Statistical Analysis Plans

PROFESSOR CARROL GAMBLE

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Introduction

SAPs topic discussed at Nov 2012 UKCRC Stats Meeting

- Lack of guidance about the content of statistical analysis plans
  - ICH E3 which focuses on Clinical Study Report contents
  - ICH E9- Statistical Principles
- Variation in practice

Publication of SAPs has been highlighted as a solution to selective reporting of outcomes and analyses

Aim

To produce comprehensive guidance for SAPs

- increase efficiency & quality of SAPs to reduce selective reporting
- Stakeholder engagement: funders, regulators, pharmaceutical industry, journal editors, UKCRC registered CTUs

Areas of activity:

- Comprehensive search for Guidance
- Survey of UKCRC registered CTU Network to establish current practice
- Delphi survey to establish consensus on what should be included
- Critical review of draft guidance
- Piloting of guidance

Identification of Guidance- funders

Contacted all major RCT funding bodies, regulators, charitable organisations and national/international bodies

Contacted 39 and 28 responses received (Response rate ~ 72%)

No guidelines on SAPs other than ICH E9

Identification of Guidance- journals

Move to publication of SAPs

- Question what journals are using to assess quality of SAPs?

Publication Journal	Publish SAPs	Submission	Guidance
Trials	✓	✗	✗
JAMA	✗	✓	✗
BMJ	✗	✗	✗
NEJM	✓	✓/✗	✗
Lancet	✗	✗	✗

No information on website but response from BMJ: "We don't have any specific advice on reporting statistical analysis plans, but I can see that this would be useful." BMJ

submitted as a separate PDF file. A statistical analysis plan may be included with the protocol" NEJM

No information on website but response from Trials: "We encourage publication of study protocols and SAP is generally considered a part of this. We ask that sufficient detail is given in the SAP so an independent researcher is able to rerun the analyses; however, this is enforced through the peer review process, rather than through specifying set items." TRIALS

"All manuscripts reporting clinical trials must include a copy of the trial protocol including the complete statistical analysis plan" JAMA

Identification of Guidance- CTUs

Guidance documents referred to when developing a SAP template or when writing a SAP:

Guidelines Used	Number of CTUs % (N)
ICH E9	85% (39)
ICH E3	61% (28)
PSI Guidelines	35% (16)
Guidelines produced by another CTU	33% (15)
MRC CT Toolkit	13% (6)
Other: Common option-CONSORT guidelines	13% (6)
SPIRIT Guidelines	9% (4)

SAPS Publicly accessible-CTU survey

How often do you make SAPs publicly accessible	Number of CTUs % (N)
Always	7% (3)
Sometimes	26% (12)
Made available if requested	35% (16)
Not currently but plan to in future	15% (7)
Never	17% (8)

Delphi Survey

Aim - to establish consensus on content of SAPs.

73 Participants-

- CTUs,
- contributors to CONSORT and SPIRIT guidelines,
- methodologists,
- pharmaceutical industry statisticians,
- journal editors
- regulators.

List of components identified using copies of SOPS for SAPS and SAPs returned in response to survey

Listing sent to co-applicants to review

Comprehensive list of 89 components to consider for inclusion within SAP

Delphi survey

Two rounds

Round 1- list of 89 items each person asked to score between 1 and 9

- Opportunity to add items

Summarise scores- show responders their scores against other responders

Round 2 - ask to rescore and score new items

Delphi Survey

Response rate – 77% (56/73)

Results:

- Consensus In – 32% (28/89)
- Consensus Out – 0%
- Borderline Consensus – 11% (10/89)
- No Consensus – 57% (51/89)

Additional Components suggested - 21

Response rate – 96% (54/56)

- Missing – 2/56
  - Reasons: illness and on A/L

Results:

- Consensus In – 42% (46/110)
- Consensus Out – 1% (1/110)
- No Consensus – 47% (52/110)
- Borderline Consensus In – 8% (9/110)
- Borderline Consensus Out – 2% (2/110)

Consensus Meeting

Consensus Meeting members

- CTU stats; representation from MHRA; pharmaceutical industry statisticians; journal editors

Meeting focused on components that achieved borderline consensus in, borderline consensus out and no consensus

Consensus In: 61 Items

Consensus Out: 29 Items

Related to SAP and important to document but elsewhere: 17 Items

3 items considered duplicates

Guidance context

- Intended for later phase RCTs
- Protocol is compliant with the SPIRIT
- The SAP applies to a clean/validated dataset
- The SAP is not a standalone document

  -Should be read in conjunction with the protocol

  -Avoid replicating large chunks of the protocol referencing it instead

Critical review and piloting

Critical review

- Presented at a UKCRC registered CTU statistics network meeting
- Attendees asked to comment on wording; item order; ambiguity; issues in putting the guidance in to practice
- Reordering and combining of a few items

Piloting:

- positive feedback
- no changes

JAMA | Special Communication

Guidelines for the Content of Statistical Analysis Plans in Clinical Trials

Carrol Gamble, PhD; Ashma Krishan, BSc; Deborah Stocken, PhD; Steff Lewis, PhD; Edmund Juszczak, MSc; Caroline Doré, BSc; Paula R. Williamson, PhD; Douglas G. Altman, DSc; Alan Montgomery, PhD; Pilar Lim, PhD; Jesse Berlin, ScD; Stephen Senn, PhD; Simon Day, PhD; Yolanda Barbachano, PhD; Elizabeth Loder, MD, MPH

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 trial units (n = 46, 1 unit had 2 responders) and a Delphi survey (n = 73 invited participants) was conducted to establish consensus on SAPs. The Delphi survey was sent to statisticians in trial units who completed the survey of current practice (n = 46), CONSORT (Consolidated Standards of Reporting Trials) and SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) guideline authors (n = 16), pharmaceutical industry statisticians (n = 3), journal editors (n = 9), and regulators (n = 2) (3 participants were included in 2 groups each), culminating in a consensus meeting attended by experts (N = 12) with representatives from each group. The guidance subsequently underwent critical review by statisticians from the surveyed trial units and members of the expert panel of the consensus meeting (N = 51), followed by piloting of the guidance document in the SAPs of 5 trials.

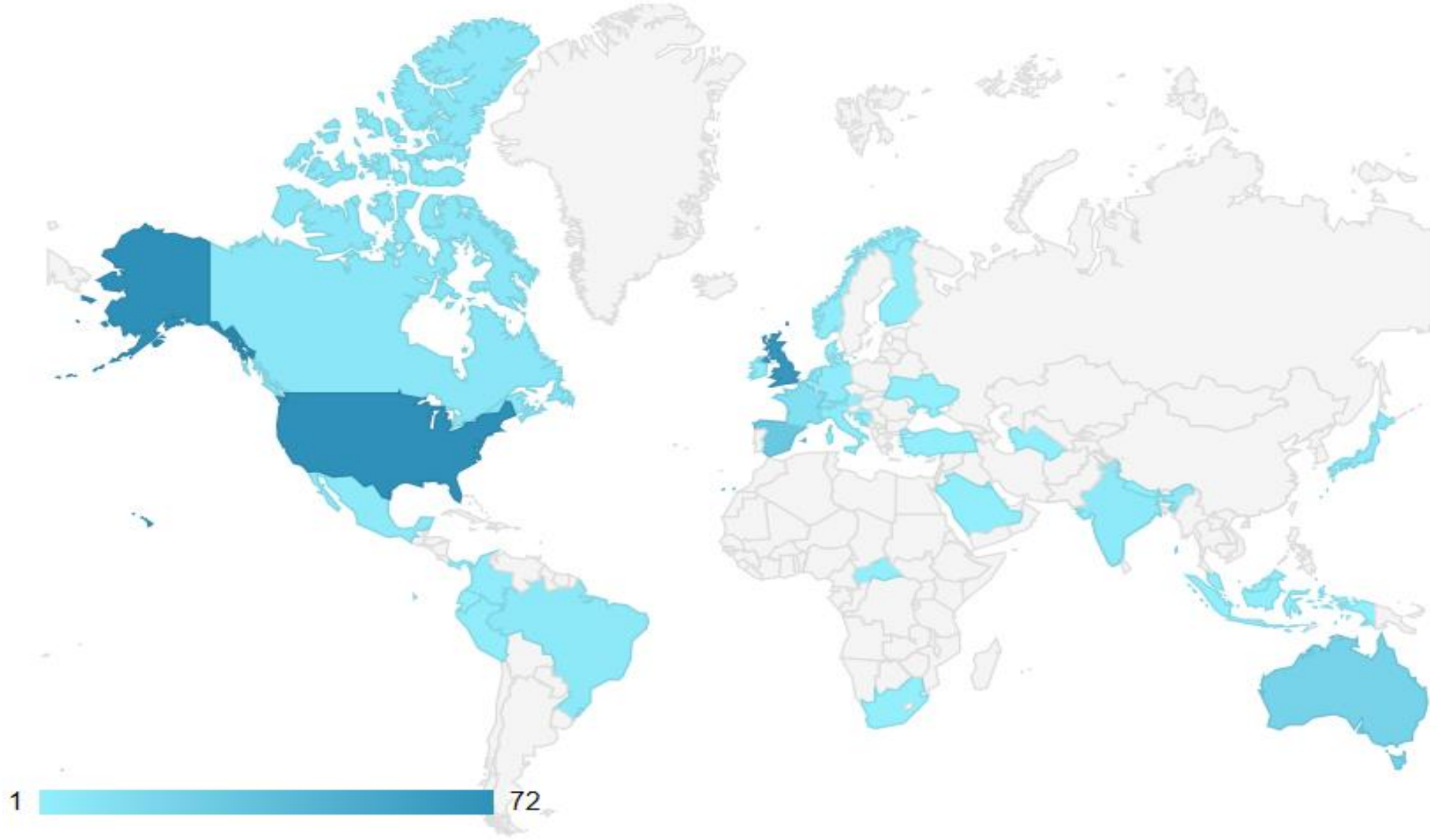
FINDINGS No existing guidance was identified. The registered trials unit survey (46 responses) highlighted diversity in current practice and confirmed support for developing guidance. The Delphi survey (54 of 73, 74% participants completing both rounds) reached consensus on 42% (n = 46) of 110 items. The expert panel (N = 12) agreed

Editorial page 2301

Supplemental content

CME Quiz at jamanetwork.com/learning and CME Questions page 2348

11 citations as at 15 June 2018



Geographical breakdown

Country	Count	As %
United States	72	17%
United Kingdom	66	16%
Spain	30	7%
Australia	22	5%
France	13	3%
Netherlands	7	2%
Canada	7	2%
Switzerland	6	1%
Brazil	6	1%
Other	66	16%
Unknown	120	29%

Geographical breakdown Demographic breakdown

1

Geographical breakdc

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Geographical breakdown

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ct-toolkit.ac.uk/routemap/statistical-data-analysis

Clinical Trials Toolkit

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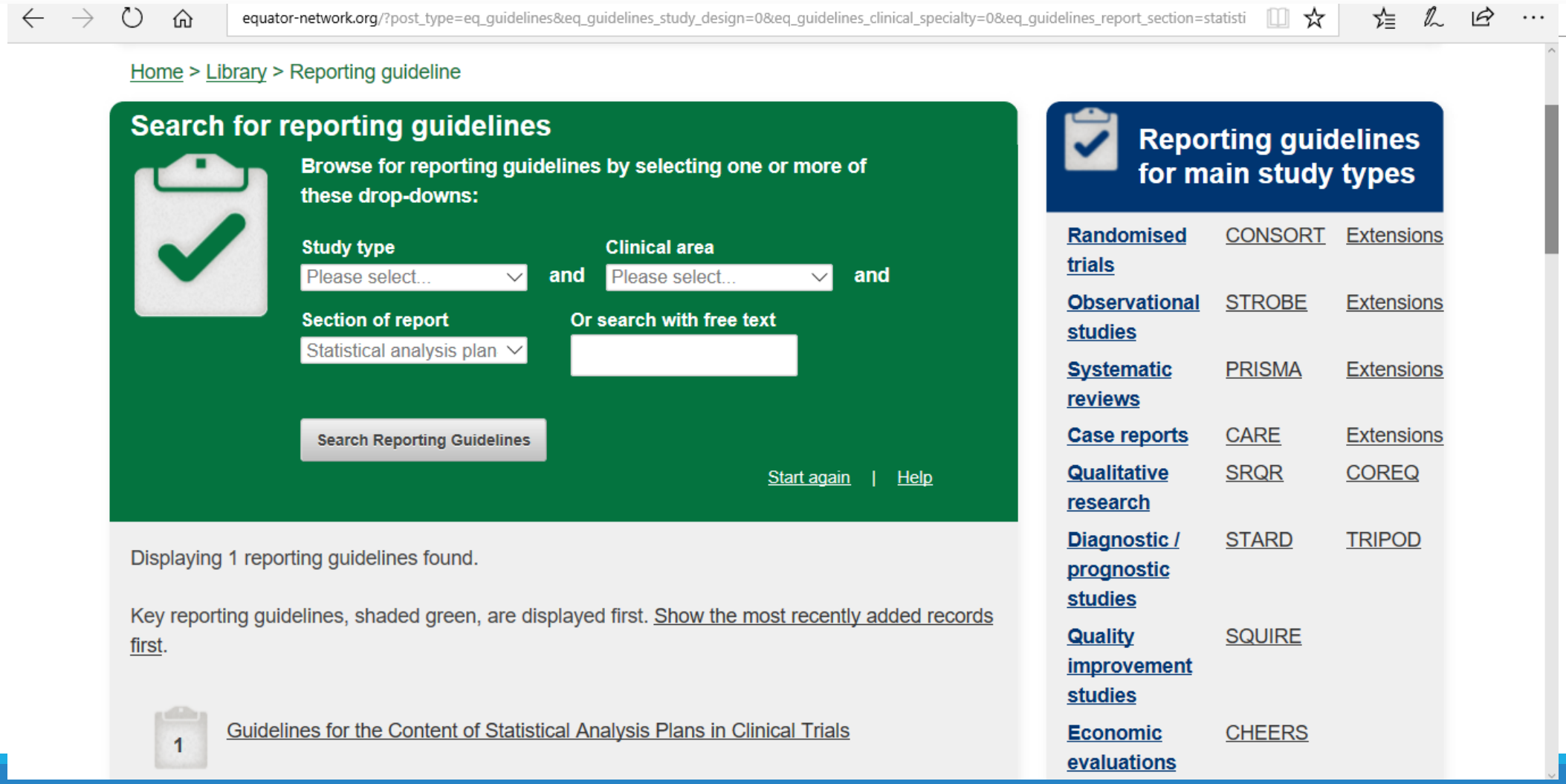

Extensions

Health economic plans

Observational studies

- Institute of Social and Preventive Medicine at Bern, Switzerland
- University of Groningen, The Netherlands

Early phase studies

- Group identified within UKCRC registered CTU network

Next steps

- increase public accessibility
- US National Institutes of Health Final Rule for Clinical Trials Registration and Results Information Submission, which in addition to posting of results within ClinicalTrials.gov also requires posting of the statistical analysis plan