Differential reporting of group sequential RCTs: shortcomings of the CONSORT 2010 statement

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Outline

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Introduction

1. A Group Sequential (GS) design is the most popular and well-understood in confirmatory trials
2. Statistical inference penalty (Tsiatis et al 1984; Whitehead 1986; Kim 1989; Li 1999)
   - There is no such thing as a free lunch
   - Inappropriate use of traditional methods overestimates the treatment effect (Montori et al 2005; Bassler et al 2008; Wilcox et al 2008; Wittes 2012)
3. Some adaptive designs related concerns have been raised when trials are stopped early (Dimairo et al: under peer review)
   - Robustness in decision making and acceptability to change medical practice
4. Could it be partly linked to transparency and adequate reporting of the trial conduct?
5. CONSORT Statements have been instrumental in enhancing trial reporting

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Goals

1. Investigate compliance in the reporting of GS RCTs
2. Investigate shortcoming of the CONSORT 2010 statement in enhancing reporting of GS RCTs
   - Some recent proposed (Detry et al 2012) and researcher-led modifications

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Review of confirmatory RCTs

1. Searching Ovid MEDLINE (1st January 2001 to 23rd September 2014)
2. Supplemented with known GS RCTs from another audit study
3. Employed free text search of keywords often associated with GS methodology
4. Prospectively planned, frequentist designed and analysed GS RCTs reporting primary results

Assessment of compliance in reporting

1. Two independent reviewers
2. Predefined compliance criteria (absent/totally complete/partially complete/cannot access/NA)
3. Used all cited accessible publications

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Characteristics of reviewed GS RCTs

1. 68/284 (24%) eligible RCTs reviewed: cross-sector funded
2. Most RCTs published in high impact peer-reviewed journals
   - Median (IQR) Impact Factor (2013/2014) of 17.5 (6.6 to 30.4)
3. 62(91%) investigated at least some form of pharmacological intervention
4. 46(68%) journals endorsed the CONSORT
5. 46(68%) stopped early, predominantly for futility or efficacy
   - Median (IQR) sample size/event rate distribution 65% (50% to 85%), with minimum of 19%

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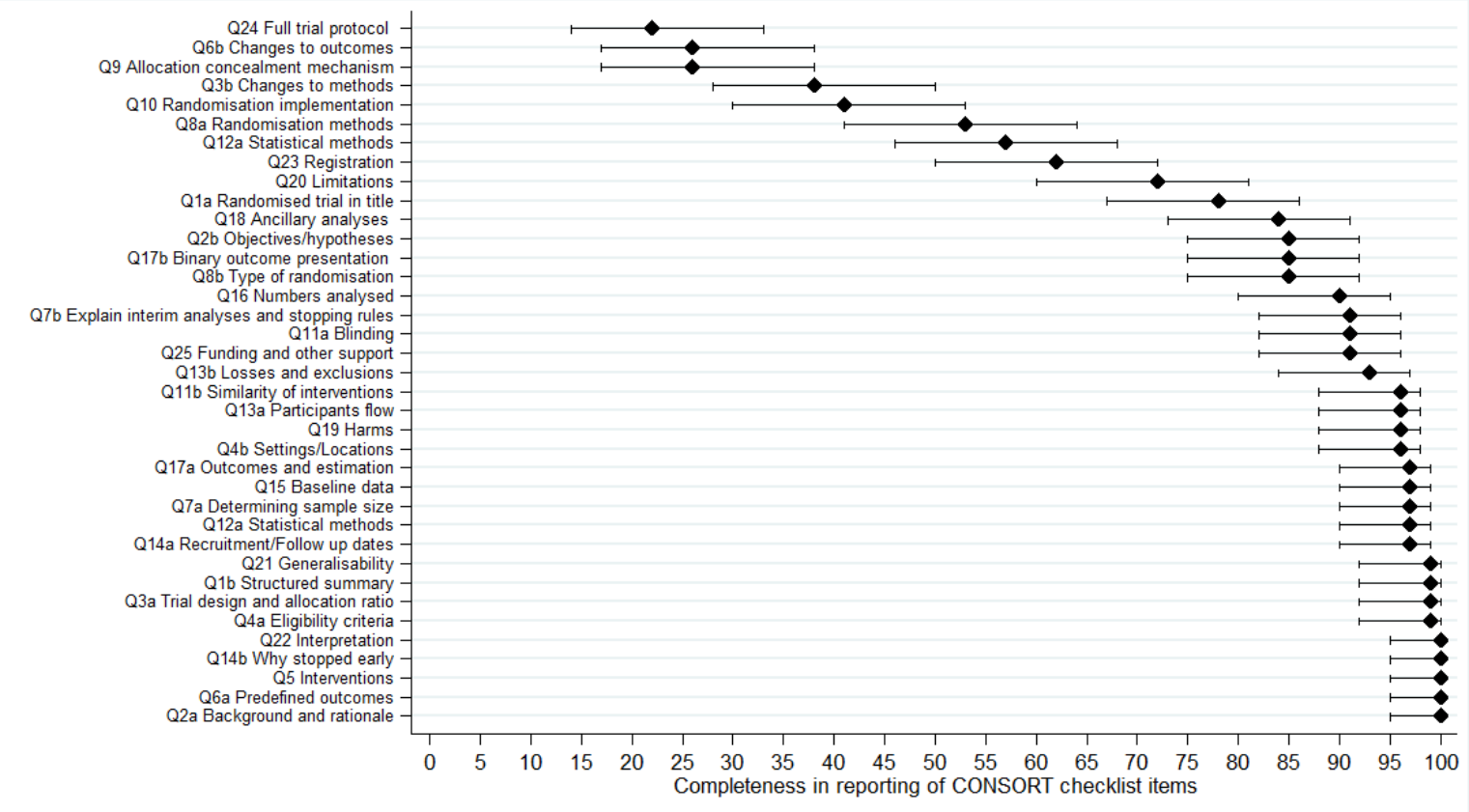
Reporting of general RCT items



- Most of the CONSORT checklist items were reported adequately
- However, some were poorly considered: methods to generate randomisation lists, details of randomisation concealment, and implementation of the randomisation
- Compliance in some items could not be assessed due to lack of access to trial protocols and amendments

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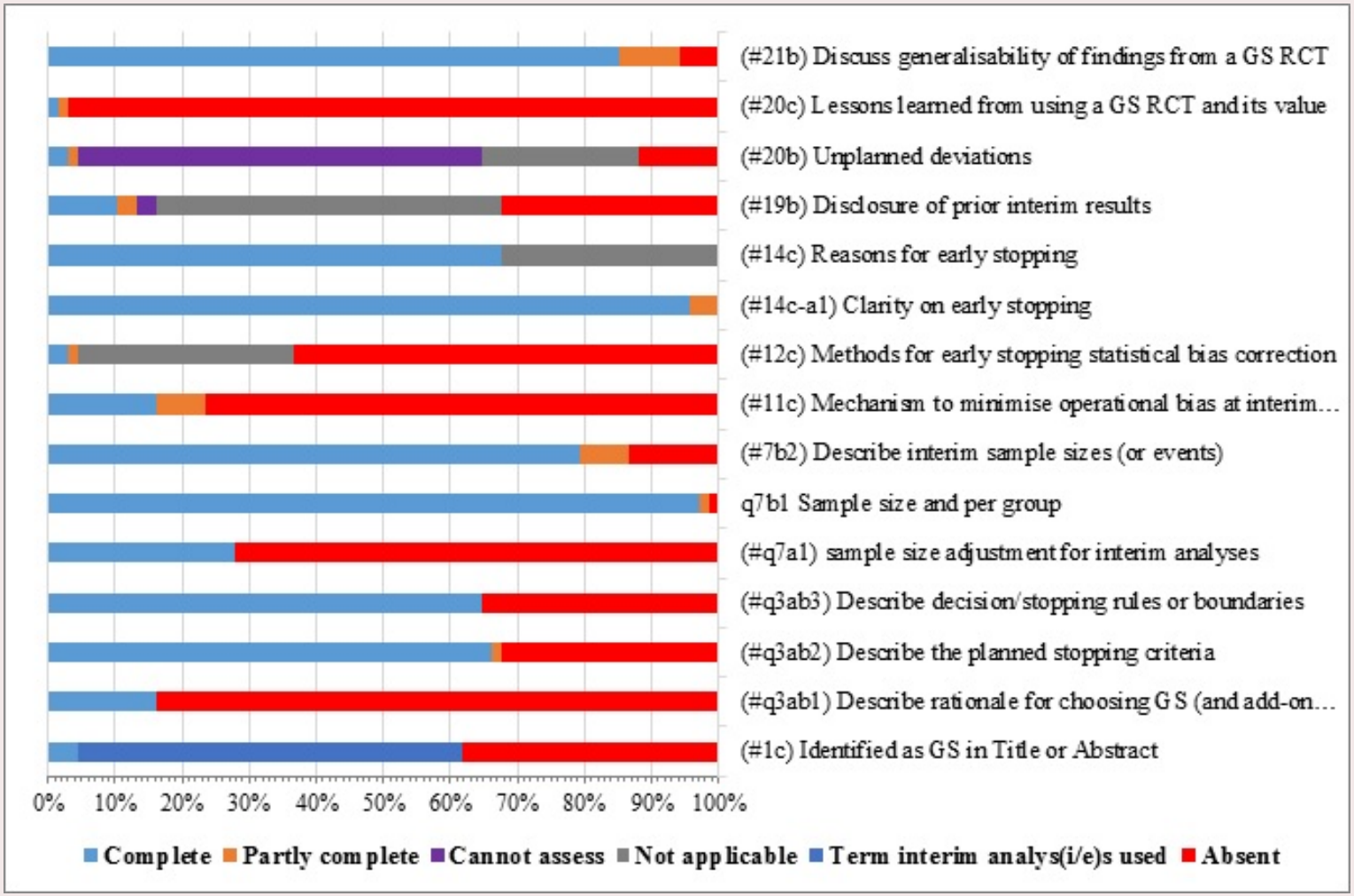
Reporting of GS specific items



- Only 3/46(7%) reported early stopping bias correction (point estimates, confidence intervals and p-values)

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Conclusions

1. Scientific rigour and adequate transparent reporting is imperative
2. Implications of suboptimal reporting/underuse of early stopping bias correction are unknown
3. Poor reporting may not necessarily mean methods are not being implemented
4. However, research consumers may presume otherwise if not documented
5. Suboptimal reporting could partly explain aforementioned concerns
6. Urgent need for an adaptive designs tailored CONSORT extension
7. Accessible publication of protocols and related amendments is paramount

Limitations

1. Inaccessible protocols (and amendments) limited assessment of some items
2. Restricted database search

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