The SPIRIT Initiative: Defining standard protocol items

October 11, 2012

An-Wen Chan, MD DPhil
Women’s College Hospital & Research Institute
University of Toronto
Importance of trial protocols

Trial registries

Journals

Regulators/Policymakers

Healthcare providers

Trialists

Scientific & ethics review

Origin of subsequent reporting

Transparency

Patients & Trial participants

Funders

Ethics boards
Protocols facilitate transparency

**Primary outcome:**
- % change in Hgb\textsubscript{A1C}

**Diabetes trial**
- Drug intervention

**Protocol**
- $P \geq 0.05$

**Publication**
- Primary outcome: Withdrawal rate
- $P < 0.05$

Chan AW et al, *JAMA* 2004; *CMAJ* 2004
Current landscape of protocols

- Incomplete information
- Variable standards
- Variable format
Protocols lack important information

% of protocols with inadequate information

- Allocation concealment: 59%
- Blinding: 34%
- Power calculation: 40%
- Harms reporting system: 41%
- Primary outcomes: 25%

Protocols lack important information

- 1st outcome analysis: 20%
- Handling of missing data: 77%
- Handling of deviations: 47%
- Adjusted analyses: 67%
- Subgroup analyses: 95%

Objective

To improve content and quality of clinical trial protocols through evidence-based guidance
Definition of protocol

- Pre-trial document submitted for ethics approval
  - Background & objectives
  - Population & interventions
  - Methods & statistical analyses
  - Ethical and administrative aspects

- Evolving document
  - Transparent audit trail

- Related documents (SAP, contracts)
Methods

SPIRIT 2012 Checklist

Explanatory document

Systematic reviews:
- Existing protocol guidelines
- Evidence for key protocol items

Delphi consensus survey

Consensus meetings
Systematic review of protocol guidelines

- 40 guidelines identified → 7 specific to RCTs
- No formal consensus methods or systematic retrieval of evidence
- >380 protocol elements
  - Most were found in only 1 guideline

Tetzlaff J et al, Systematic Reviews 2012
Delphi consensus survey

- Preliminary checklist based on systematic review
- 3 survey rounds from Aug – Nov 2007
  - 96 participants from 17 countries
- Items rated from 1-10
  - Ratings and comments circulated in each round
  - Median $\geq 8 \rightarrow$ Included
  - Median $\leq 5 \rightarrow$ Excluded

Tetzlaff J et al, Trials 2012
Consensus meetings
(December 2007 and September 2009)

- 20 participants
  - Trialists, methodologists, industry, ethicists, funders, journal editors

- Review of protocol items from Delphi survey
Systematic review of evidence

10725 citations screened
(MEDLINE, EMBASE, Cochrane Methodology Register)

2433 articles reviewed

376 methodologic articles included
Evolution of SPIRIT Checklist

Systematic review of protocol guidelines

Delphi consensus survey

Consensus meetings

Systematic review of evidence

59 items

71 items

33 items
SPIRIT 2012 Checklist

- 33 items in five categories
  - Administrative information
  - Introduction
  - Study methods
  - Ethical considerations & dissemination
  - Appendices

<table>
<thead>
<tr>
<th>TIMEPOINT**</th>
<th>Enrollment</th>
<th>Allocation</th>
<th>Post-allocation</th>
<th>Close-out</th>
</tr>
</thead>
<tbody>
<tr>
<td>-t&lt;sub&gt;1&lt;/sub&gt;</td>
<td></td>
<td>0</td>
<td>t&lt;sub&gt;1&lt;/sub&gt;</td>
<td></td>
</tr>
<tr>
<td>t&lt;sub&gt;1&lt;/sub&gt;</td>
<td></td>
<td>t&lt;sub&gt;2&lt;/sub&gt;</td>
<td>t&lt;sub&gt;3&lt;/sub&gt;</td>
<td>etc.</td>
</tr>
<tr>
<td>t&lt;sub&gt;x&lt;/sub&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**ENROLLMENT:**
- Eligibility screen: X

**INTERVENTIONS:**
- Intervention A: [Diagram indicating intervention]
- Intervention B: X X

**ASSESSMENTS:**
- List baseline variables: X X
- List outcome variables: X X etc. X
Scope

- All clinical trials
- Minimum content
- Relevant information from contracts & operations manuals
SPIRIT Explanation & Elaboration

- Model example
- Rationale and explanation
- References to empirical evidence and further reading

Chan AW et al, BMJ [in press]
Users

- Investigators
- Educators
- Protocol reviewers
  - Funders
  - Research ethics committees
  - Journals
Relation to other guidance

- Declaration of Helsinki
- Good Clinical Practice
- CDISC Protocol Representation Group
- PRACTIHC (Pragmatic RCTs In Health Care)
Implementation strategy

- Dissemination
- Endorsement and enforcement
- Implementation tools
- Evaluation of impact
Conclusions

- Trial protocols are central to transparency, scientific validity, and ethical rigour
- SPIRIT checklist aims to improve protocol quality
- Impact requires broad adoption

www.spirit-statement.org
Trialists/Methodologists/Statisticians
- An-Wen Chan (Chair), Univ of Toronto
- Jennifer Tetzlaff, University of Ottawa
- David Moher, University of Ottawa
- Doug Altman, University of Oxford
- Kay Dickersin, Johns Hopkins University
- Caroline Doré, UK MRC
- Peter Gøtzsche, Nordic Cochrane Centre
- Asbjørn Hróbjartsson, Nordic Cochrane
- Wendy Parulekar, NCIC CTG
- Ken Schulz, Family Health International
- Andreas Laupacis, University of Toronto

Industry
- Jesse Berlin, Johnson & Johnson
- Frank Rockhold, GSK

Journal editors
- Trish Groves, BMJ
- Bill Summerskill, Lancet
- Drummond Rennie, JAMA
- Hal Sox, Annals of Internal Medicine

Government funders
- Karmela Krleža-Jerić, Canadian Institutes of Health Research

Ethicists
- Howard Mann, University of Utah
- Genevieve Dubois-Flynn, Canadian Institutes of Health Research