MRC-NIHR Trials Methodology Research Partnership: Webinar recording

Outcome reporting bias and SAPs in clinical trials

Presented, on behalf of the MRC HTMR, by:

Carrol Gamble (University of Liverpool)

Kerry Dwan (Liverpool School of Tropical Medicine)

Paula Williamson (University of Liverpool)

03 July 2024

The slides are available below.

For any queries, please contact uktmn@nottingham.ac.uk

https://youtu.be/-Z4auJC-lbs

Dr Kerry Dwan

Senior Lecturer in Evidence Synthesis
Centre for Evidence Synthesis in Global Health

Outcome reporting bias

Outline

- Publication bias and outcome reporting bias
- Objective
- Previous version of the systematic review
- Results
- Conclusion
- Solutions

Definitions

- **Study publication bias** arises when studies are published or not depending on their results;

- **Outcome Reporting bias:** the selection on the basis of the results of a subset of the original variables recorded for inclusion in a publication;

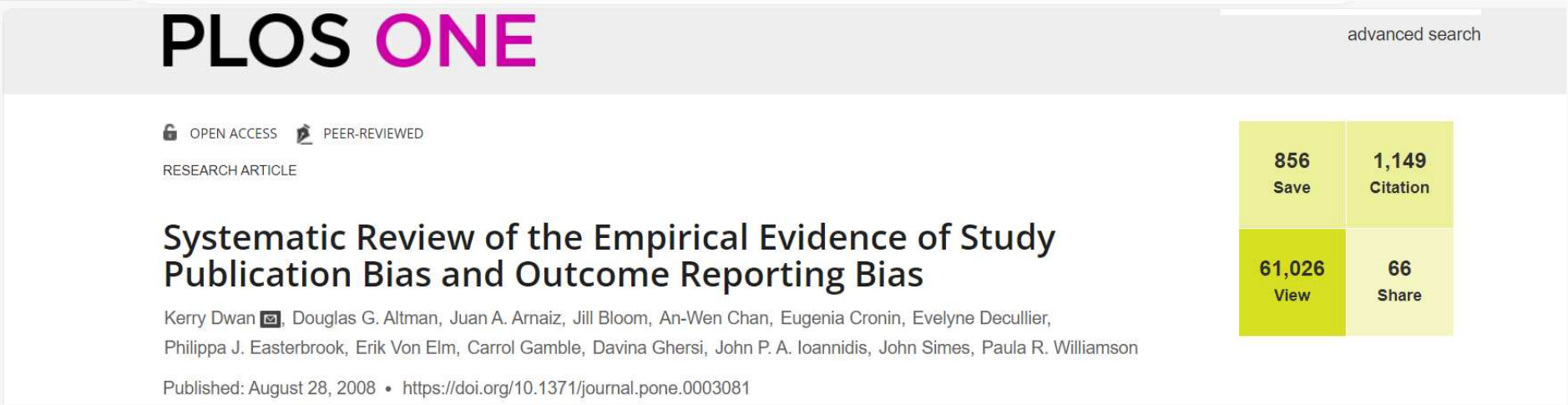
Objective

- The aim of this study was to update the original review and summarise the evidence from empirical cohort studies that have assessed study publication bias and/or outcome reporting bias in RCTs approved by a specific ethics committee or other inception cohorts of RCTs

Declan Devane, James Griffin, Jamie Kirkham, Ranjit Lall, Smitaa Patel, Sarah Rhodes, Valerie Smith, Paula Williamson

Inclusion criteria

- Inception cohort: cohorts with study protocols being registered before the start of the study i.e. submitted to an ethics committee for approval.
- Cohorts of randomised controlled trials
- ORB: comparison to protocols
- Publication bias: information from trialists



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RESEARCH ARTICLE

Systematic Review of the Empirical Evidence of Study Publication Bias and Outcome Reporting Bias

Kerry Dwan, Douglas G. Altman, Juan A. Arnaiz, Jill Bloom, An-Wen Chan, Eugenia Cronin, Evelyne Decullier, Philippa J. Easterbrook, Erik Von Elm, Carrol Gamble, Davina Ghersi, John P. A. Ioannidis, John Simes, Paula R. Williamson

Published: August 28, 2008 • https://doi.org/10.1371/journal.pone.0003081

856 Save | 1,149 Citation | 61,026 View | 66 Share

- 16 studies
  - 11 publication bias
  - 5 outcome reporting bias
- Fully reported: OR 2.2 to 4.7 if statistically significant

- Reports vs protocols: 40–62% at least one primary outcome changed, newly introduced or omitted

PLOS ONE

PUBLISH ABOUT BROWSE SEARCH

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RESEARCH ARTICLE

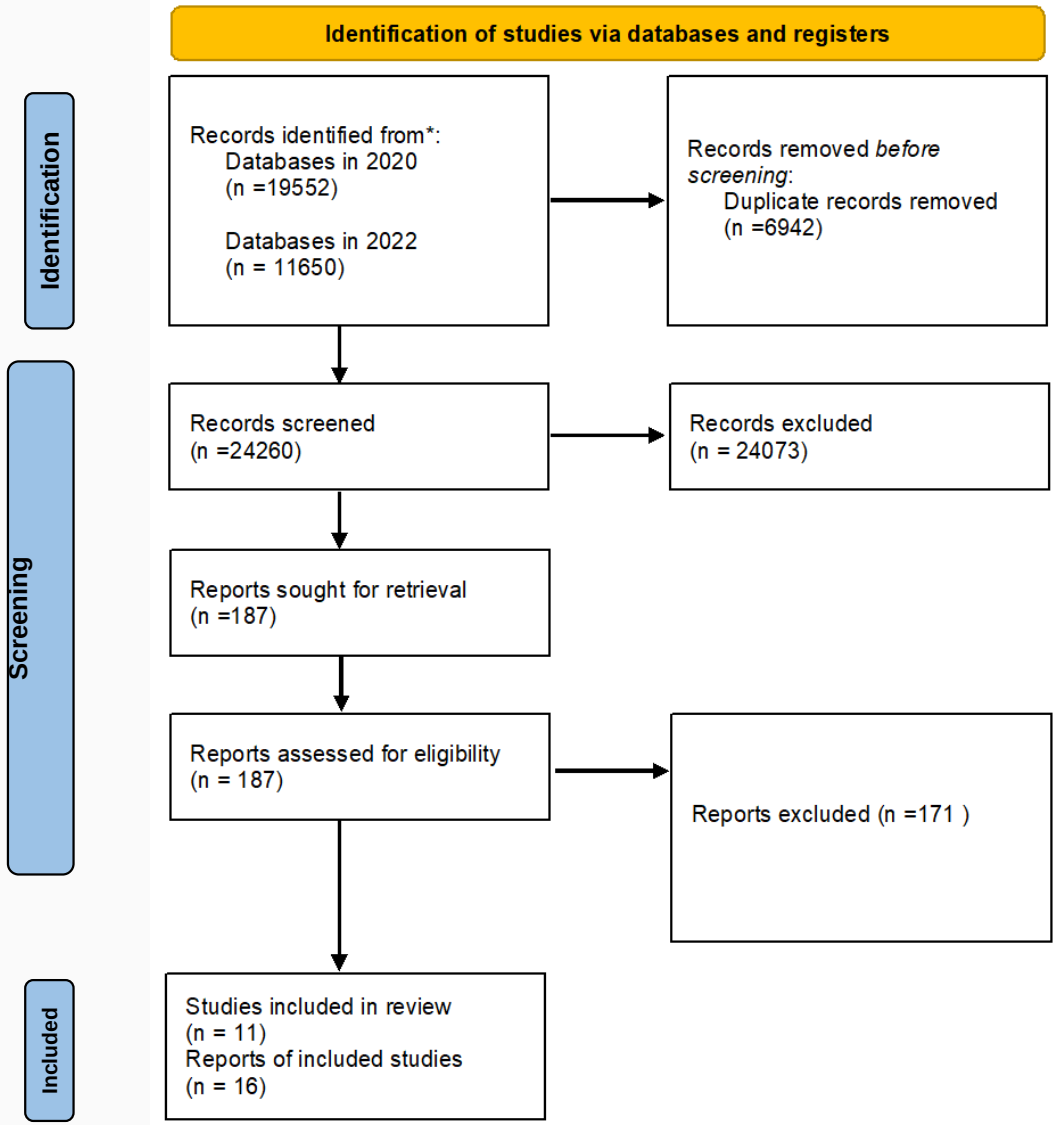
Systematic Review of the Empirical Evidence of Study Publication Bias and Outcome Reporting Bias — An Updated Review

Kerry Dwan, Carrol Gamble, Paula R. Williamson, Jamie J. Kirkham, for the Reporting Bias Group

Published: July 5, 2013 • https://doi.org/10.1371/journal.pone.0066844

642 Save | 793 Citation | 26,773 View | 57 Share

- 20 studies
  - 15 publication bias
  - 5 outcome reporting bias



In December 2023 we checked studies that had cited either version of the review

Results – included studies

- 11 new studies

- 29 studies in total
  - 19 publication bias
  - 8 outcome reporting bias
  - 2 both types of bias

- 2 previously included studies now excluded

Description of included studies

- Published 1991-2022

- Protocols approved 1963-2017
- Followed up 1988-2022
- Funding varied from 100% non profit to 100% pharmaceutical industry
- Protocols approved by:
    - Ethics committee 16,
    - NIH/ Health research councils 6,
    - Institutional review board 5,
    - Pharmacy 1,
    - AIDS clinical trials group 1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(Norway)
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Somalia
Ken.
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Congo
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Tanz.
Sri
Lanka
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Venez.
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Quality assessment

- 1. Was there complete follow up (after data-analysis) of all the trials in the cohort?
  - Yes ≥90%.
  - No < 90%.
  - Unclear.

Yes: 18 studies
NO: 11 studies
Loss to follow up
13-48%

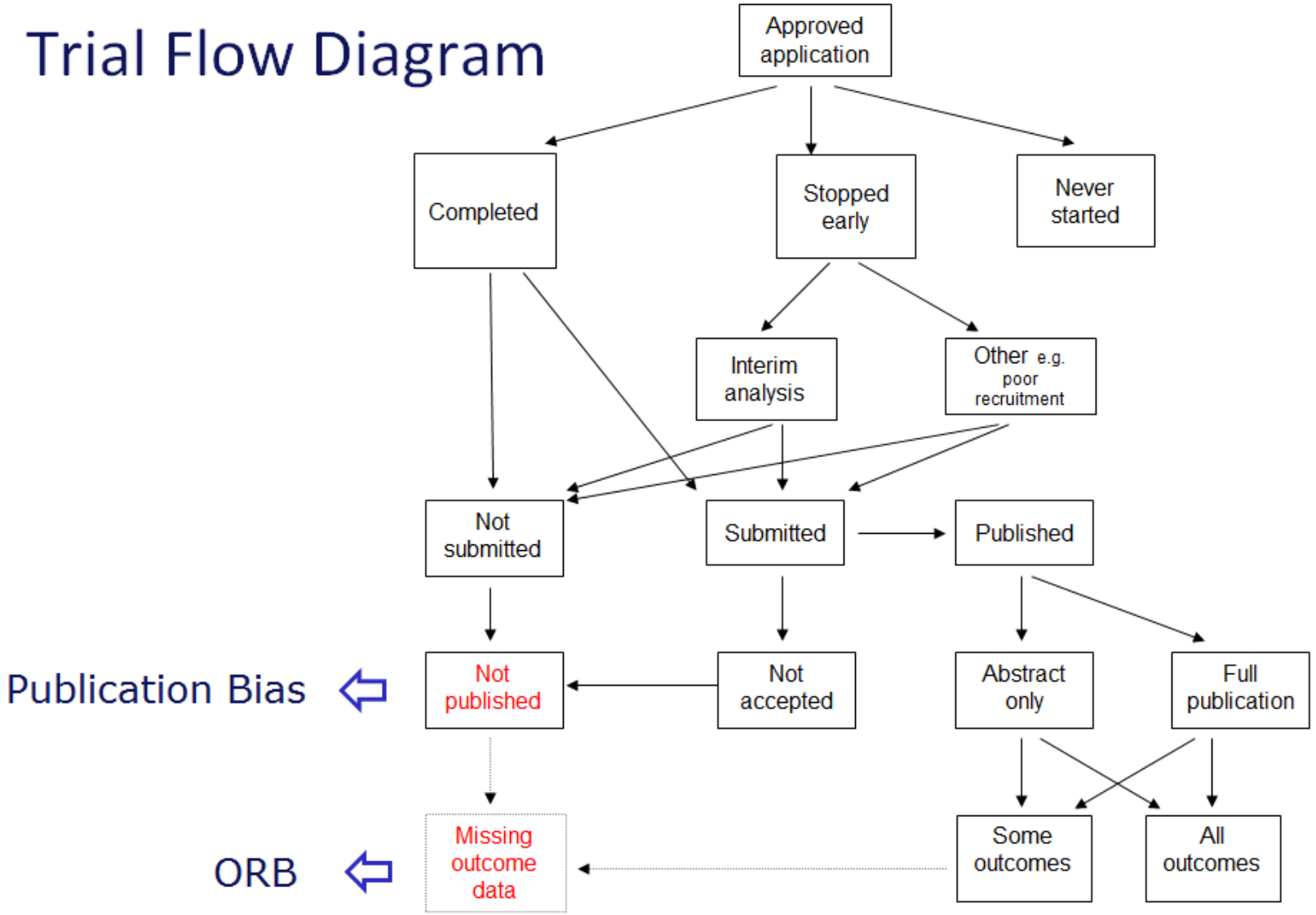
- 2. Was publication ascertained through personal contact with the investigators?
  - Yes =personal contact with investigators, or searching the
  - literature and personal contact with the investigator.
  - No= searching the literature only.
  - Unclear.

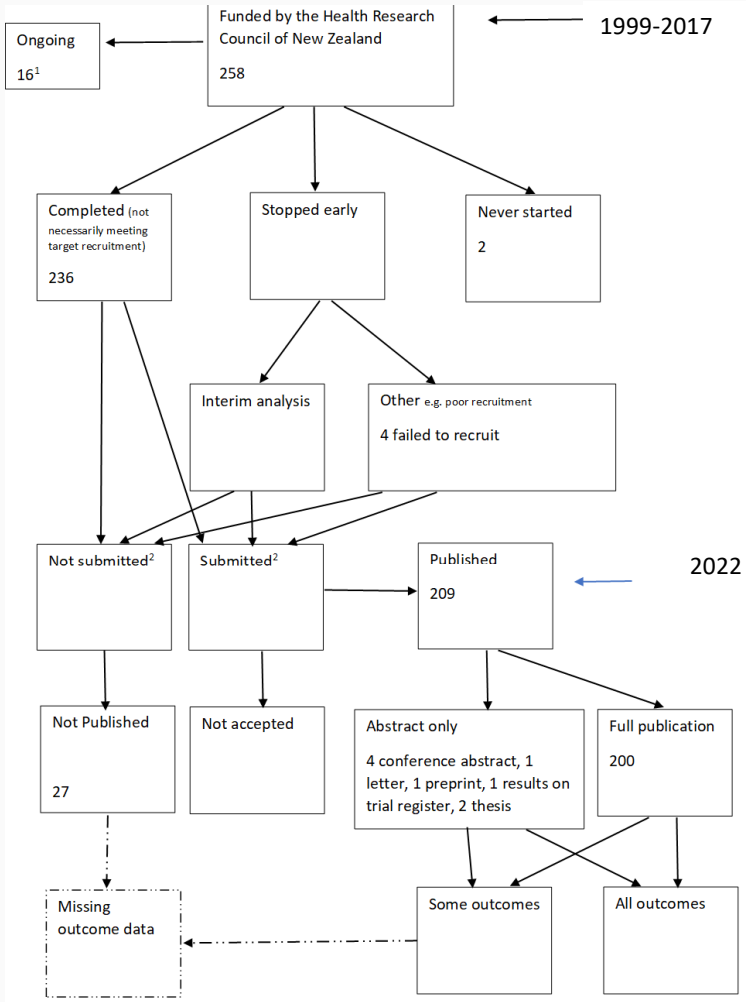
- 3. Were positive and negative findings clearly defined?
  - Yes =clearly defined.
  - No= not clearly defined.
  - Unclear.

Yes 19
No 2
NA 8

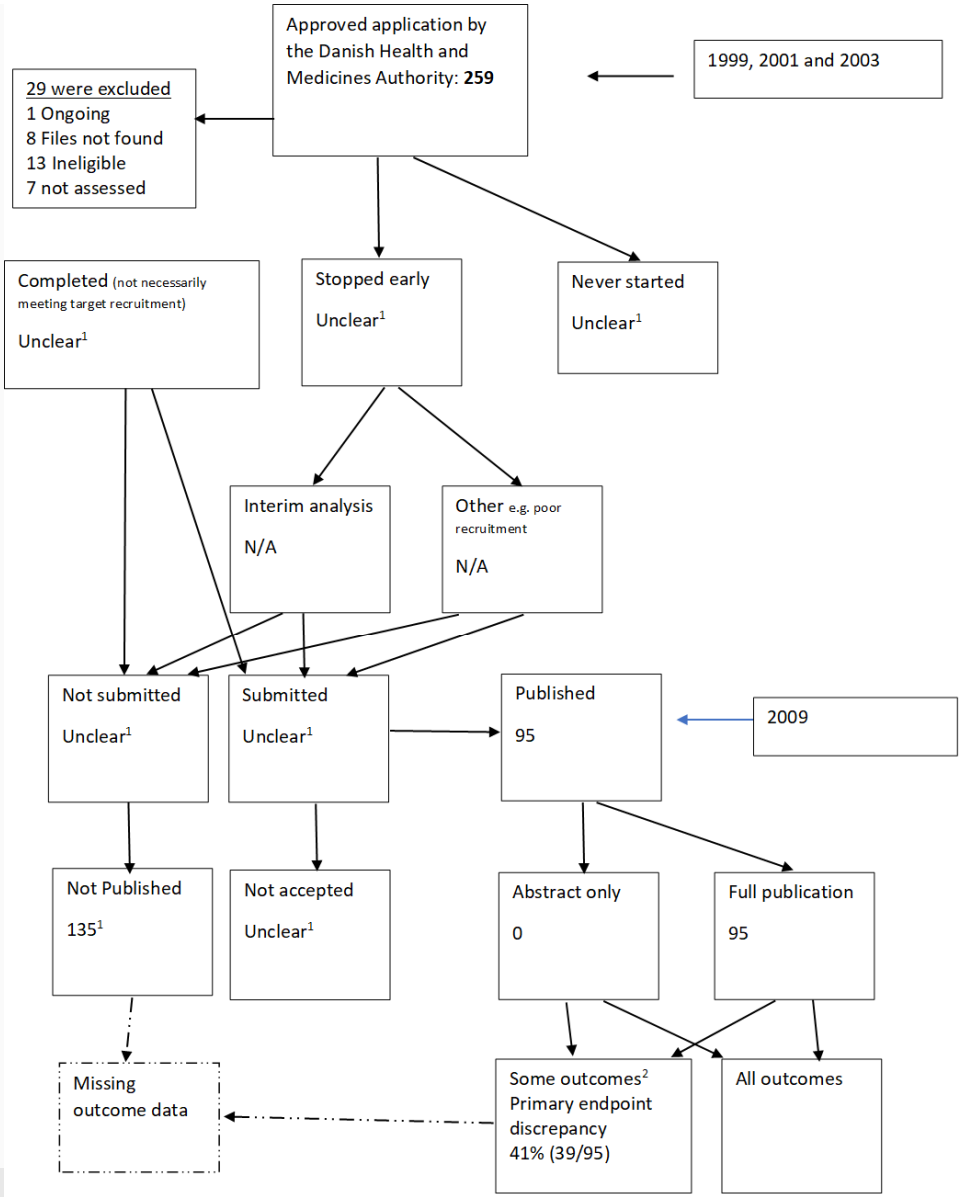
- 4. Were protocols compared to publications? (outcome reporting bias only)
  - Yes =protocols were compared to publications.
  - No= protocols were not considered in the study.
  - Unclear.

Trial Flow Diagram





Between 1999 and 2017, almost 9 out of every 10 HRC-funded trials had been registered and a similar proportion of completed trials had been published with no difference in time to publication based on type of result. However, only a slim majority of trials had published within the 2-year time frame set by the WHO.



Results

- Primary outcome same in protocol and publication: 40-74% (8 studies)

- Primary outcome downgraded: 4%-34% (4 studies)
- Primary outcome omitted: 2%-31% (7 studies)
- Non primary outcome changed to primary: 4-19% (3 studies)
- New primary outcome: 0-18% (7 studies)

Results

- Fully reported: OR 2.2 to 4.7 if statistically significant (3 studies)

- Discrepant reporting: OR 1.38 (95% CI: 1.07, 1.78) if statistically significant (1 study)

Outcome reporting bias

- 1990s: Reporting of trials is frequently incomplete, biased and inconsistent with protocols.

- 2000s:
  - About half of cancer trials specified QoL outcomes in their protocols. However, only 20% reported any QoL data in associated publications. (protocols approved 2000-2003)
  - Overall consistency between protocols and their corresponding published reports was low. (protocols approved 1999-2003)
  - Publication bias and outcome reporting bias is common in papers reporting RCTs in schizophrenia and bipolar disorder. (protocols approved 2000-2011)

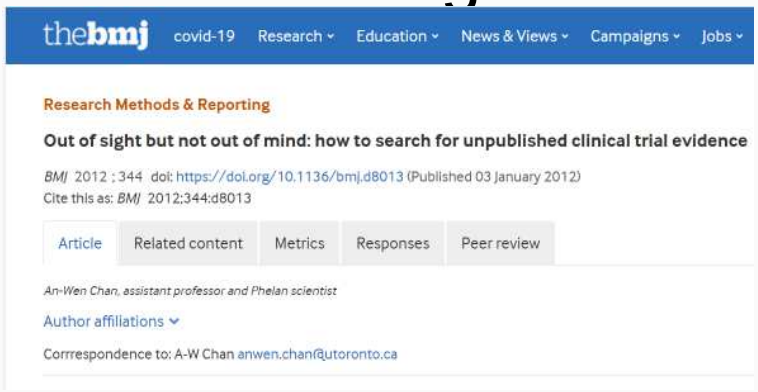
Conclusions

- ORB is still a problem
- Improvement in completeness of reporting is still needed.
- To eliminate undisclosed discrepancies, trial protocols should be available in the public domain at the same time when the trial is published.

Solutions to ORB

Non-Statistical Solutions

- Obtain the missing outcome data



- Trial Registries
- Results Databases
- Regulatory Online Databases
- Data Request

- Trialist and Sponsor Contact
- Conference Abstracts
- Online Search

Core outcome set

- Agreed standardised set of most important outcomes

- Disease/condition specific
- All treatment types or a particular intervention

- Both benefits and harms
- The minimum – expect others to be collected

- Focus of effectiveness trials
- Relevant within routine clinical practice

Thanks for listening

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Statistical Analysis Plans

Professor Carrol Gamble
Anna Kearney

Statistical Analysis ~~Plans~~

Protection

Prof Carrol Gamble
Anna Kearney

European Medicines Agency

September 1998
CPMP/ICH/363/96

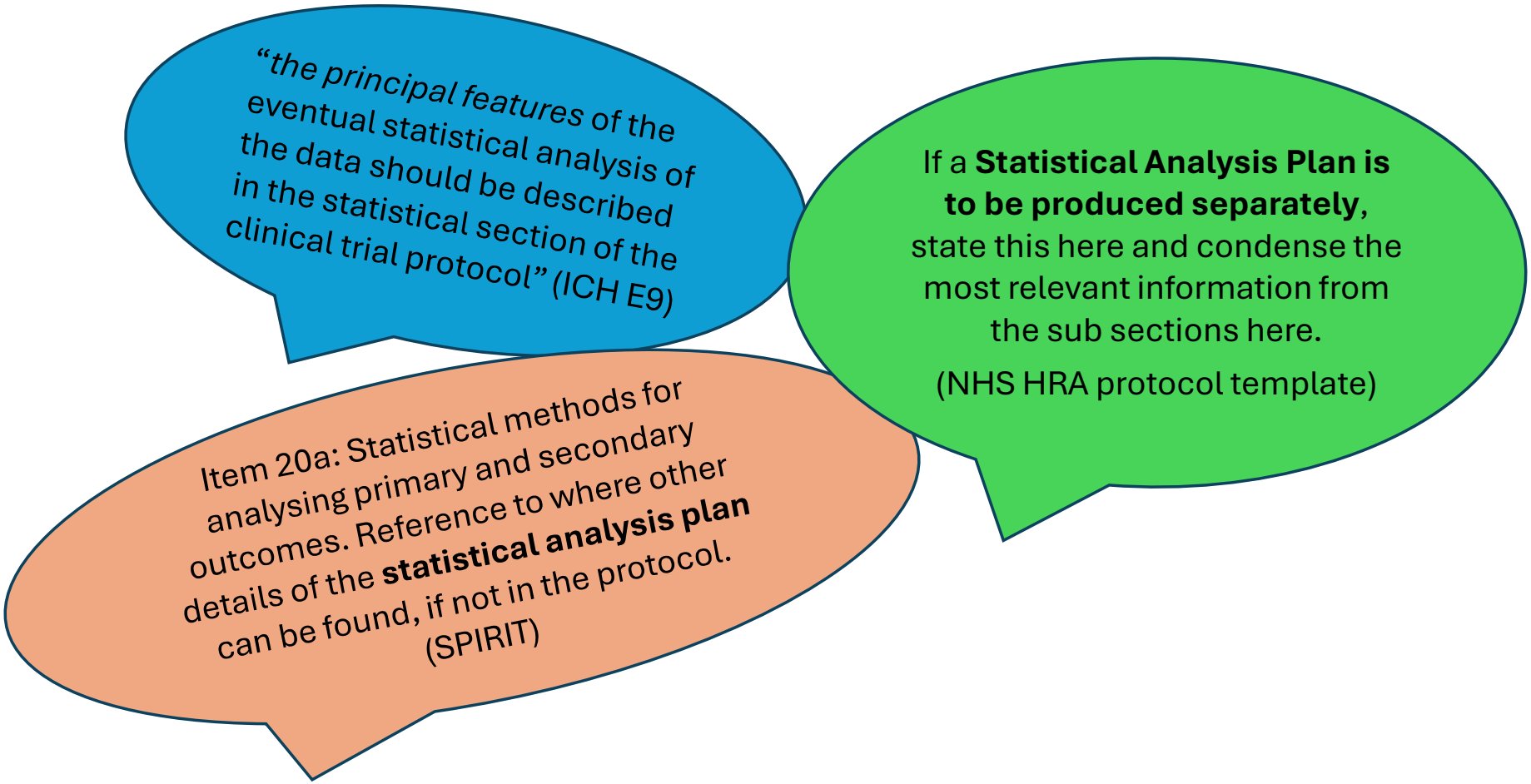
ICH Topic E 9
Statistical Principles for Clinical Trials

Step 5

"*the principal features of the eventual statistical analysis of the data should be described in the statistical section of the clinical trial protocol*" (ICH E9)

NOTE FOR GUIDANCE ON
STATISTICAL PRINCIPLES FOR CLINICAL TRIALS
(CPMP/ICH/363/96)

Protocol pre-specification of the analysis plan



ELSEVIER

Journal of Clinical Epidemiology 101 (2018) 53–60

Journal of Clinical Epidemiology

ORIGINAL ARTICLE

Pre-specification of statistical analysis approaches in published clinical trial protocols was inadequate

Lauren Greenberg[a], Vipul Jairath[b,c], Rupert Pearse[d], Brennan C. Kahan[a,*]

N=99	Adequately	Incompletely	Not mentioned
Analysis Population	8 (8%)	64 (65%)	27 (27%)
Analysis Model	27 (27%)	61 (62%)	11 (11%)
Covariates	40 (40%)	32 (32%)	27 (27%)
Handling of missing data	10 (10%)	24 (24%)	65 (66%)

No. of aspects adequately defined	No. (%)
0	39 (39%)
1	36 (36%)
2	23 (23%)
3	1 (1%)
4	0 (0%)

Cro et al. BMC Medicine (2020) 18:137
https://doi.org/10.1186/s12916-020-01590-1

BMC Medicine

RESEARCH ARTICLE Open Access

Evidence of unexplained discrepancies between planned and conducted statistical analyses: a review of randomised trials

Suzie Cro[1*], Gordon Forbes[2], Nicholas A. Johnson[1] and Brennan C. Kahan[3]

101 eligible trials in 6 leading general medical journals

88% had a publicly available pre-specified analysis plan

Conclusion: Unexplained discrepancies are common. Increased transparency is required

Only 25% had no unexplained discrepancies

61% had ≥ 1 unexplained discrepancy

15% it was impossible to determine

Methods

Used Protocols or SAPs where available

-Publication cohort RCTs published Jan-Apr 2018 in leading medical journals

Why have a SAP rather than improve protocol content?

In clinical trials it is a legal requirement to comply with trial protocol

SAP not required when the protocol contains all necessary information

Aim is replication by an independent statistician- no ambiguity

Analysis plus

data manipulation /calculations/ derivations

Protocol audience maybe inappropriate

Could lead to unnecessary protocol amendments

Loss of efficiency

Why write a SAP?

Protects scientific integrity

- Promotes thinking and transparency
- Reduces potential for selective reporting

Protects statistical time

Promotes efficiency

Who is the audience of SAP?

- Chief Investigator
- Statisticians
- PPI?

Need to be publicly available & often they aren’t

What is a Statistical Analysis Plan (SAP)?

- It describes what variables and outcomes will be collected and which statistical methods will be used to analyse them

"a document that contains a more technical and detailed elaboration of the principal features stated in the protocol and includes detailed procedures for executing the statistical analysis of the primary and secondary variables and other data". (ICH E9)

- Similar to protocols, the ability of a SAP to provide transparency is dependent on its content

SAP guidance

JAMA Network

JAMA

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December 19, 2017

Guidelines for the Content of Statistical Analysis Plans in Clinical Trials

Carrol Gamble, PhD[1]; Ashma Krishan, BSc[2]; Deborah Stocken, PhD[3,4]; Steff Lewis, PhD[5]; Edmund Juszczak, MSc[6]; Caroline Doré, BSc[7]; Paula R. Williamson, PhD[1]; Douglas G. Altman, DSc[8]; Alan Montgomery, PhD[9]; Pilar Lim, PhD[10]; Jesse Berlin, ScD[11]; Stephen Senn, PhD[12]; Simon Day, PhD[13]; Yolanda Barbachano, PhD[14]; Elizabeth Loder, MD, MPH[15]

Author Affiliations | Article Information

JAMA. 2017;318(23):2337-2343. doi:10.1001/jama.2017.18556

Editorial Comment | Related Articles

Abstract

Importance While guidance on statistical principles for clinical trials exists, there is an absence of guidance covering the required content of statistical analysis plans (SAPs) to support transparency and reproducibility.

Objective To develop recommendations for a minimum set of items that should be addressed in SAPs for clinical trials, developed with input from statisticians, previous guideline authors, journal editors, regulators, and funders.

Design Funders and regulators (n = 39) of randomized trials were contacted and the literature was searched to identify existing guidance; a survey of current practice was conducted across the network of UK Clinical Research Collaboration-registered

This Issue | Views 4,499 | Citations 1 | Altmetric 47

Editorial

December 19, 2017

More

Guidelines for Statistical Analysis Plans

David L. DeMets, PhD[1]; Thomas D. Cook, PhD[1]; Kevin A. Buhr, PhD[1]

Author Affiliations | Article Information

JAMA. 2017;318(23):2301-2303. doi:10.1001/jama.2017.18954

Related Articles

The emergence of the randomized clinical trial as the gold standard for the evaluation of new clinical interventions has been met by the emergence of a host of guidelines for the design, conduct, monitoring, analysis,[1-3] and reporting[4] of randomized clinical trials including guidance from regulatory authorities reviewing pivotal studies to support approval of products, such as drugs and devices.[5] Much of this guidance reflects the key sci

JAMA article:

- viewed 137k times
- 38,856 pdf downloads

Extensions

- Early phase extension
- Cluster – in development
- Extensions to:
  - Adaptive designs
  - Bayesian
- Observational studies

SAPs do not prevent post-hoc analyses

- *Analyses performed in the light of the data that were collected (rather than being of interest before data collection began)*
  - Sometimes requested – by research team, by journal
  - Transparency is key – declare post-hoc analyses as such, together with rationale

BMJ 2022;378:o2244
http://dx.doi.org/10.1136/bmj.o2244

Changes in response to peer review

EDITORIALS

Post-submission changes to prespecified statistical analysis plans

These plans are fundamental to research integrity, but not immutable

Nazrul Islam, [1,2] Tim J Cole, [1,3] Joseph S Ross, [1,4] Timothy Feeney, [1,5] Elizabeth Loder[1,6]

Transparency and reproducibility are two of the fundamental principles of evidence generation and revisions that would modify prespecified analyses. Although there is a strong case for adhering to a

BMJ: first publishe

SAP Guideline Citation analysis

04/04/2024

WOS citations: 248

Google scholar: 442

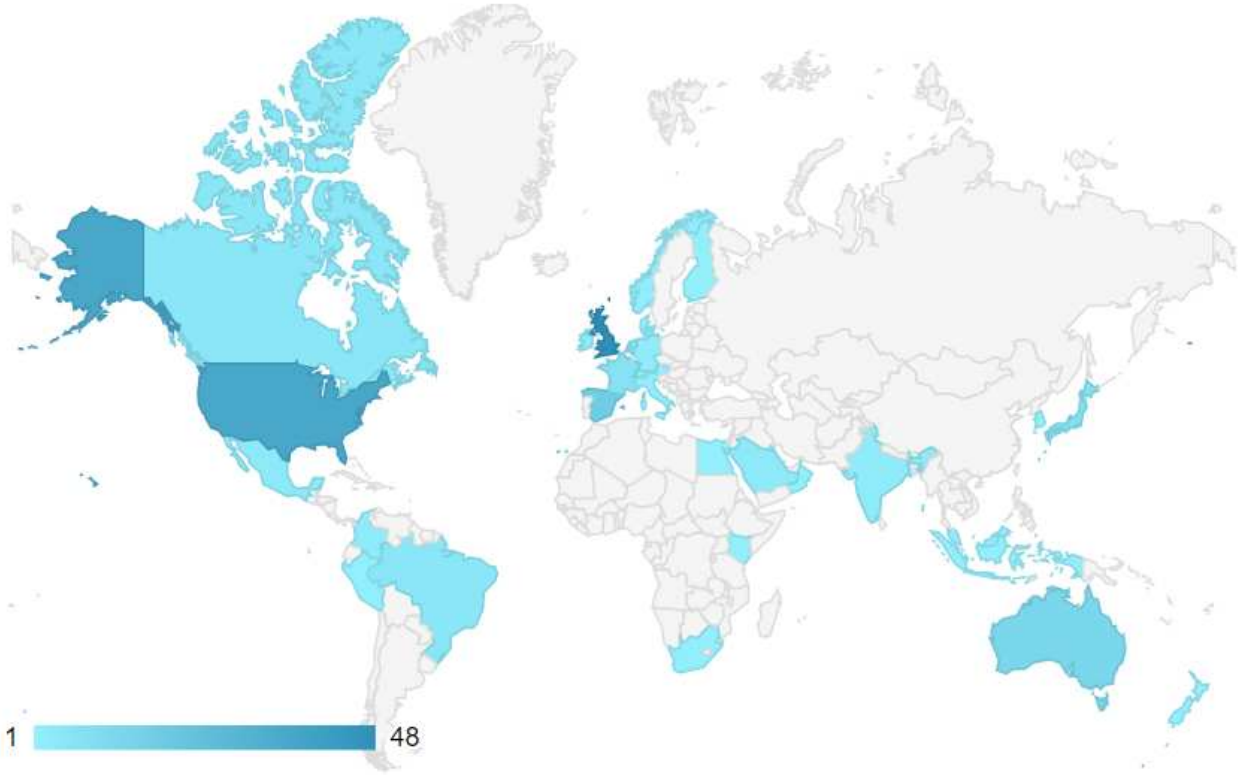
Unique records: 360

- duplicates
- records with no access
- foreign articles where citation was still not clear after using google translate
- 3 articles associated with the original communication
- False/ in-correct citations

Primary reason for citation

Primary reason	2018	2019	2020	2021	2022	2023	2024	Unk	Total
Statement SAP follows guidance	8	10	36	33	30	26	14	7	164
Future SAP will follow guidelines	1	4	6	3	5	1	2		22
Reference in a broader range of article type e.g. editorial	9	8	26	15	27	15	8	2	110
Statistical methods	2	2	3	5	4	4			20
Follows principle (e.g. Public SAP, sufficient detail SAP for replication)				1		7	2		10
Other guideline development	1	1	3		3				8
Justify approach of statistical approach	1	3	2						6
Application outside RCT		2			1				3
Other		2	3	4	2	4	1	1	17
Total	22	32	79	61	72	57	27	10	360

Altmetric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241
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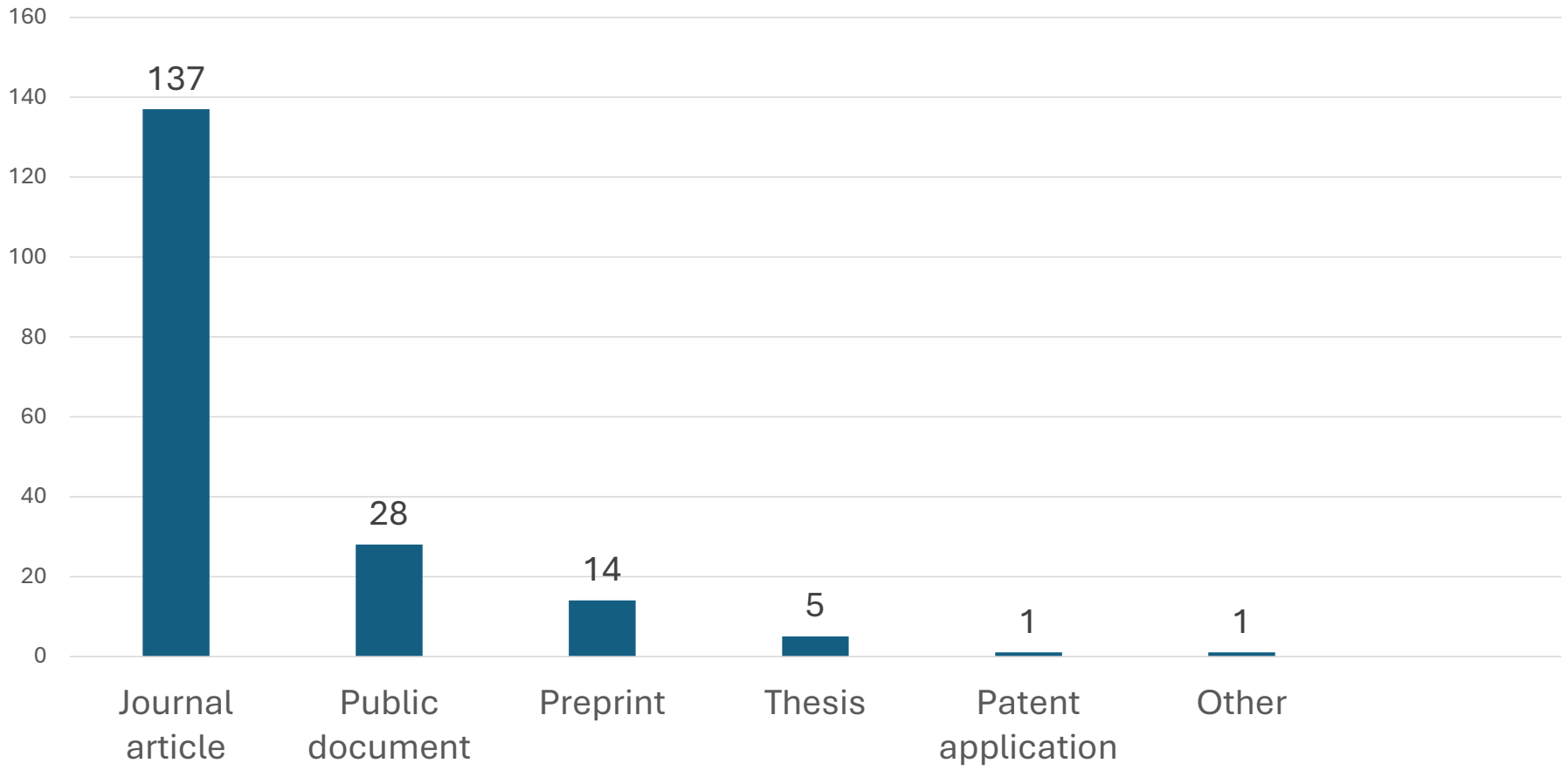
First Author country

	2018	2019	2020	2021	2022	2023	2024	Unk	Total
UK	2	7	12	12	7	8	4	3	55
Denmark		1	10	5	3	4	5	2	30
Australia		1	6	4	6	2	1		20
USA	3	2	3	2	3	2	1		16
Canada	1	1	1	3	2	5			13
Netherlands			4	3	1		1		9
China		1		1	5		1		8
Germany	1		1		1	1		1	5
Sweden				2	2				4
Finland		1	1			1	1		4
Norway				1	1		1	1	4
Unknown	1			2					3
Italy			1			2			3
India					1	1			2
Brazil					1		1		2
Chile	1			1					2
Singapore			1						1
Czech republic						1			1
France					1				1
Vietnam			1						1
Saudi Arabia			1						1
UK/ USA					1				1
Total	9	14	42	36	35	27	16	7	186

Document type



Design	Count
Parallel RCT	130
Cluster RCT	20
Factorial RCT	5
Pilot/ feasibility studies	4
Multiple study designs e.g. RCT and observational	3
Phase 2	3
Observational studies	6
Adaptive RCT	3
Survey	2
Sequential RCT	1
Crossover RCT	1
Meta analysis	5
Other	3
Total	186

Study design for papers

Conclusions

SAP Guidance has filled a need

Some reluctance to adopt guidance in case viewed as policy

Calls to make SAPs publicly available continue

Increased ability

Needs to extend beyond later phase

Reduce selective reporting & defend against such perceptions

Increase reproducibility of research