated with bias if the sponsor controls key aspects of the trial [12].

We found that methodological details in published HIV clinical trial protocols are still quite deficient five years after the publication of the SPIRIT guideline. These results are in agreement with available empirical evidence on deficient important methodological aspects of protocols [9,7]. Of note, allocation concealment and implementation of randomization were missing in about half of protocols. These elements are associated with the successful implementation of randomisation, the core procedure that renders randomised controlled trials to be regarded as the 'gold standard' in clinical research. Poor implementation of randomisation could result in selection bias creeping into studies thus undermining the internal validity of the trial, often resulting in exaggerated effect sizes [13].

Also poorly reported was the analysis population relating to protocol non-adherence. This was not reported in about a third (30%) of the protocols. Analysis by intention to treat is recommended for randomised controlled trials as it gives more conservative view of the intervention effects [14]. It is important that this item be reported in protocols so as to enable assessment of protocols for selection bias and attrition bias depending on the chosen primary analysis population.

It is important to note that though methodological elements were not adequately reported in the protocols, their implementation during trial conduct may be satisfactory if they are adequately explained in procedure manuals. However these manuals are normally unavailable for the various stakeholders reviewing protocols and research reports, hence the need to adequately and consistently report them in all trial documents.

Data quality is key to collection of valid and reliable trial data. In the included protocols, though data collection plans were reported in all protocols, about two thirds of these reports were incomplete. The missing information related to the data quality processes, and references to where data collection forms could be accessed.

The data management item also missed key data security and quality processes. Data collection and management flaws can introduce bias into the study thus reducing internal validity of the trial.

Periodic independent trial auditing is an important check that verifies and ensures that trial conduct is being done according to standard policies and procedures, including basic good clinical practices. This aspect was reported in only 15% of trial protocols despite its importance in ensuring participant protection and data integrity. Other aspects of data monitoring such as Data Monitoring Committees and interim analyses plans were also poorly reported possibly due to the minimal risk presented by the interventions in the trials, since the majority were behavioural in nature.

Poor reporting of the study dissemination plans has implications on the ethical obligation to publish research results and transparency of research. Lack of dissemination plans also drives publication bias as null and negative results are less likely to be submitted for publication [15].

We compared completeness of trial protocols published prior to, and after the publication to SPIRIT guidelines. We found statistically insignificant difference in the reporting of protocols between the two time periods. This could be due to variations in implementation policies of the SPIRIT statement by the different publishing journals and awareness of the existence of the guidelines by protocol authors. Thus, the guideline did not have a significant association with protocol completeness on the included HIV protocols since its publication in comparison to the time prior to its publication.

The results of this study show that there is room for improvement in the reporting of published HIV trial protocols which should be considered by HIV trialists as they publish their protocols. This is more so important given the pandemic nature of HIV where flawed study designs may impact health at the world population level. We also noted the unavailability of published protocols investigating pharmacological agents in the databases searched. This could be related to the fact that these are mostly industry funded. However, all protocols should be published in order to fulfil the research transparency agenda.

However, the lack of compliance is not surprising given that there are varying levels of guideline endorsement and implementation. Currently the SPIRIT statement has been endorsed by various journals, regulators, research funders, trial groups as well as patient groups [11]. Levels of endorsement range from general statements of support, investigator encouragement and explicit requirements to use the checklist [16]. Strong endorsement policy with intentional implementation is likely to result in more improvement in the completeness and reporting of all checklist items [17]. This will ensure that HIV trials are of high scientific rigor given the significance of the disease. We recommend a bigger study which incorporates the individual journal endorsement level with respect to SPIRIT implementation. In addition, a follow-up study comparing the reporting of the protocols against completed study reports would be helpful to see if any discrepancies exist. It will also be worthwhile to conduct a survey on the SPIRIT guideline implementation strategies that are being utilised by journals.

#### **4.2 Strengths and weaknesses**

The main strength of the study is the use of systematic methods in conducting the survey. The study included protocols from periods prior to and post SPIRIT publication which allowed for a comparison of the two periods.

The study had various limitations. Though we searched multiple databases, our search likely missed other protocols which may be published in journals which are not indexed in these databases. Overall, this limits the generalizability of these study results in the HIV field.

The use of a composite score assumes that each of the 51 items on the SPIRIT checklist are equally important. This may not be the case as readers perspectives vary. In addition, the different research biases associated with the checklist items variably affect trial results. However, we decided to look at all the SPIRIT checklist items so as to get a general sense of adherence of protocols to the checklist as a whole.

However, we did not account for the journal endorsement status at the actual time when the included protocol was published. It is possible that some protocols were published in the study defined post-SPIRIT era, prior to the journals endorsing, or actively implementing the SPIRIT statement. This could have biased the results towards the null.

## **5. Conclusion**

There is need for improvement in the reporting of recommended SPIRIT 2013 items in HIV intervention protocols. Detailed methodological aspects relating to intervention allocation, blinding, data management, study monitoring and dissemination policy information were often missing in the protocols. We recommend future research comparing HIV trial protocols and reports after trial conduct, as well as on the awareness of SPIRIT guidelines among researchers.

## **6. Funding**

This research did not receive any specific grant from funding agencies in the public, commercial or not-for-profit sectors.

## **7. Conflict of interest**

The authors have no conflicts of interest to declare.

## **8. Data access**

The data for the study is attached as a supplementary file.

## **Appendices**

**Appendix A: PRISMA checklist**

**Appendix B: Protocol version 2.0 and Summary of changes**

**Appendix C: Search strategy**

**Appendix D: Adapted study data extraction checklist**

**Appendix E: Excluded protocols**

**Appendix F: Table of included protocols characteristics and references**

**Appendix G: Generalised estimation equations analyses output**

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## Appendix A: PRISMA checklist

Section/topic	#	Checklist item	Reported on page #
<b>TITLE</b>			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	6
<b>ABSTRACT</b>			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	7
<b>INTRODUCTION</b>			
Rationale	3	Describe the rationale for the review in the context of what is already known.	9,10
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	10
<b>METHODS</b>			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	Not registered
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	11
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	11
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	37
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	12
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	12
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	40
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	n/a
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	n/a
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., $I^2$ ) for each meta-analysis.	n/a
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	n/a
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	13

<b>RESULTS</b>			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	13,14
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	14,45
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	n/a
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	n/a
Synthesis of results	21	Present the main results of the review. If meta-analyses are done, include for each, confidence intervals and measures of consistency"	15-19
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	n/a
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	19
<b>DISCUSSION</b>			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	19
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	22
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	23
<b>FUNDING</b>			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	23

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

## Appendix B: Protocol Version 2.0

# Completeness of HIV intervention trial protocols: a protocol for a systematic survey

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Protocol version 2.0 dated May 24, 2018

## Abbreviations

CONSORT	Consolidated Standards of Reporting Trials
IEC	Independent Ethics Committee
NIHR-HTA	National Institutes of Health Research- Health Technology Assessment
PRO	Patient Reported Outcomes
PRISMA-P	Preferred Reporting Items for Systematic review and Meta-Analysis Protocols
RCT	Randomised Controlled Trial
SPIRIT	Standard Protocol Items: Recommendations for Interventional Trials

## Keywords

HIV treatment efficacy, HIV prevention efficacy, randomised controlled trials, clinical trials, protocol reporting, protocol completeness, SPIRIT guideline, SPIRIT checklist

## Introduction

A clinical trial protocol is an important document for trial implementation. The Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guideline specifies that a protocol should provide sufficient detail to enable understanding of the background, rationale, objectives, study population, interventions, methods, statistical analyses, ethical considerations, dissemination plans and administration of the trial. It should be detailed enough to allow replication of key aspects of trial methods and conduct. The level of clarity and transparency should allow proper appraisal of the scientific and ethical rigor from ethics approval all the way to dissemination of results [5]. Beyond study implementation, the protocol is used by systematic reviewers and journal editors for assessment of bias and peer review respectively [6].

Given the diversity of stakeholders who use protocols, it is therefore imperative that the content reported in a trial protocol be both transparent and adequately detailed to sufficiently address the needs of all the users of protocols. However, there is empirical evidence on the lack of information such as unclear descriptions of allocation concealment in 83% of protocols reviewed, which potentially introduces selection bias during trial conduct [7]. Sample size and statistical plans were also found to be discrepant between protocol and final study publications in 82% of studies, which is associated with biased trial results and conclusions[3]. Biased results and conclusions may result in ill-informed policies to the detriment of human health. Poor reporting of methodological details may necessitate protocol amendments which increases the costs of the trial.

The above empirical evidence underscores the need for guidance on good protocol reporting. Several guidelines for protocol writing are available and a review of these guidelines in 2012 revealed great variation in the scope and recommendations given [6]. The review also showed that the guidelines lacked citation of broad stakeholder involvement in their development or

the use of empirical evidence to support their recommendations. To address these deficiencies, the SPIRIT initiative was launched bringing together international stakeholders, to systematically produce a comprehensive evidence informed guideline to help improve the completeness and transparency of trial protocols. The SPIRIT guideline was published in January 2013 as a 33-item evidence based checklist for high quality protocol content[8]. An explanation and elaboration document was also published with important information and examples for each checklist item[5].

Availability of the SPIRIT guideline alone does not guarantee improvement in the quality of protocols. Turner et al [18] showed 85% relative benefit of endorsement of the Consolidated Standards of Reporting Trials (CONSORT) statement on completeness of randomised trial reports when compared with journals that did not endorse the CONSORT guideline. The various stakeholders such as trial investigators, research sponsors, ethics committees, trial registries and journal editors need to endorse and intentionally implement the guideline in order to see the outcome of improved protocol quality. Currently, the SPIRIT guideline has been endorsed by various journals, regulators, research funders, trial groups as well as patient groups[11]. Implementation of the SPIRIT guidelines in protocol development is expected to ultimately increase the robustness of medical literature used to inform health care decisions.

There are few published studies that have measured the impact the SPIRIT guidelines on protocol reporting quality. A study evaluating reporting quality of protocols in the National Institute for Health Research Health Technology Assessment (NIHR-HTA) database revealed that on average 63% of SPIRIT recommendations were reported [9]. However, this study was done seven months after the publication of SPIRIT guideline, hence the impact may not have been realised at that time. There is a published protocol for a systematic review that will assess planned statistical methods for surgical protocols using the SPIRIT guidelines [19]. This study will focus on specific areas of the SPIRIT checklist hence it does not give the overall completeness of the whole protocol. Given the highlighted importance of protocol reporting and how different sections of the protocol may potentially introduce bias, more studies are needed to assess the completeness of protocols in different research fields against the full SPIRIT checklist.

HIV is a fast evolving field of public health concern, with various interventions and strategies being tested in treatment, prevention and care services and procedures. There is no published data on protocol completeness since the publication of the SPIRIT guidelines. Our study seeks to measure the adherence to SPIRIT guidelines, of randomised controlled trial protocols on HIV interventions evaluating the efficacy or effectiveness of treatments, services or

procedures. A study focusing on protocol quality in this area will be useful to HIV research stakeholders as it will provide feedback on quality of protocols and highlight areas of improvement. The results will be disseminated in peer-reviewed publications.

### **Research question and objectives**

#### **Research question**

What is the status of protocol reporting quality for HIV randomised controlled trial protocols evaluating the efficacy or effectiveness of treatments, prevention strategies and services or procedures?

#### **Research objectives**

- 1] To determine how many items of SPIRIT guideline are documented in the trial protocol,
- 2] To determine the association of protocol characteristics with the number of items of the SPIRIT guideline reported in trials protocols.

### **Methods**

#### **Study design**

The study will be systematic survey of protocols for HIV evaluating the efficacy or effectiveness of treatments, prevention strategies and care services or procedures for completeness based on the SPIRIT checklist recommendations. The protocol will follow the Preferred Reporting Items for Systematic review and Meta-Analysis Protocols (PRISMA-P) checklist recommendations [20].

#### **Eligibility criteria**

Eligible RCT study protocols should meet the following criteria:

- It should be a protocol or methods paper for an RCT (cluster, parallel, factorial or pragmatic design) and should not report trial outcomes.
- The RCT must investigate efficacy or effectiveness of pharmacological or non-pharmacological agents for HIV treatment, care and prevention.
- The RCT must be for HIV related services or procedures
- The RCT should not be a pilot or feasibility study to determine feasibility of conducting an efficacy study.
- The protocols should be published between 2008 and 2018.

#### **Search strategy**

We will search the following databases MEDLINE (PubMed), EMBASE(OVID) and Cinahl (EBSCOHost) and clinical trials registries listed on the SPIRIT website [21] for protocols. The search strategy will include the terms randomized controlled trial, HIV and protocol and their synonyms. Reference lists of all included protocols will be manually searched to ensure that there are no relevant study protocols that have been missed by the database search.

#### **Data screening, extraction and synthesis**

Two reviewers will independently screen titles and abstracts from the search output and extract data of eligible trial protocols. Disagreements will be resolved through consensus. Data

regarding compliance of the protocols with each of the 51 SPIRIT checklist items (all subsections of the 33 items on the checklist are counted individually) will be extracted using a standard data extraction form. We will also extract information on whether: the journal/ trial registry endorses the SPIRIT guideline, the protocol was for a single or multi-centre study, the protocol was for an intervention for treatment, care, prevention, services or procedures related to HIV, the study was industry or non-industry funded and year of publication 2008 -2013 (2008- 2013 pre-SPIRIT era; 2014 -2018 post SPIRIT era).

### **Sample size**

Sample size will be calculated based on a score of the number of items of the SPIRIT checklist reported in the trial protocols. A survey assessing the quality of reporting randomised protocols in the NIHR HTA programme database found that studies reported a mean score of 32 SPIRIT checklist items, range 16-41 (standard deviation 6.25) [9]. To estimate a similar mean score, (with a 95% confidence level of  $\pm 3$  scores) of items of the SPIRIT guideline documented in published randomized trial protocols for prevention and treatment of HIV, we require 37 protocols. We will test the association of five potential factors (listed under data extraction and synthesis) with the number of items of the SPIRIT checklist reported in published protocols. After an upward adjustment of 10 studies for each factor included in the analysis, 87 protocols will be required. We will randomly select protocols from the eligible protocols list, if we find more eligible protocols than the required sample size.

### **Statistical analysis**

We will summarize the characteristics of included protocols using mean (standard deviation) or median (interquartile range) for continuous variables depending on the distribution, and categorical data using count (percent). We will use count (percent) to summarize items of SPIRIT guideline documented in published protocols. We will use generalized estimation equations (GEE), that assume a Poisson distribution and an unstructured covariance matrix to explore factors associated with the number of items of SPIRIT guideline complied with, in protocol reports. Incidence rate ratio estimates will be reported for the GEE model. We will report estimates with the corresponding 95% confidence interval (CI). Alpha of 0.05 will be used as the criterion for statistical significance. We will control for the following factors in our models: 1) whether the journal or trial registry endorses the SPIRIT guideline, 2) whether the proposed study was a single or multi-site, 3) whether the proposed study was on prevention or treatment of HIV disease, 4) year of publication (2008 to 2012 (pre-SPIRIT) and 2013 to 2018 (post SPIRIT) and 5) whether the study was industry funded or non-industry funded. All analyses will be done using STATA version 15.



**Ethical considerations**

For this type of study formal ethics approval is not required. Funding sources will have no role in study design; analysis and interpretation of data; in the writing of the report; and in the decision to submit the article for publication.

**Dissemination**

The results of this study will be disseminated in peer reviewed publications and presented at conferences.

**Conflict of interest**

None declared.

**Budget**

The anticipated costs for this study are publication costs. The cost is estimated to be R32 000 (£1 800).

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### Protocol Summary of changes

**Project title:** Completeness of HIV treatment and prevention trial protocols: a protocol for a systematic survey

Summary of changes from Protocol version 1.0 dated April 24, 2018 to Protocol version 2.0 dated May 24, 2018

<b>Protocol Version 1.0</b> <b>Dated</b> April 24, 2018	<b>Protocol Version 2</b> <b>dated</b> May 24, 2018	<b>Rationale</b>
<b>Title page 1</b> Completeness of HIV treatment and prevention trial protocols: a protocol for a systematic survey	<b>Title page 1</b> Completeness of HIV <u>intervention</u> trial protocols: a protocol for a systematic survey	Title changed to match broader scope of trial
<b>Introduction page 5</b> HIV treatment and prevention is a fast evolving field of public health concern with no identified published data on protocol completeness. A study focusing on protocol quality in this area will be useful to HIV research stakeholders as it will provide feedback on quality of protocols and highlight areas of improvement. The results will be disseminated in peer-reviewed publications.	<b>Introduction page 5</b> HIV is a fast evolving field of public health concern, <u>with various interventions and strategies being tested in treatment, prevention and care services and procedures. There is no published data on protocol completeness since the publication of the SPIRIT guidelines. Our study seeks to measure the adherence to SPIRIT guidelines, of randomised controlled trial protocols on HIV interventions evaluating the efficacy or effectiveness of treatments, services or procedures.</u>	We reframed the scope of the study following advice from search specialist and Prof T. Lehana pertaining to availability of published study protocols.
<b>Research question page 5</b> What is the status of protocol reporting quality for HIV treatment efficacy and prevention efficacy trial protocols?	<b>Research question page 5</b> What is the status of protocol reporting quality for HIV <u>randomised controlled trial protocols evaluating the efficacy or effectiveness of treatments, prevention strategies and services or procedures?</u>	Research scope broadening
<b>Study design page 6</b> The study will be systematic survey of protocols for HIV treatment efficacy and prevention efficacy for completeness based on the SPIRIT checklist recommendations.	<b>Study design page 6</b> The study will be systematic survey of protocols for HIV <u>evaluating the efficacy or effectiveness of treatments, prevention strategies and care services or procedures</u> for completeness based on the SPIRIT checklist recommendations.	Research scope broadening
<b>Eligibility criteria page 6</b> It should be a protocol or methods paper for an RCT, cluster RCT or other RCT	<b>Eligibility criteria page 6</b> It should be a protocol or methods paper for an RCT ( <u>cluster, parallel, factorial or</u>	Refining eligibility criteria to match new scope of study

<p>design and should not report trial outcomes. The RCT must investigate efficacy of pharmacological agents, in any dosage form, for HIV treatment or prevention.</p>	<p><u>pragmatic design</u>) and should not report trial outcomes. The RCT must investigate efficacy <u>or effectiveness of pharmacological or non-pharmacological agents for HIV treatment, care and prevention.</u> <u>The RCT must be for HIV related services or procedures</u></p>	
<p><b>Search strategy page 6</b> The search strategy will include the terms randomized control*, RCT, intervention study, HIV disease, HIV/AIDS, HIV infection immunodeficiency, immune-suppression, treatment efficacy, prevention efficacy</p>	<p><b>Search strategy page 6</b> The search strategy will include the terms randomized <u>controlled trial, HIV and protocol and their synonyms</u></p>	Refining of search strategy
<p><b>Data screening, extraction and synthesis page 6</b> We will also extract information on whether: the journal/ trial registry endorses the SPIRIT guideline, the protocol was for a single or multi-centre study, the protocol was for an intervention on treatment, care or prevention of HIV, the study was industry or non-industry funded and year of publication 2008 -2013 (2008-January 2013 pre-SPIRIT era; February 2013 -2018 post SPIRIT era).</p>	<p><b>Data screening, extraction and synthesis page 6</b> We will also extract information on whether: the journal/ trial registry endorses the SPIRIT guideline, the protocol was for a single or multi-centre study, the protocol was <u>for an intervention for treatment, care, prevention, services or procedures related to HIV</u>, the study was industry or non-industry funded and year of publication 2008 -2013 <u>(2008- 2013 pre-SPIRIT era; 2014 -2018 post SPIRIT era).</u></p>	Revised definition of pre and post SPIRIT era to allow for transition period after guideline publication.

## Appendix C: Search strategy

### MSc Clin Epi research project

**Title:** What is the adherence to SPIRIT guidelines of randomised controlled trial protocols on HIV interventions evaluating the efficacy or effectiveness of treatments, services or procedures?

#### Electronic databases/registries to search

- Medline (PubMed)
- CENTRAL (Wiley Cochrane Library)
- EMBASE (Ovid)
- Africa-Wide Information (EBSCOhost)
- LILACS (Virtual Health Library)
- Web of Science – Core Collection
- ClinicalTrials.gov (<https://www.clinicaltrials.gov/>)

#### Medline (PubMed)

#1 Search All Fields (HIV OR hiv-1 OR hiv-2\* OR hiv1 OR hiv2 OR hiv infect\* OR human immunodeficiency virus OR human immune deficiency virus OR human immuno-deficiency virus OR human immune-deficiency virus OR ((human immun\*) AND (deficiency virus)) OR acquired immunodeficiency syndromes OR acquired immune deficiency syndrome OR acquired immuno-deficiency syndrome OR acquired immune-deficiency syndrome OR ((acquired immun\*) AND (deficiency syndrome)) OR HIV/AIDS)

#2 Search (HIV infections [MeSH] OR HIV [MeSH])

#3 (#1 OR #2)

#4 protocols OR proposals OR protocol OR proposal OR "Clinical Protocols" [Mesh]

#5 randomized controlled trial [pt] OR controlled clinical trial [pt] OR random [Title/Abstract] OR randomized [Title/Abstract] OR randomised [Title/Abstract] OR randomly [Title/Abstract] OR randomize [Title/Abstract] OR randomise [Title/Abstract] OR trial [Title/Abstract] OR experimental [Title/Abstract] OR experiment OR placebo [Title/Abstract] OR clinical trials as topic [mesh: noexp]

#6 #3 AND #4 AND #5

#7 animals [Mesh] NOT humans [Mesh]

#8 #6 NOT #7

Search date: 29 May 2018

No date limitations

Number of search results retrieved: 1871

#### CENTRAL (Wiley Cochrane Library)

#1 HIV or hiv-1 or hiv-2\* or hiv1 or hiv2 or hiv infect\* or human immunodeficiency virus or human immune deficiency virus or human immuno-deficiency virus or human immune-deficiency virus

#2 (human immun\*) and (deficiency virus) or acquired immunodeficiency syndromes or acquired immune deficiency syndrome or acquired immuno-deficiency syndrome or acquired immune-deficiency syndrome

#3 acquired immun\* and deficiency syndrome

#4 "HIV/AIDS"

#5 MeSH descriptor: [HIV] explode all trees

#6 MeSH descriptor: [HIV Infections] explode all trees

#7 #1 or #2 or #3 or #4 or #5 or #6

#8 protocols or proposals or protocol or proposal

#9 MeSH descriptor: [Clinical Protocols] explode all trees

#10 #8 or #9

#11 randomized controlled trial or controlled clinical trial or random OR randomized or randomised or randomly or randomize or randomise or trial or experimental or experiment or placebo

#12 MeSH descriptor: [Clinical Trials as Topic] explode all trees

#13 MeSH descriptor: [Randomized Controlled Trials as Topic] explode all trees

#14 MeSH descriptor: [Controlled Clinical Trials as Topic] explode all trees

#15 #11 or #12 or #13 or #14

#16 #7 AND #10 AND #15

#17 MeSH descriptor: [Humans] explode all trees

#18 MeSH descriptor: [Animals] explode all trees

#19 #18 not #17

#20 #16 not #19

Search date: 29 May 2018  
 No date limitations  
 Number of search results retrieved: 1083

**EMBASE (Ovid)**

- 
- 1 \*Human immunodeficiency virus/
  - 2 \*Human immunodeficiency virus infection/
  - 3 (human immunodeficiency virus or human immune deficiency virus or human immuno-deficiency virus or human immune-deficiency virus).ab.
  - 4 (human immunodeficiency virus or human immune deficiency virus or human immuno-deficiency virus or human immune-deficiency virus).ti.
  - 5 (hiv-1\* or hiv-2\* or hiv1 or hiv2).ti. or (hiv-1\* or hiv-2\* or hiv1 or hiv2).ab.
  - 6 1 or 2 or 3 or 4
  - 7 (acquired immunodeficiency syndromes or acquired immune deficiency syndrome or acquired immuno-deficiency syndrome or acquired immune-deficiency syndrome).ti. or (acquired immunodeficiency syndromes or acquired immune deficiency syndrome or acquired immuno-deficiency syndrome or acquired immune-deficiency syndrome).ab.
  - 8 (acquired immun\* and deficiency syndrome).ti. or (acquired immun\* and deficiency syndrome).ab.
  - 9 6 or 7 or 8
  - 10 (protocols or proposals or protocol or proposal).ab. or (protocols or proposals or protocol or proposal).ti.
  - 11 controlled clinical trial.mp. or Controlled Clinical Trial/
  - 12 randomized controlled trial.mp. or Randomized Controlled Trial/
  - 13 (randomized or randomised or randomly or randomize or randomise or trial or experimental or experiment or placebo).ab. or (randomized or randomised or randomly or randomize or randomise or trial or experimental or experiment or placebo).ti.
  - 14 clinical protocol/
  - 15 10 or 14
  - 16 11 or 12 or 13
  - 17 9 and 15 and 16
  - 18 animal/
  - 19 human/
  - 20 18 not 19
  - 21 17 not 20

Search date: 1 June 2018  
 No date limitations  
 Number of search results retrieved: 1080

**Africa-Wide Information (EBSCOhost)**

#1 All fields: (HIV OR hiv-1 OR hiv-2\* OR hiv1 OR hiv2 OR hiv infect\* OR human immunodeficiency virus OR human immune deficiency virus OR human immuno-deficiency virus OR human immune-deficiency virus OR ((human immun\*) AND (deficiency virus)) OR acquired immunodeficiency syndromes OR acquired immune deficiency syndrome OR acquired immuno-deficiency syndrome OR acquired immune-deficiency syndrome OR ((acquired immun\*) AND (deficiency syndrome)) OR HIV/AIDS)

#2 All fields: (protocols OR proposals OR protocol OR proposal)

#3 All fields: (randomized controlled trial or controlled clinical trial or random OR randomized or randomised or randomly or randomize or randomise or trial or experimental or experiment or placebo)

#4 #1 AND #2 AND #3

Search date: 31 May 2018  
 No date limitations  
 Number of search results retrieved: 459

**LILACS (Virtual Health Library)**

HIV\$ OR immune deficiency OR immune-deficiency OR immunodeficiency OR HIV/AIDS [Words] and protocols OR proposals OR protocol OR proposal [Words] and random\$ OR trial OR blind\$ OR control\$ OR compar\$ [Words]

Search date: 31 May 2018

No date limitations

Number of search results retrieved: 168

**Web of Science – Core Collection**

((TOPIC: (((((HIV\* OR "HIV infect\*") OR immune deficiency) OR immune-deficiency) OR immunodeficiency) OR HIV AIDS) AND TOPIC: (((protocols OR proposals) OR protocol) OR proposal)) AND TOPIC: (((((((((((randomized controlled trial OR controlled clinical trial) OR random) OR randomized) OR randomised) OR randomly) OR randomize) OR randomise) OR trial) OR experimental) OR experiment) OR placebo))

Timespan: All years. Indexes: SCI-EXPANDED, SSCI, CPCI-S.

Search date: 31 May 2018

No date limitations

Number of search results retrieved: 2139

**ClinicalTrials.gov (clinicaltrials.gov)**

(protocols OR proposals OR protocol OR proposal) | Interventional Studies | (HIV OR immune deficiency OR immune-deficiency OR immunodeficiency OR HIV/AIDS)

Search date: 31 May 2018

No date limitations

Number of search results retrieved: 576

**In summary:**

From all the databases, I imported a total of 7283 records (459 Africa-wide + 1082 CENTRAL + 576 clinicaltrials.gov + 1080 EMBASE + 1946 PubMed + 2139 Web of Science) into Endnote.

I have de-duplicated the findings: 2412 duplicates were removed

Numbers of records to screen: 4871

## Appendix D: Study checklist

Table B1. Study checklist for data collection

REF ID Number				Extracted by (initials)		
Topic	Item #	SPIRIT Checklist item description	Vote			
			Yes (1)	No (0)	N/A (leave blank)	
<b>Administrative information</b>						
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym				
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry				
	2b	All items from the World Health Organization Trial Registration Data Set				
Protocol version	3	Date and version identifier				
Funding	4	Sources and types of financial, material, and other support				
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors				
	5b	Name and contact information for the trial sponsor				
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities				
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)				
<b>Introduction</b>						
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention				
	6b	Explanation for choice of comparators				
Objectives	7	Specific objectives and hypotheses				
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)				
<b>Methods: Participants, interventions, and outcomes</b>						
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained				
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)				
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered				
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)				
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)				
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial				
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended				
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended				
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations				
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size				
<b>Methods: Assignment of interventions (for controlled trials)</b>						
Allocation Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided				



		in a separate document that is unavailable to those who enrol participants or assign interventions			
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned			
Allocation implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions			
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how			
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial			
Methods: Data collection, management, and analysis					
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol			
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols			
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol			
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol			
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)			
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)			
Methods: monitoring					
Monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed			
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial			
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct			
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor			
Ethics and dissemination					
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval			
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)			
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)			
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable			
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial			
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site			
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators			

Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation			
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions			
	31b	Authorship eligibility guidelines and any intended use of professional writers			
	31c	Plans, if any, for granting public access to the full protocol, participant- level dataset, and statistical code			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates			
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable			
Additional information					
Year of protocol publication					
Journal name					
Journal SPIRIT endorsement		Yes = 1      No =0			
Study setting		Single site =0                  Multi-center =1			
Funding source		Non-industry =0                  Industry =1			
Short description of intervention					

## Instructions for data collection.

1. Read the protocol and capture and rate each checklist item.
2. After reading a section meant to address a particular aspect of the protocol as defined by the checklist items, highlight the section and insert a comment on the PDF document that shows the checklist item it talks about and comment on whether the issue is adequately/completely addressed as per the SPIRIT checklist.
3. Enter the rating on the data extraction worksheet based on the judgement made from the comment in the document.
4. After rating each item and collecting the additional information on the data extraction form save the PDF document with comments with new file name (eg Ref ID 2071 extracted).

**Appendix E: Excluded protocols**

<b>Study</b>	<b>Reason for exclusion</b>
Skowron 1990	outside selected time period
Thabane 2011	duplicate
Strathdee 2015	not RCT
Naserbakht 2014	duplicate
Oyeledun 2014	duplicate
McCoy 1990	outside selected time period
Martinez 2018	Pilot study
Lebouche 2015	pilot study
Lebouche 2014	Pilot study
Laisaar 2013	not protocol
Hirshfield 2016	Not HIV treatment, prevention or care intervention or outcomes
Hargreaves 2016	Not HIV treatment, prevention or care intervention or outcomes
Jongbloed 2016	Pilot study
Jones 2015	duplicate
James 1995	outside selected time period
Iwuji 2013	Pilot study
Inwani 2017	Pilot study
Garner 2017	Not HIV treatment, prevention or care intervention or outcomes
Fowler 2014	not protocol
Fielding 2015	Not targeting HIV
Hanke 2000	not protocol
Gwadz 2017	not RCT
Grangeiro 2015	not RCT
Darbes 2014	duplicate
Cote 2015	Not HIV treatment, prevention or care intervention or outcomes

Coovadia 2012	not protocol
Conrad 2014	not protocol
Cobbing 2015	Not HIV treatment, prevention or care intervention or outcomes
Coates 2014	not protocol
Callahan 2007	Not protocol
Claborn 2018	Pilot study
Anon 2016	not protocol
Achillion 2010	not RCT
Achillion 2008	not RCT
Abramsky 2012	Not HIV treatment, prevention or care intervention or outcomes
Aboulker 1998	not RCT
Bigna 2013	Not HIV treatment, prevention or care intervention or outcomes
Beattie 2016	Not HIV treatment, prevention or care intervention or outcomes
Beattie 2015	Not HIV treatment, prevention or care intervention or outcomes
Bozzette 1990	Outside selected time period
Belenko 2013	Not HIV treatment, prevention or care intervention or outcomes

**Appendix F: Included protocols characteristics and their references**

Table of individual protocol characteristics

Study ID	Year published	Journal	Study design	Setting	Geo region	Population	Funding	Intervention category	Intervention target
Ezeanolue 2013	2013	Implementation Science	CRT	Single	Africa	Adults	Non-Industry	HIV prevention and treatment	Testing, linkage and retention in care
Woelk 2016	2016	Trials	CRT	Multiple	Africa	Adults	Non-Industry	HIV prevention and treatment	Testing, linkage and retention in care
Chang 2017	2017	Trials	CRT	Multiple	Africa	Adults	Non-Industry	HIV prevention and treatment	Testing, linkage and retention in care
Choko 2017	2017	Trials	CRT	Multiple	Africa	Adults	Non-Industry	HIV prevention and treatment	Testing, linkage and retention in care
Nosyk 2015	2015	Contemporary Clinical Trials	Stepped wedge CRT	Multiple	N. America	Adults	Non-Industry	HIV prevention and treatment	Testing, linkage and retention in care
Aliyu 2013	2013	Contemporary Clinical Trials	CRT	Multiple	Africa	Adult women	Non-Industry	HIV prevention and treatment	Testing, linkage and retention in care
Tomlinson 2016	2016	Trials	CRT	Multiple	Africa	Children 1-5years	Non-Industry	HIV prevention and treatment	Testing, linkage and retention in care
Odeny 2018	2018	Trials	CRT	Multiple	Africa	Adult women	Non-Industry	HIV prevention and treatment	Adherence and retention in care
Wechsberg 2014	2014	BMC public health	CRT	Multiple	Africa	Adult women	Non-Industry	HIV prevention and treatment	Risk reduction and Testing
Gwadz 2015	2015	BMC public health	Parallel RCT	Single	N. America	Adults	Non-Industry	HIV prevention and treatment	Testing, linkage and retention in care
Wamuti 2015	2015	Implementation Science	CRT	Multiple	Africa	Adults	Non-Industry	HIV prevention and treatment	Testing, linkage and retention in care
Sando 2014	2014	Trials	CRT	Multiple	Africa	Adult women	Non-Industry	HIV prevention and treatment	Testing, linkage and retention in care
McCrimmon 2018	2018	Trials	CRT	Multiple	Asia	Adult women	Non-Industry	HIV prevention and treatment	Testing and viral load suppression

Mustanski 2017	2017	JMIR Research protocols	Parallel RCT	Multiple	N. America	MSM	Non-Industry	HIV prevention	Risk reduction and Testing
Jones 2014	2014	Trials	CRT	Multiple	Africa	Adults	Non-Industry	HIV prevention	Testing, linkage and retention in care
Brody 2018	2018	Trials	Parallel RCT	Multiple	Asia	Adult women	Non-Industry	HIV prevention	Testing, linkage and retention in care
Kuhns 2017	2017	BMC public health	Parallel RCT	Multiple	N. America	Adults	Non-Industry	HIV prevention	Protected sex and STI prevention
Tomlinson 2011	2011	Trials	CRT	Single	Africa	Adult women	Non-Industry	HIV prevention	Testing, linkage and retention in care
Hayes 2014	2014	Trials	CRT	Multiple	Africa	Adults	Non-Industry	HIV prevention	Testing, linkage and retention in care
Chambers 2016	2016	BMC public health	Parallel RCT	Single	N. America	Adults	Non-Industry	HIV prevention	Risk reduction and Testing
Koblin 2017	2017	JMIR Research protocols	Parallel RCT	Single	N. America	YMSM and YTWS M	Non-Industry	HIV prevention	Testing
Liu 2016	2016	BMJ open	Parallel RCT	Single	Asia	MSM	Non-Industry	HIV prevention	Risk reduction and Testing
Lukhele 2016	2016	JMIR Research protocols	Parallel RCT	Single	Africa	Adults	Non-Industry	HIV prevention	Risk reduction and Testing
Nagot 2012	2012	BMC Infectious diseases	Parallel RCT	Multiple	Africa	Adult women and infants	Non-Industry	HIV prevention	Therapy option
Naserbakht 2014	2014	Iranian journal of psychiatry	Parallel RCT	Multiple	Middle East	Adults	Non-Industry	HIV prevention	Risk reduction and Testing
Pinchoff 2016	2016	Trials	CRT	Multiple	Africa	Adults	Non-Industry	HIV prevention	Risk reduction and Testing
Reimers 2016	2016	Journal of acquired immune deficiency syndromes	CRT	Multiple	Africa	Adult women	Non-Industry	HIV prevention	Adherence and retention in care
Oyeledun 2014	2014	Journal of acquired immune deficiency syndromes	CRT	Multiple	Africa	Adult women	Non-Industry	HIV prevention	Retention in care
Stephenson 2018	2018	JMIR Research protocols	Parallel RCT	Multiple	N. America	YMSM and	Not stated	HIV prevention	Risk reduction

						YTWS M			and Testing
Tucker 2017	2017	Trials	Stepped wedge CRT	Multiple	Asia	MSM	Non- Industry	HIV prevention	Risk reduction and Testing
Llewellyn 2012	2012	BMC Infectious diseases	Parallel RCT	Multiple	Europe	MSM	Non- Industry	HIV prevention	Risk reduction and Testing
Stephenson 2017	2017	JMIR Research protocols	Parallel RCT	Multiple	N. America	MSM	Not stated	HIV prevention	Risk reduction and Testing
Yan 2017	2017	BMC public health	Parallel RCT	Multiple	Asia	Adults	Non- Industry	HIV prevention	Risk reduction and Testing
Yuen 2013	2013	BMC public health	Parallel RCT	Multiple	Asia	Adult women	Non- Industry	HIV prevention	Risk reduction and Testing
Peltzer 2011	2011	BMC public health	CRT	Multiple	Africa	Adults	Non- Industry	HIV prevention	Testing, linkage and retention in care
Hamilton 2014	2014	Implementation Science	Parallel RCT	Multiple	N. America	Adults	Non- Industry	HIV prevention	Risk reduction and Testing
Zou 2017	2017	BMJ open	Parallel RCT	Multiple	Asia	MSM	Non- Industry	HIV prevention	Risk reduction and Testing
Andersson 2013	2013	Trials	CRT	Multiple	Africa	Adult women	Non- Industry	HIV prevention	Risk reduction and Testing
Dorward 2017	2017	BMJ open	Parallel RCT	Single	Africa	Adults	Non- Industry	HIV treatment and care	Testing and viral load suppression
Elul 2014	2014	BMC Infectious diseases	CRT	Multiple	Africa	Adults	Non- Industry	HIV treatment and care	Testing, linkage and retention in care
Fairall 2008	2008	Trials	CRT	Multiple	Africa	Adults	Non- Industry	HIV treatment and care	Therapy initiation
Fatti 2018	2018	Trials	CRT	Multiple	Africa	Adults	Non- Industry	HIV treatment and care	Retention in care
vanderKop 2013	2013	BMJ open	Parallel RCT	Single	Africa	Adults	Non- Industry	HIV treatment and care	Retention in care
Wagner 2016	2016	Trials	Parallel RCT	Multiple	N. America	Adults	Non- Industry	HIV treatment and care	Adherenc e
Kiene 2017	2017	BMC Infectious diseases	CRT	Multiple	Africa	Adults	Non- Industry	HIV treatment and care	Testing, linkage and retention in care
Hoffman 2017	2017	Trials	CRT	Multiple	Africa	Adults	Non- Industry	HIV treatment and care	Retention in care

Finocchario-Kessler 2015	2015	Implementation Science	CRT	Multiple	Africa	Infants	Non-Industry	HIV treatment and care	Testing, linkage and retention in care
LeGrand 2018	2018	JMIR Research protocols	Parallel RCT	Multiple	N. America	YMSM and YTWS M	Non-Industry	HIV treatment and care	Testing, linkage and retention in care
McNairy 2015	2015	Implementation Science	CRT	Multiple	Africa	Adults	Non-Industry	HIV treatment and care	Testing, linkage and retention in care
Chibweshah 2016	2016	Journal of acquired immune deficiency syndromes	Parallel RCT	Multiple	Africa	Infants	Non-Industry	HIV treatment and care	Testing, linkage and retention in care
Christopoulos 2014	2014	BMC Infectious diseases	Parallel RCT	Single	N. America	Adults	Non-Industry	HIV treatment and care	Retention in care
Yotebieng 2017	2017	BMC health services research	CRT	Multiple	Africa	Adults	Non-Industry	HIV treatment and care	Testing, linkage and retention in care
Mbuagbaw 2011	2011	Trials	Parallel RCT	Single	Africa	Adults	Non-Industry	HIV treatment and care	Adherence
Mavhu 2017	2017	Trials	CRT	Multiple	Africa	Adolescents	Industry	HIV treatment and care	Adherence and retention in care
Mao 2017	2017	BMC health services research	CRT	Multiple	Asia	Adults	Non-Industry	HIV treatment and care	Testing, linkage and retention in care
Lippman 2016	2016	Trials	CRT	Multiple	Africa	Adults	Non-Industry	HIV treatment and care	Testing, linkage and retention in care
Lippman 2017	2017	Implementation Science	CRT	Multiple	Africa	Adults	Non-Industry	HIV treatment and care	Testing, linkage and retention in care
Sam-Agudu 2017	2017	Trials	CRT	Multiple	Africa	Adolescents	Non-Industry	HIV treatment and care	Retention in care
Oberje 2013	2013	BMC health services research	Parallel RCT	Multiple	Europe	Adults	Non-Industry	HIV treatment and care	Adherence
L'Engle 2015	2015	JMIR Research protocols	CRT	Multiple	Africa	Adults	Non-Industry	HIV treatment and care	Adherence and retention in care
Lowther 2012	2012	BMC Infectious diseases	Parallel RCT	Multiple	Africa	Adults	Non-Industry	HIV treatment and care	Palliative care
Pence 2012	2012	Contemporary Clinical Trials	Parallel RCT	Multiple	N. America	Adults	Non-Industry	HIV treatment and care	Adherence
Walsh 2017	2017	Trials	Stepped wedge CRT	Multiple	Africa	Adults	Non-Industry	HIV treatment and care	Therapy initiation



Wagner 2016	2016	JMIR Research protocols	Parallel RCT	Single	N. America	Adults	Non-Industry	HIV treatment and care	Adherence
Wilson 2017	2017	Trials	Stepped wedge CRT	Multiple	Africa	Adolescents	Non-Industry	HIV treatment and care	Retention in care
Wirtz 2017	2017	JMIR Research protocols	Parallel RCT	Single	Asia	YMSM and YTWSM	Non-Industry	HIV treatment and care	Testing, linkage and retention in care
Wagner 2016	2016	JMIR Research protocols	Parallel RCT	Multiple	Africa	Adults	Non-Industry	HIV treatment and care	Adherence and retention in care
Bassett 2013	2013	BMC Infectious diseases	Parallel RCT	Multiple	Africa	Adults	Non-Industry	HIV treatment and care	Testing, linkage and retention in care
Lester 2009	2009	Trials	Parallel RCT	Multiple	Africa	Adults	Non-Industry	HIV treatment and care	Adherence
Stephenson 2017	2017	JMIR Research protocols	Parallel RCT	Multiple	N. America	MSM	Not stated	HIV treatment and care	Testing, linkage and retention in care
Awiti 2016	2016	BMC medical informatics and decision making	Parallel RCT	Multiple	Africa	Adult women	Non-Industry	HIV treatment and care	Retention in care
Amstutz 2018	2018	BMC Infectious diseases	Parallel RCT	Multiple	Africa	Adults	Non-Industry	HIV treatment	Therapy switch
Cote 2012	2012	Trials	Parallel RCT	Single	N. America	Adults	Non-Industry	HIV treatment	Adherence
Crane 2016	2016	JMIR Research protocols	Parallel RCT	Single	N. America	Adults	Non-Industry	HIV treatment	Adherence
Rosen 2017	2017	BMJ open	Parallel RCT	Multiple	Africa	Adults	Non-Industry	HIV treatment	Therapy initiation
DeCosta 2010	2010	BMC medical research methodology	Parallel RCT	Multiple	Asia	Adults	Non-Industry	HIV treatment	Adherence
Guwatudde 2012	2012	BMC Infectious diseases	Parallel RCT	Single	Africa	Adults	Non-Industry	HIV treatment	Immune boost
Kamwesiga 2011	2011	Trials	Parallel RCT	Multiple	Africa	Adults	Industry	HIV treatment	Immune boost
Laurens 2016	2016	Trials	Parallel RCT	Multiple	Africa	Adults	Non-Industry	HIV care	OI prophylaxis

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## Appendix G: Generalised estimation equations analyses output

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### 1. Univariate analysis for publication period

The publication period was coded as pre-SPIRIT (2008 to 2013) =0 and post-SPIRIT (2014 to 2018) = 1. The GEE model was offset by 1 for inapplicable items. The model was adjusted for journal clustering. There was no statistically significant association between publication period and number of SPIRIT checklist items reported.

```
. xtgee spirit_score pubyear2, family(poisson) link(log)
i(journalclust)offset(lnapplicable_items) corr(exchangeable) vce(robust
>) eform
```

Iteration 1: tolerance = .03254896  
Iteration 2: tolerance = .00393008  
Iteration 3: tolerance = .00020671  
Iteration 4: tolerance = 8.182e-06  
Iteration 5: tolerance = 3.522e-07

GEE population-averaged model	Number of obs	=	79
Group variable: journalclust	Number of groups	=	12
Link: log	Obs per group:		
Family: Poisson	min	=	1
Correlation: exchangeable	avg	=	6.6
	max	=	28
	Wald chi2(1)	=	2.07
Scale parameter: 1	Prob > chi2	=	0.1503

(Std. Err. adjusted for clustering on journalclust)

-----						
	Robust					
spirit_score	IRR	Std. Err.	z	P> z	[95% Conf. Interval]	
-----						
pubyear2	1.051612	.0367945	1.44	0.150	.9819137	1.126258
_cons	.6006125	.0246593	-12.42	0.000	.5541745	.6509417
lnapplicable_items	1 (offset)					

Note: \_cons estimates baseline incidence rate (conditional on zero random effects).

### 2. Univariate analysis for study setting

The study setting was coded as single site =0 and multi-site=1. The model was adjusted for journal clustering. There was no statistically significant association between study setting and number of SPIRIT checklist items reported.

```
. xtgee spirit_score singlelevsmultisite , family(poisson) link(log) i( journalclust )
offset(lnapplicable_items) corr(exchangeable)
```

```
> ) vce(robust) eform
```

```
Iteration 1: tolerance = .02248596
Iteration 2: tolerance = .00650162
Iteration 3: tolerance = .00052308
Iteration 4: tolerance = .00002396
Iteration 5: tolerance = 1.213e-06
Iteration 6: tolerance = 6.031e-08
```

```
GEE population-averaged model      Number of obs   =    79
Group variable:      journalclust   Number of groups =    12
Link:                log            Obs per group:
Family:              Poisson                min =    1
Correlation:         exchangeable         avg  =    6.6
                                                max  =    28
                                                Wald chi2(1)   =    0.14
Scale parameter:      1              Prob > chi2     =    0.7077
```

(Std. Err. adjusted for clustering on journalclust)

```
-----+-----
          |               Robust
spirit_score | IRR      Std. Err.      z    P>|z|    [95% Conf. Interval]
-----+-----
singlevsmultisite| 1.023059   .0622046    0.37  0.708   .9081244   1.15254
      _cons | .6111217   .028753   -10.47  0.000   .5572873   .6701566
Inapplicable_items|          1 (offset)
```

Note: \_cons estimates baseline incidence rate (conditional on zero random effects).

### 3. Univariate analysis for type of intervention

Two dummy variables were created since there were three categories: HIV prevention, HIV treatment and prevention, HIV care and treatment. HIV prevention was the reference category. The treatvsprev2 dummy variable = HIV prevention and treatment. The model was adjusted for journal clustering. There was no statistically significant association between type of intervention and number of SPIRIT checklist items reported.

```
. xtgee spirit_score treatvsprev2 , family(poisson) link(log) i( journalclust )
offset(Inapplicable_items) corr(exchangeable) vce
> (robust) eform
```

```
Iteration 1: tolerance = .02490265
Iteration 2: tolerance = .00509635
Iteration 3: tolerance = .00035103
Iteration 4: tolerance = .00001437
Iteration 5: tolerance = 7.051e-07
```

```
GEE population-averaged model      Number of obs   =    79
Group variable:      journalclust   Number of groups =    12
```

```

Link:          log          Obs per group:
Family:       Poisson      min =      1
Correlation:  exchangeable avg =      6.6
                                   max =      28
                                   Wald chi2(1) = 0.58
Scale parameter: 1          Prob > chi2  = 0.4465
    
```

(Std. Err. adjusted for clustering on journalclust)

	IRR	Robust Std. Err.	z	P> z	[95% Conf. Interval]	
treatvsprev2	1.029212	.0389278	0.76	0.446	.9556744	1.108408
_cons	.6202574	.0228264	-12.98	0.000	.5770939	.6666493
Inapplicable_items	1 (offset)					

Note: \_cons estimates baseline incidence rate (conditional on zero random effects).

#### 4. Univariate analysis for type of intervention

Two dummy variables were created since there were three categories: HIV prevention, HIV treatment and prevention, HIV care and treatment. HIV prevention was the reference category. The treatvsprev3 dummy variable = HIV treatment and care. The model was adjusted for journal clustering. There was no statistically significant association between type of intervention and number of SPIRIT checklist items reported.

```

. xtgee spirit_score treatvsprev3 , family(poisson) link(log) i( journalclust )
offset(Inapplicable_items) corr(exchangeable) vce
> (robust) eform
    
```

```

Iteration 1: tolerance = .02069848
Iteration 2: tolerance = .00530636
Iteration 3: tolerance = .00039882
Iteration 4: tolerance = .00001575
Iteration 5: tolerance = 7.186e-07
    
```

```

GEE population-averaged model          Number of obs = 79
Group variable:      journalclust      Number of groups = 12
Link:                log                Obs per group:
Family:              Poisson            min = 1
Correlation:         exchangeable        avg = 6.6
                                   max = 28
                                   Wald chi2(1) = 0.00
Scale parameter:     1                  Prob > chi2  = 0.9950
    
```

(Std. Err. adjusted for clustering on journalclust)

	Robust
--	--------

spirit_score	IRR	Std. Err.	z	P> z	[95% Conf. Interval]	
treatvsprev3	1.000172	.0276529	0.01	0.995	.9474153	1.055866
_cons	.6225471	.0187249	-15.76	0.000	.5869078	.6603506
Inapplicable_items	1 (offset)					

Note: \_cons estimates baseline incidence rate (conditional on zero random effects).

### 5. Multivariate analysis with all factors

The model was adjusted for journal clustering. There was no statistically significant association between type of intervention and number of SPIRIT checklist items reported. None of the factors evaluated were significantly associated with number of checklist items reported.

```
. xtgee spirit_score pubyear2 singlelevsmultisite treatvsprev2 treatvsprev3, family(poisson)
link(log) i( journalclust)offset(lnapp
> llicable_items) corr(exchangeable) vce(robust) eform
```

```
Iteration 1: tolerance = .01939099
Iteration 2: tolerance = .00501982
Iteration 3: tolerance = .00035611
Iteration 4: tolerance = 7.509e-06
Iteration 5: tolerance = 1.752e-07
GEE population-averaged model
Group variable:      journalclust      Number of obs   =    79
Link:                log                Number of groups =    12
Family:              Poisson              Obs per group:
Correlation:         exchangeable          min =           1
                                                avg =           6.6
                                                max =           28
                                                Wald chi2(4)    =    8.26
Scale parameter:    1                    Prob > chi2     =   0.0826
```

(Std. Err. adjusted for clustering on journalclust)

spirit_score	IRR	Robust Std. Err.	z	P> z	[95% Conf. Interval]	
pubyear2	1.045058	.0361428	1.27	0.203	.9765671	1.118353
singlelevsmultisite	1.012966	.0535807	0.24	0.808	.9132105	1.123619
treatvsprev2	1.028805	.0522055	0.56	0.576	.9314081	1.136387
treatvsprev3	1.013578	.0396017	0.35	0.730	.9388574	1.094245
_cons	.5903524	.0412208	-7.55	0.000	.5148455	.6769331
Inapplicable_items	1 (offset)					

Note: \_cons estimates baseline incidence rate (conditional on zero random effects).  
closed on: 19 Nov 2018, 20:52:07

# Part B

## Appendix H: Turnitin report



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## Appendix I: Contemporary Clinical Trials Journal Instructions to authors

# CONTEMPORARY CLINICAL TRIALS COMMUNICATIONS

- **Guide for Authors**

### AUTHOR INFORMATION PACK

#### GUIDE FOR AUTHORS

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- Full postal address

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- All tables (including titles, description, footnotes)
- Ensure all figure and table citations in the text match the files provided • Indicate clearly if color should be used for any figures in print *Graphical Abstracts / Highlights files* (where applicable)

*Supplemental files* (where applicable)

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---

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Reference to a book:

[2] W. Strunk Jr., E.B. White, The Elements of Style, fourth ed., Longman, New York, 2000. Reference to a chapter in an edited book:

[3] G.R. Mettam, L.B. Adams, How to prepare an electronic version of your article, in: B.S. Jones, R.Z. Smith (Eds.), Introduction to the Electronic Age, E-Publishing Inc., New York, 2009, pp. 281–304. Reference to a website:

[4] Cancer Research UK, Cancer statistics reports for the UK. <http://www.cancerresearchuk.org/aboutcancer/statistics/cancerstatsreport/>, 2003 (accessed 13 March 2003).

Reference to a dataset:

[dataset] [5] M. Oguro, S. Imahiro, S. Saito, T. Nakashizuka, Mortality data for Japanese oak wilt disease and surrounding forest compositions, Mendeley Data, v1, 2015. <https://doi.org/10.17632/xwj98nb39r.1>.

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