

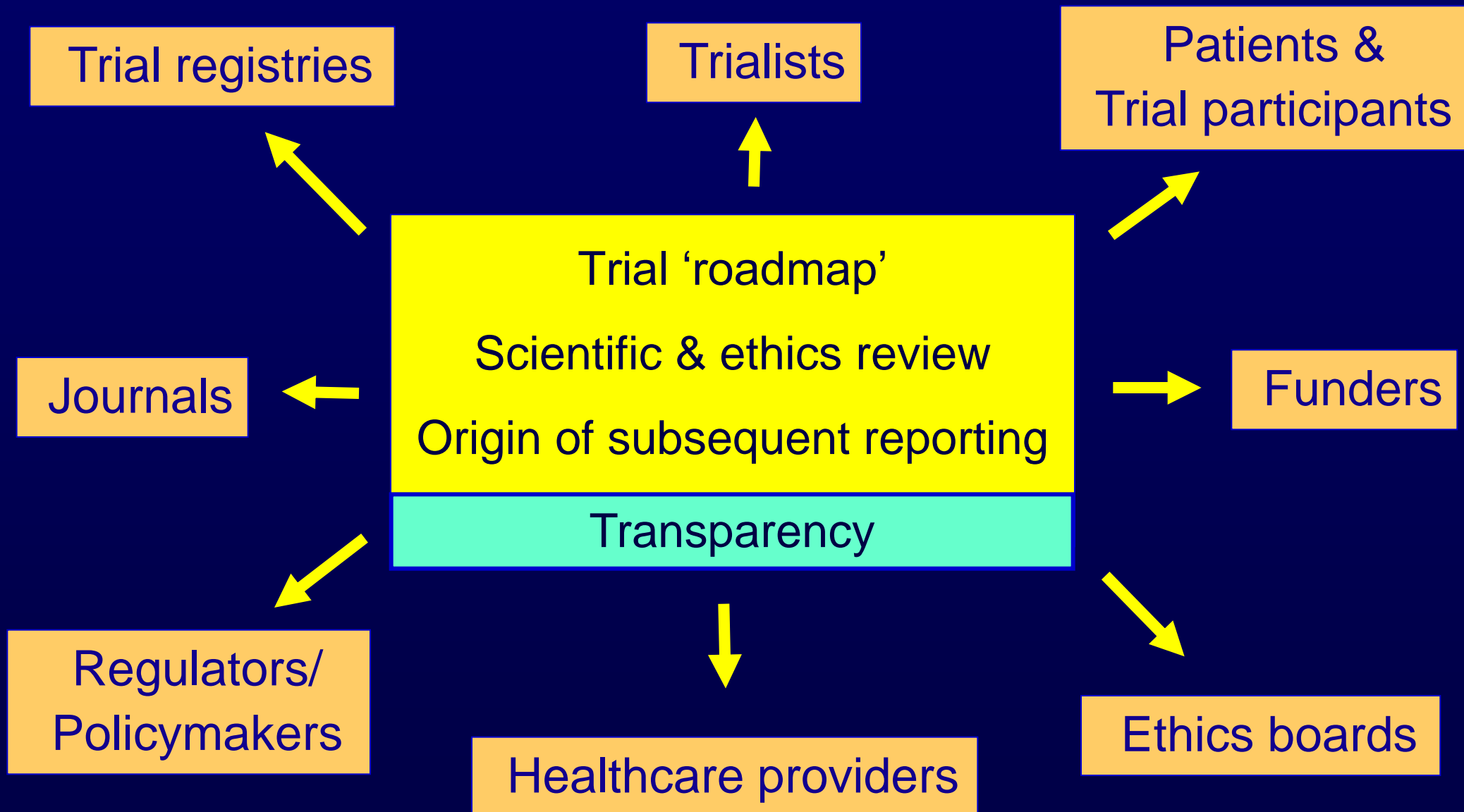


# The SPIRIT Initiative: Defining standard protocol items

October 11, 2012

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University of Toronto

# Importance of trial protocols



# Protocols facilitate transparency

Diabetes trial  
Drug intervention

**Protocol**

Primary outcome:  
% change in Hgb<sub>A1C</sub>

$P \geq 0.05$

**Publication**

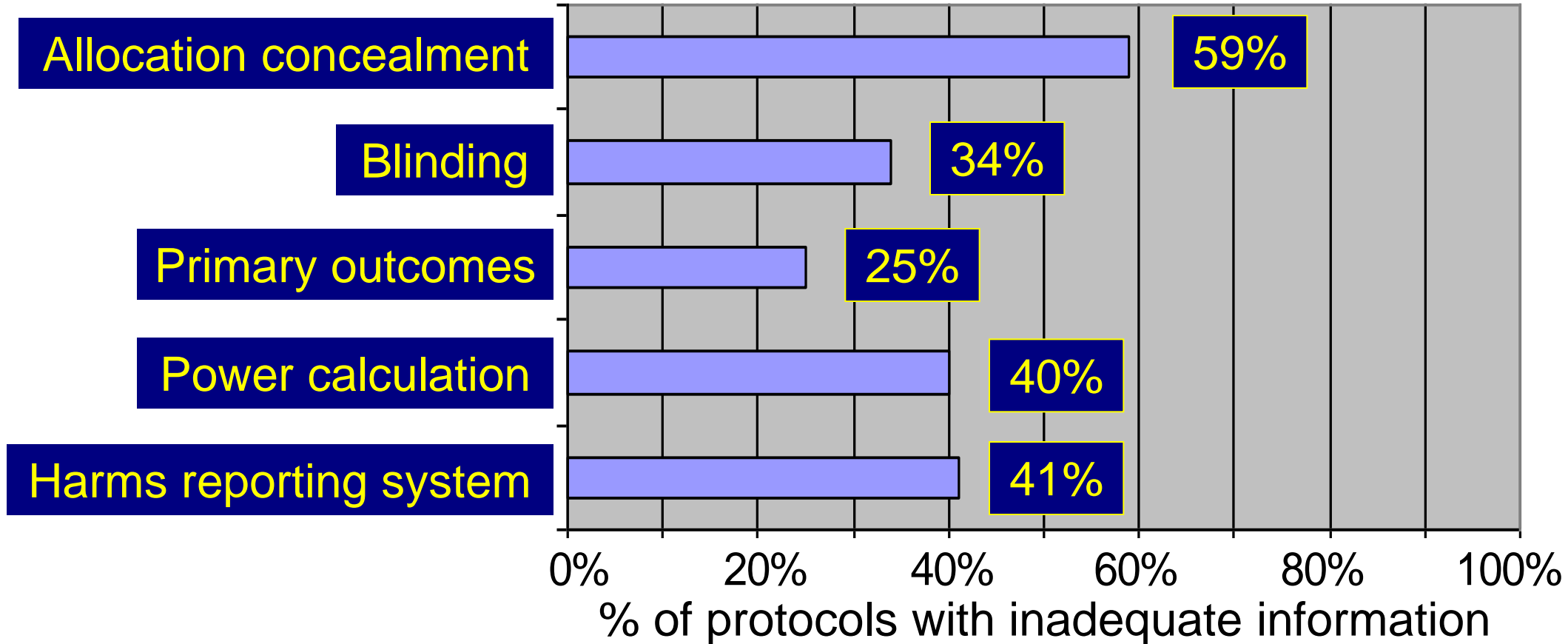
Primary outcome:  
Withdrawal rate

$P < 0.05$

# Current landscape of protocols

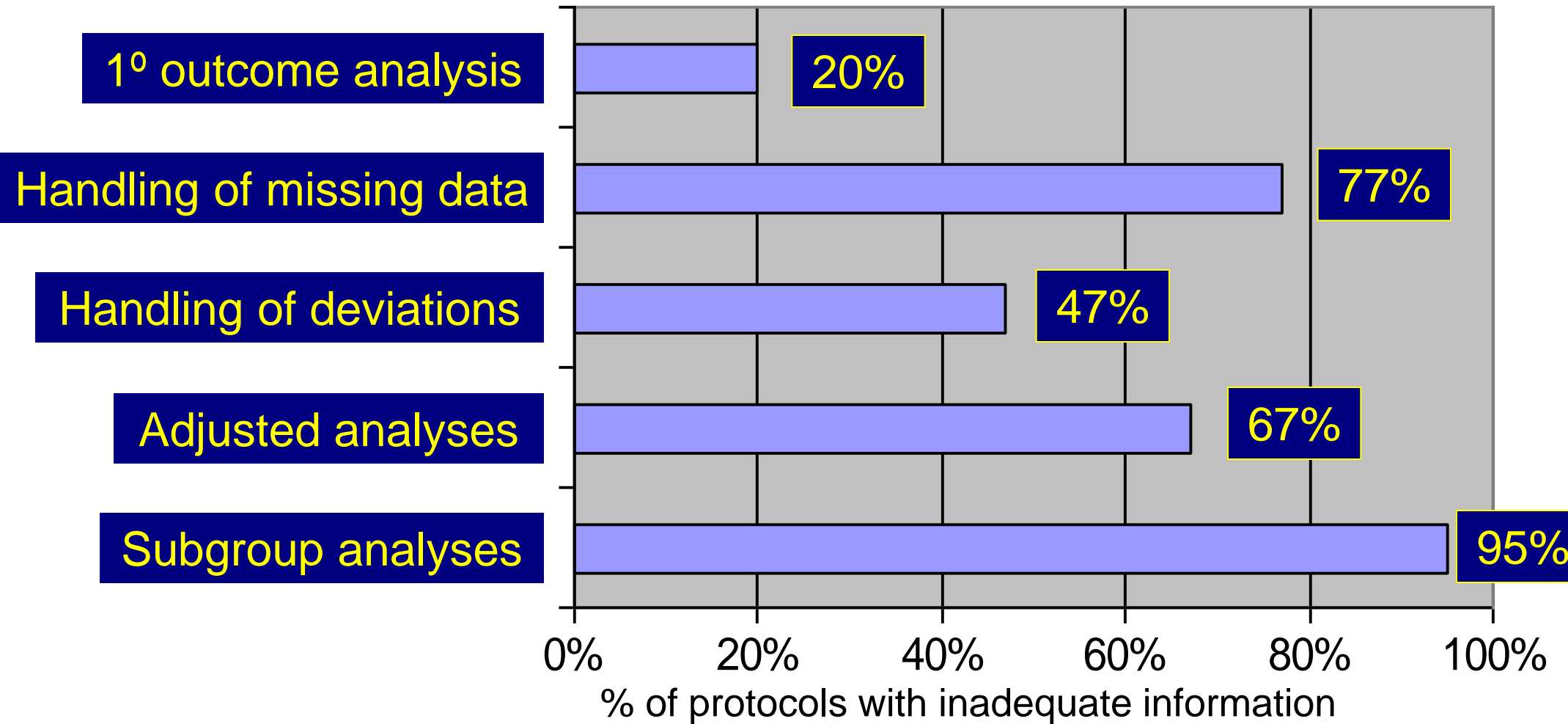
- Incomplete information
- Variable standards
- Variable format

# Protocols lack important information



Mhaskar R *et al*, *J Clin Epid* 2012; Chan AW *et al*, *BMJ* 2008, *JAMA* 2004;  
Scharf O, *J Clin Oncol* 2006; Pildal J, *BMJ* 2005; Hróbjartsson A *et al*, *J Clin Epid* 2009

# Protocols lack important information





## 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

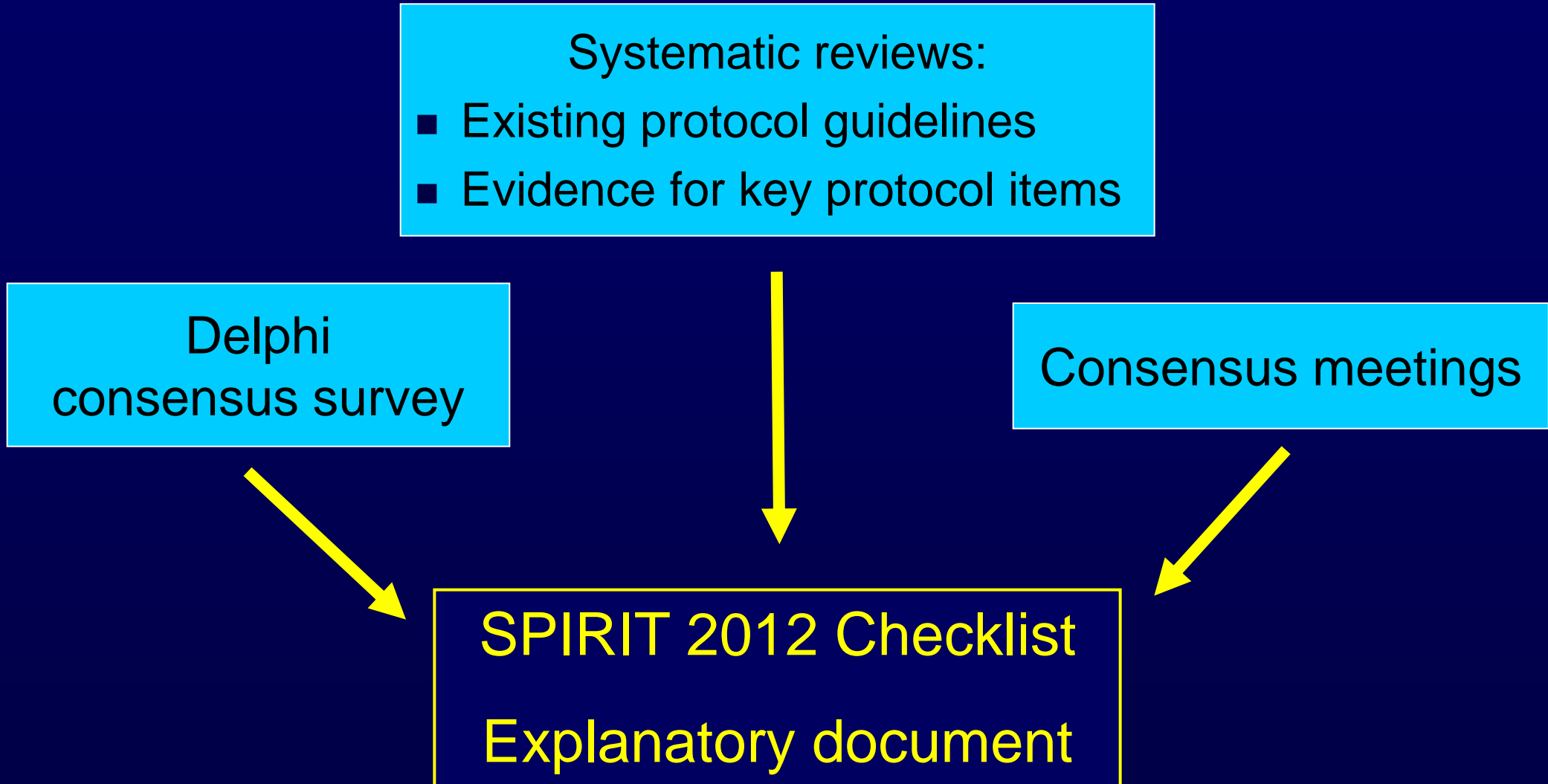
Systematic reviews:

- Existing protocol guidelines
- Evidence for key protocol items

Delphi  
consensus survey

Consensus meetings

SPIRIT 2012 Checklist  
Explanatory document



# 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

# 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)

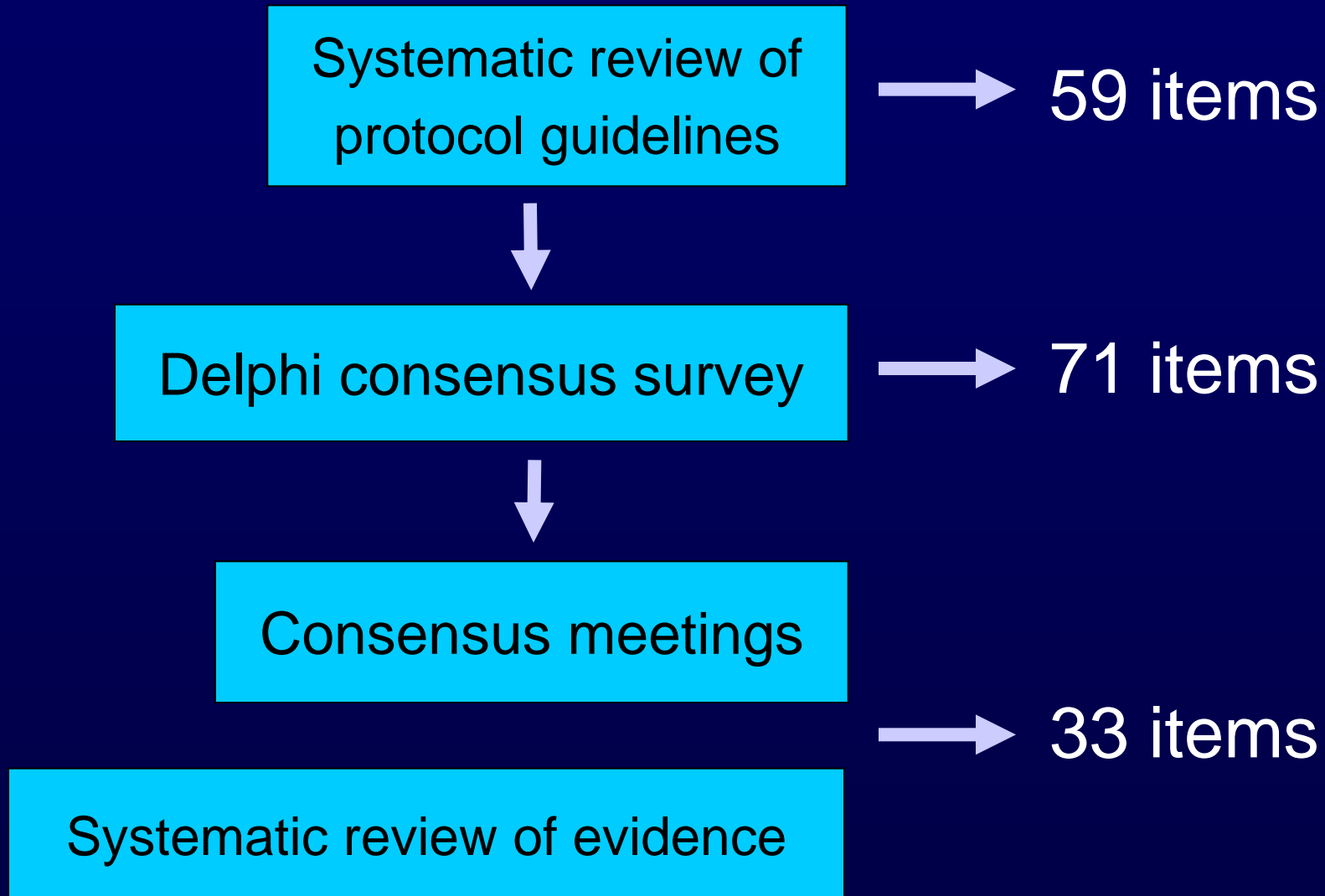


2433 articles reviewed



376 methodologic articles  
included


# Evolution of SPIRIT Checklist



# SPIRIT 2012 Checklist

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

*Chan AW et al, Annals Intern Med [in press]*

	STUDY PERIOD							
	Enrollment	Allocation	Post-allocation					Close-out
TIMEPOINT**	$-t_1$	0	$t_1$	$t_2$	$t_3$	$t_4$	etc.	$t_x$
<b>ENROLLMENT:</b>								
Eligibility screen	X							
<b>INTERVENTIONS:</b>								
<i>[Intervention A]</i>								
<i>[Intervention B]</i>			X		X			
<b>ASSESSMENTS:</b>								
<i>[List baseline variables]</i>	X	X						
<i>[List outcome variables]</i>				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](http://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