SPIRIT | CONSORT SURROGATE
Reporting Guidelines for Surrogate Endpoints

SPIRIT-Surrogate and CONSORT-Surrogate extension items

Anthony Manyara, PhD

University of BRISTOL
MRC/CSO Social and Public Health Sciences Unit
UKRI Medical Research Council
CHIEF SCIENTIST OFFICE
University of Glasgow

Scope and use

SPIRIT | CONSORT SURROGATE
Reporting Guidelines for Surrogate Endpoints

- Relevant to trials using a surrogate endpoint as a primary outcome
- Minimum set of items to be reported; items can be extrapolated to non-randomized, observational, or other studies is possible
- Flexibility in order of reporting items
- The SPIRIT-Surrogate extension includes **nine** items *modified* from the SPIRIT 2013 checklist
- The CONSORT-Surrogate extension includes **nine** items *modified* from the CONSORT 2010 checklist and **two** *new* items

Abstract/Introduction

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Main SPIRIT or CONSORT item section	**Surrogate extension item**	***Extension item applies to:***
Abstract/Trial summary	**1a.** State a) that the primary outcome is a surrogate endpoint, and b) the target outcome(s) whose intervention effect is being substituted for.	*SPIRIT-Surrogate CONSORT-Surrogate*
Introduction/Background/ Objectives	**1b.** State a) that the primary outcome is a surrogate endpoint, and b) the target outcome(s) whose intervention effect is being substituted for.	*SPIRIT-Surrogate CONSORT-Surrogate*

Example: "**The primary outcome was** the peak change of urinary neutrophil gelatinase-associated lipocalin within 48 h, **a surrogate marker [endpoint] of kidney injury**." Panagiotou 2020

Outcomes

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Outcomes	**2.** State the practical or scientific reason(s) for using a surrogate endpoint as a primary outcome.	*SPIRIT-Surrogate* *CONSORT-Surrogate*
	3. State what other surrogate endpoints were considered and why the current one(s) were chosen.	*SPIRIT-Surrogate*
	4. Justification for selected surrogate endpoint: a) evidence (or lack thereof) of surrogate endpoint validation b) evidence (or lack thereof) of validity being specific to the context used, e.g., intervention; disease; population	*SPIRIT-Surrogate* *CONSORT-Surrogate*

Example: "We used surrogate endpoints for this trial because **of a number of practical constraints**, including the trial cost, rapidly evolving evidence in this field, and concern about the feasibility of conducting a long-term intervention in a vulnerable population. However, the endpoints selected have been validated as having prognostic significance for CVD events"
Howard 2008

Example: "The primary efficacy endpoint was the change in daytime ambulatory systolic blood pressure from baseline to 2 months. **Systolic blood pressure is a validated surrogate endpoint for prediction of cardiovascular events and mortality based on a meta-analysis** of 123 blood pressure lowering drug trials, with 613,815 participants demonstrating a strong association between the treatment effect of systolic blood pressure and cardiovascular events" Azizi 2021

Sample size

Sample size	**5.** Clarify if the sample size will be/was estimated to demonstrate that a minimum effect on the surrogate endpoint would be predictive of a benefit on the target outcome(s).	*SPIRIT-Surrogate* *CONSORT-Surrogate*

Example: "The assumptions for the power calculation (threshold of **a 40-m increase as the [surrogate threshold effect] minimal clinically important improvement** in 6-minute walk test distance, with an SD of 80m) were based on (1) a meta-regression of prior randomized clinical trials in patients with pulmonary arterial hypertension ref (due to the lack of such data in patients with HFpEF) and (2) clinical consensus among members of the trial's steering committee."
Shah 2019

Patient and public engagement

Ethics/Patient and public engagement	**6.** State whether and how trial participants will be/were engaged and informed before enrolment that the trial was designed to evaluate an intervention's effect using a surrogate endpoint.	*SPIRIT-Surrogate* *CONSORT-Surrogate*

All participants [received] adequate information about the nature, purpose, possible risks, and benefits of the trial [given the use of a surrogate endpoint as the primary outcome], and alternative therapeutic choices using an informed consent protocol approved by the IRB. All participants [were] given ample time and opportunity to ask questions and consider participation in the trial Koshizaka M, 2017; modified

Results

Results/Outcomes and estimation	7. If the primary outcome is a composite outcome that includes a surrogate endpoint; report the intervention effect on all components.	*CONSORT-Surrogate*

Table 8. Description of events related to progression-free survival
(Per-protocol population)

Characteristic	Robotic Cystectomy (N=150) n (%)	Open Cystectomy (N=152) n (%)
Total events	49 (32.7)	50 (32.9)
Death from bladder cancer	28 (18.7)	32 (21.3)
Non-cancer death	10 (6.7)	11 (7.2)
Recurrence, alive at last contact	11 (7.3)	7 (4.6)

Parekh DJ 2018

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Discussion and interpretation

Harms/Discussion	**8.** Comment on whether the trial design (including sample size and follow-up period), given the use of a surrogate endpoint, adequately captures the potential harms of the intervention being tested.	*SPIRIT-Surrogate* *CONSORT-Surrogate*
Statistical methods/Discussion	**9.** State what the plans are to conduct subsequent analyses/studies to verify current findings on the target outcome(s).	*SPIRIT-Surrogate* *CONSORT-Surrogate*
Discussion/Interpretation	**10.** Interpretation of findings of the trial in the context of using a surrogate primary endpoint, including its known validity for intervention effects on the target outcome and the potential benefit-risk assessments of the tested intervention for participants.	*CONSORT-Surrogate*

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Data access

Dissemination/Data access	**11.** If surrogate and target outcome data will be/were collected in the trial, state the open access arrangements for the data for future secondary research.	*SPIRIT-Surrogate* *CONSORT-Surrogate*

Conclusion

- Surrogate extensions aimed to inform better patient care, health care decisions, and policies
- Extensions intended to enhance completeness, transparency, replicability of methods, efficiency of research, interpretation and utility of findings
- Use of appropriate extensions by trial authors, journal editors, reviewers, and funders should be encouraged
- Despite the important contribution of both extensions, direct assessment and reporting of intervention effects on target outcomes whenever possible remains crucial