PROTOCOL SUMMARY

The quality of reporting of randomised controlled trials in asthma: systematic review protocol

Chara Ntala1, Panagiota Birmili1, Allison Worth2, Niall H Anderson2, *Aziz Sheikh2

1 University of Patras, Medical School, University Campus, PC 26504, Rio, Patras, Greece
2 Allergy and Respiratory Research Group, Centre for Population Health Sciences, The University of Edinburgh, Edinburgh, UK

Received 23rd August 2012; revised 11th October 2012; accepted 12th October 2012; online 24th January 2013

© 2013 Primary Care Respiratory Society UK. All rights reserved.
C Ntala et al. Prim Care Respir J 2013; 22(1): PS1-PS8
http://dx.doi.org/10.4104/pcrj.2013.00003

Keywords asthma, randomised controlled trials

Background

The randomised controlled trial (RCT) is the most robust design to assess the efficacy and effectiveness of treatments. As a result of this realisation, clinical decision-making in recent years has been directed away from reliance based solely on the doctor’s clinical experience towards a paradigm based on evidence derived from RCTs. The results of large RCTs have subsequently been translated into guidelines containing evidence-graded recommendations which clinicians are encouraged to use as the basis of good clinical practice. If, however, the ‘raw material’ is flawed, the conclusions cannot be trusted, hence the need to appraise critically the quality of the underpinning trial evidence.

Quality is a multidimensional concept which relates to the design, conduct, and analysis of a trial, its clinical relevance, and its reporting. In most cases, the RCT report is the only source for clinicians, guideline developers, and other researchers to judge the validity and generalisability of the results, so the quality of reporting of trials is of inherent interest. More recently, there have been no recent assessments of the quality of RCTs reporting in the asthma literature. The only previous study on clinical trials of asthma treatments was undertaken for the period 1984–1997 and was published in 2002 in two reports.18,19 This initially involved a comparison between RCTs published in Spanish and English language journals, and this was then followed by a secondary analysis of a subsection of the same dataset focusing solely on the quality of RCTs in English. There have, however, been no recent assessments of the quality of RCTs reporting in the asthma literature. The only previous study on clinical trials of asthma treatments was undertaken for the period 1984–1997 and was published in 2002 in two reports.18,19 This initially involved a comparison between RCTs published in Spanish and English language journals, and this was then followed by a secondary analysis of a subsection of the same dataset focusing solely on the quality of RCTs in English.18,19 The first article showed poorer reporting quality of the RCTs in Spanish publications and a strong association between the type of journal, type of intervention, and the comparison measure used and reporting quality. Moreover, this study highlighted the necessity for better reporting in general in the asthma literature, leading the authors to advocate the more widespread use of a checklist by authors and editors in order to improve reporting standards.

Building on this earlier work, we will examine the quality of reporting of asthma clinical RCTs in the contemporary asthma literature. Our secondary aim is to investigate if there is an association between specific trial characteristics that have previously been identified in the literature in influencing reporting quality and the actual quality of the trial reports.

* Corresponding author: Professor Aziz Sheikh, Allergy and Respiratory Research Group, Centre for Population Health Sciences, The University of Edinburgh, Medical School, Teviot Place, Edinburgh EH8 9AG, UK. Tel: +44 (0)131 651 4151 Fax: +44 (0)131 650 9119 E-mail: aziz.sheikh@ed.ac.uk

PRIMARY CARE RESPIRATORY JOURNAL
www.thepcj.org
http://dx.doi.org/10.4104/pcrj.2013.00003
Objectives
The primary objective is to assess the contemporary quality of reporting of RCTs in the asthma literature for the period 2010–2012. The secondary objectives are to identify factors associated with better reporting quality, that is:

- Are trials reported as full papers (abstracts), editorials, comments, letters, case reports, audits, guidelines, historical articles
- Methodological, epidemiological and qualitative studies
- Study protocols
- Pilot studies and phase I, II, and IV trials
- Secondary analysis of trials
- Studies reporting updates of previously published RCTs

Review strategy
Searches will be undertaken independently by two reviewers (CN and PB) with support from AW and AS. The references will be imported into EndNote and duplicates will be deleted. Both reviewers will independently review the titles for potentially eligible studies. They will not be blinded to study details. If they are unsure or there are disagreements they will read the abstract also. Full text copies of potentially relevant studies will be obtained and CN and PB will assess their eligibility for inclusion against the criteria mentioned above. A kappa statistic will be calculated to measure the level of agreement. Where the reviewers agree, they will either include or exclude the study as appropriate. Disagreements will be resolved through discussion with AW or AS as arbiters. The studies that will be excluded after reading the full paper (‘near-misses’) will be reported in a table with reasons for exclusion. The whole process will be documented on a PRISMA flow chart.

Data extraction and quality assessment strategy
Data will be extracted independently by two reviewers (CN and PB) from the selected studies using an appropriate electronic customised data extraction form (see Appendices 2–4). The reviewers will not be masked to study details. There will be pilot testing of the data extraction sheet, disagreements will be discussed, and modifications will be made if required. In case of multiple reports of the same study, we will extract data directly into a single data extraction form. Disagreements will be resolved through discussion with AS as arbiter. We will extract data on general characteristics of the trials (see Appendix 2) and use a modified 38-item CONSORT-based checklist (see Appendix 3) that consists of all the CONSORT checklist items plus one additional item from the non-pharmacological treatments extension. The assessment of the adequacy of reporting will be done according to the CONSORT 2010 guidelines and its extensions. Each item can be characterised as ‘yes’ if it is clearly and adequately reported, or ‘no’ if it is partially unclear or not reported at all. If an item is not applicable to a specific study we will characterise it as ‘N/A’. Each ‘yes’ answer will receive a score of 1 and each “no” answer will be scored as 0. The overall quality scoring of the trial will be calculated as a proportion of the ‘yes’ rated applicable items (possible range 0–38 points). In addition, we will score the overall quality of reporting using key parameters of internal validity summarised in the Cochrane Risk of Bias tool (see Appendix 4) and we will categorise the studies into those at (1) low risk of bias and (2) moderate/high risk of bias. A kappa statistic will be calculated to measure the level of agreement. Where the reviewers agree, they will either include or exclude the study as appropriate. Disagreements will be resolved through discussion with AS as arbiter. We will extract data on general characteristics of the trials (see Appendix 2) and use a modified 38-item CONSORT-based checklist (see Appendix 3) that consists of all the CONSORT checklist items plus one additional item from the non-pharmacological treatments extension. The assessment of the adequacy of reporting will be done according to the CONSORT 2010 guidelines and its extensions. Each item can be characterised as ‘yes’ if it is clearly and adequately reported, or ‘no’ if it is partially unclear or not reported at all. If an item is not applicable to a specific study we will characterise it as ‘N/A’. Each ‘yes’ answer will receive a score of 1 and each “no” answer will be scored as 0. The overall quality scoring of the trial will be calculated as a proportion of the ‘yes’ rated applicable items (possible range 0–38 points). In addition, we will score the overall quality of reporting using key parameters of internal validity summarised in the Cochrane Risk of Bias tool (see Appendix 4) and we will categorise the studies into those at (1) low risk of bias and (2) moderate/high risk of bias.

The following data will be extracted:

General characteristics
- Journal name
- Journal type (general medicine or specialty)
- Journal impact factor
- Country of study (high-income, middle-income, low-income)
Quality of reporting in asthma RCTs

- Funding source (soley industry, part industry, non-industry, none, unknown)
- Trial design (parallel or cluster)
- Conceptual framework (superiority, non-inferiority, equivalence)
- Type of intervention (drug or non-pharmacological)
- Number of participating centres (multiple or single centre).

Analysis and data synthesis

We will calculate the proportion of the trials that have clearly and adequately reported each CONSORT item with a 95% confidence interval (CI). An overall quality score will also be calculated for each trial as a percentage of all the adequately reported applicable items with a 95% CI, which will be used to inform a global assessment of the quality of reporting. The general characteristics data will be presented as numbers and percentages with 95% CI when categorical and as mean and SD or median and IQR with 95% CI when continuous. SPSS software will be used to identify the variables associated with 'low risk of bias' studies with Fisher's exact test, and overall quality scores for subgroups with different trial characteristics will be compared with appropriate two-sample methods (rank-based or Normality-based, depending on the distributional characteristics of the overall quality score). We will report on the quality of reporting of asthma trials and make recommendations for researchers and journal editors regarding the conduct, reporting, and publication of asthma trials. In our description of the studies we will make reference to the setting and population in which the study was undertaken. In concluding, we will consider the quality and relevance of the body of work for informing clinical decision-making.

Handling editor Anthony D’Urso

Acknowledgements

We are grateful to the following colleagues for their help in conducting the study: Marshall Dozier, Senior Liaison Librarian, for her contribution to the creation and implementation of the search strategy and data management, and Ulugbek Nurmatov, Clinical Research Fellow, for his advice on conducting the study: Marshall Dozier, Senior Liaison Librarian, for her contribution to the creation and implementation of the search strategy and data management, and Ulugbek Nurmatov, Clinical Research Fellow, for his advice on the data extraction and quality assessment tools.

Conflicts of interest

The authors declare that they have no conflicts of interest in relation to this protocol. AS is Joint Editor-in-Chief of the PCRI, but was not involved in the editorial review of, nor the decision to publish, this article.

Contributorship

AS conceived the study; all authors developed the protocol and contributed to writing the protocol.

Funding

CN's Erasmus LLP placement with The University of Edinburgh's Allergy and Respiratory Research Group was supported by the Erasmus-European Commission.

References

1. Moher D, Jadad AR, Nichol G, Pennman M, Tugwell P, Walsh S. Assessing the quality of randomized controlled trials: an annotated bibliography of scales and checklists. Control Clin Trials 1995;16(6):62-73. http://dx.doi.org/10.1016/0197-2456(94)00031-W
2. Travers J, Marsh S, Williams M, et al. External validity of randomised controlled trials in asthma: to whom do the results of the trials apply? Thorax 2007;62(3):219-23. http://dx.doi.org/10.1136/thx.2006.066837
3. Juni P, Altman DG, Egger M. Systematic reviews in health care: assessing the quality of controlled clinical trials. BMJ 2001;323(7303):42-6. http://dx.doi.org/10.1136/bmj.323.7303.42
4. Rios LJ, Odueyeungbo A, Motiri MO, Rahman MO, Thabane L. Quality of reporting of randomized controlled trials in general endocrinology literature. J Clin Endocrinol Metab 2008;93(10):3810-6. http://dx.doi.org/10.1210/jc.2008-0817
5. Moher D, Hopewell S, Schulz KE, et al. CONSORT 2010 explanation and elaboration: updated guidelines for reporting parallel group randomised trials. Int J Surg 2012;10(1):28-55. http://dx.doi.org/10.1016/j.ijsu.2011.10.001
6. Begg C, Cho M, Eastwood S, et al. Improving the quality of reporting of randomized controlled trials: The CONSORT statement. JAMA 1996;276(6):637-8. http://dx.doi.org/10.1001/jama.276.6.637
7. Piaggio G, Elbourne DR, Altman DG, Pocek SJ, Evans SJ. Reporting of noninferiority and equivalence randomized trials: an extension of the CONSORT statement. JAMA 2006;295(10):1152-60. http://dx.doi.org/10.1001/jama.295.10.1152
8. Campbell MK, Elbourne DR, Altman DG. CONSORT statement: extension to cluster randomised trials. BMJ 2004;328(7441):702-8. http://dx.doi.org/10.1136/bmj.328.7441.702
9. Zwaneinstein M, Treweek S, Gagnier JI, et al. Improving the reporting of pragmatic trials: an extension of the CONSORT statement. BMJ 2008;337:a2390. http://dx.doi.org/10.1136/bmj.a2390
10. Ioannidis JP, Evans SJ, Gotzsche PC, et al. Better reporting of harms in randomized trials: an extension of the CONSORT statement. Ann Intern Med 2004;141:781-8.
11. Bouton J, Moher D, Altman DG, Schulz KE, Ravaud P. Extending the CONSORT statement to randomized trials of nonpharmacologic treatment: explanation and elaboration. Ann Intern Med 2008;148(4):295-309.
12. Gagnier JJ, Boon H, Rochon P, Moher D, Barnes J, Bombardier C. Reporting randomized, controlled trials of herbal interventions: an elaborated CONSORT statement. Ann Intern Med 2006;144(5):364-7.
13. Hopewell S, Clarke M, Moher D, et al. CONSORT for reporting randomized controlled trials in journal and conference abstracts: explanation and elaboration. PLoS Med 2008;5(1):e20. http://dx.doi.org/10.1371/journal.pmed.0050020
14. Li R, Chu R, Fraumeni M, Thabane L. Quality of randomized controlled trials reporting in the primary treatment of brain tumors. J Clin Oncol 2006;24(7):1136-44. http://dx.doi.org/10.1200/JCO.2005.03.1179
15. Artilha H, Malmivaara A, Kurz R, Autti-Ramo I, Makela M. Quality of reporting of randomized, controlled trials in cerebral palsy. Pediatrics 2006;117(6):2222-30. http://dx.doi.org/10.1542/peds.2005-1630
16. Rensar ED, Volmink J, Zwaneinstein M, Swynghel GH. Randomised trials in the South African Medical Journal, 1948-1997. S Afr Med J 2002;91(11):901-3.
17. Gluud C, Nikolova D. Quality assessment of reports on clinical trials in the Journal of Hepatology. J Hepatol 1998;29(2):321-7. http://dx.doi.org/10.1016/S0168-8278(98)80021-4
18. Quinones D, Llorca J, Dierssen Y, Delgado-Rodriguez M. Quality of published clinical trials on asthma. J Asthma 2003;40(6):709-19. http://dx.doi.org/10.1080/01650290312334394
19. Quinones D, Llorca J, Prieto-Salceda D, Delgado-Rodriguez M. [Quality of clinical trials published in Spain on asthma in comparison to trials in English language journals]. Arch Bronconeumol 2002;38(12):574-9.
20. Kjaergard LL, Nikolova D, Gluud C. Randomized clinical trials in hepatology: predictors of quality. Hepatology 1999;30(5):1134-8. http://dx.doi.org/10.1002/hep.510300510
21. Hopewell S, Dutton S, Yu LM, Chan AW, Altman DG. The quality of reports of randomized trials in 2000 and 2006: comparative study of articles indexed in PubMed. BMJ 2010;340:c723. http://dx.doi.org/10.1136/bmj.c723
22. Farrokhyar F, Chu R, Whitlock R, Thabane L. A systematic review of the quality of publications reporting coronary artery bypass grafting trials. Can J Surg 2007;50(4):266-77.
23. The World Bank Group. Countries and economies. 2012. http://data.worldbank.org/country/ (accessed 26 July 2012).
24. Thomson Reuters. ISI Web of Knowledge Impact Factors 2012. http://www.isinet.com/products/journals/impact_factors.html (accessed 15 Aug 2012).
25. Higgins JPT GSe Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. www.cochrane-handbook.org.
26. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. PLoS Med 2009;6(7):e1000100. http://dx.doi.org/10.1371/journal.pmed.1000100
Appendix 1: Details of search strategy

MEDLINE 2010-present
1. exp Asthma/
2. asthma$.mp.
3. (antiasthma$ or anti-asthma$).mp.
4. Respiratory sounds/
5. wheez$.mp.
6. Bronchial Spasm/
7. bronchospas$.mp.
8. (bronch$ adj3 spasm$).mp.
9. bronchoconstrict$.mp.
10. exp Bronchoconstriction/
11. (bronch$ adj3 constrict$).mp.
12. Bronchial Hyperreactivity/
13. Respiratory Hypersensitivity/
14. ((bronchial$ or respiratory or airway$ or lung$) adj3 (hypersensitiv$ or hyperreactiv$ or allerg$ or insufficiency)).mp.
15. or/1-14
16. clinical trial.pt.
17. (randomized or randomised).ab,ti.
18. placebo.ab,ti.
19. dt.fs.
20. randomly.ab,ti.
21. trial.ab,ti.
22. groups.ab,ti.
23. (cluster adj2 (design or random?ed)).mp.
24. or/16-23
25. 15 and 24
26. Animals/
27. Humans/
28. 26 not (26 and 27)
29. 25 not 28
30. limit 29 to yr="2010 -Current"
31. *new england journal of medicine*.jn.
32. lancet.jn.
33. jama.jn.
34. *annals of internal medicine*.jn.
35. *plos medicine public library of science*.jn.
36. british medical journal.jn.
37. *archives of internal medicine*.jn.
38. canadian medical association journal.jn.
39. bmc medicine.jn.
40. mayo clinic proceedings.jn.
41. *american journal of respiratory & critical care medicine*.jn.
42. thorax.jn.
43. european respiratory journal.jn.
44. chest.jn.
45. respiratory research.jn.
46. pulmonary pharmacology & therapeutics.jn.
47. *international journal of tuberculosis & lung disease*.jn.
48. pediatric pulmonology.jn.
49. respiratory medicine.jn.
50. respiriology.jn.
51. 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50
52. 30 and 51
## Appendix 2: General characteristics of trials

| General information | Comments |
|---------------------|----------|
| Identification of reviewer | | |
| Date of data extraction | | |
| Study number-identifier | | |
| Notes | | |

| Author | |
| Article title | |
| Publication date | |

| General characteristics | Comments |
|--------------------------|----------|
| Journal name | | |
| Journal type | General medical Specialty | |
| Journal impact factor | | |
| Country of study | | |

| Funding source | Soley industry Part industry Non-industry None Unknown | |
|----------------|-----------------------------------------------------------|-----|
| Trial design | Parallel Cluster | |
| Conceptual framework | Superiority Non-inferiority Equivalence | |
| Type of intervention | Drug Non-pharmacological | |
| Number of centres | Single Multiple | |
# Appendix 3: Modified 38-Item CONSORT-based 2010 checklist

| Section/topic          | Item no | Description                                                                 | Adequately reported | Comments |
|------------------------|---------|-----------------------------------------------------------------------------|---------------------|----------|
| Title and abstract     | 1       | Identification as a randomised trial in the title                          | Yes/No              | N/A      |
|                        | 2       | Structured summary of trial design, methods, results, and conclusions       | Yes/No              |          |
| Introduction           |         |                                                                             |                     |          |
| Background and objectives | 3   | Scientific background and explanation of rationale                          | Yes/No              |          |
|                        | 4       | Specific objectives or hypotheses                                           | Yes/No              |          |
| Methods                |         |                                                                             |                     |          |
| Trial design           | 5       | Description of trial design (such as parallel, factorial) including allocation ratio | Yes/No              |          |
|                        | 6       | Important changes to methods after trial commencement (such as eligibility criteria), with reasons | Yes/No              |          |
| Participants           | 7       | Eligibility criteria for participants                                       | Yes/No              |          |
|                        | 8       | Settings and locations where data were collected                            | Yes/No              |          |
| Interventions          | 9       | Interventions for each group with sufficient details to allow replication, including how and when they were actually administered | Yes/No              |          |
| Outcomes               | 10      | Completely defined pre-specified primary and secondary outcome measures including how and where they were assessed | Yes/No              |          |
|                        | 11      | Any changes to trial outcomes after the trial commenced, with reasons      | Yes/No              |          |
| Sample size            | 12      | How was sample size determined                                              | Yes/No              |          |
|                        | 13      | When applicable, explanation of any interim analyses and stopping guidelines | Yes/No              |          |
| Randomisation          |         |                                                                             |                     |          |
| Sequence generation    | 14      | Method used to generate the random allocation sequence                       | Yes/No              |          |
|                        | 15      | Type of randomisation; details of any restriction (such as blocking and block size) | Yes/No              |          |
| Allocation concealment mechanism | 16 | Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned | Yes/No              |          |
| Randomisation          | 17      | Who generated the random allocation sequence who enrolled participants, and who assigned participants to interventions | Yes/No              |          |
| Blinding               | 18      | If done, who was blinded after assignment to interventions (e.g. participants, care providers, those assessing outcomes) and how | Yes/No              |          |
|                        | 19      | If relevant, description of the similarity of interventions                 | Yes/No              |          |
| Statistical methods    | 20      | Statistical methods used to compare groups for primary and secondary outcomes | Yes/No              |          |
|                        | 21      | Methods for additional analyses such as subgroup analyses and adjusted analyses | Yes/No              |          |
| Results                |         |                                                                             |                     |          |
| Participant flow       | 22      | For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome | Yes/No              |          |
|                        | 23      | For each group, losses and exclusions after randomisation, together with reasons | Yes/No              |          |
| Implementation of interventions | 24 | Details of the experimental treatment and comparator as they were implemented | Yes/No              |          |
## Appendix 3: Modified 38-Item CONSORT-based 2010 checklist continued

| Section/topic      | Item no | Description                                                                 | Adequately reported | Comments |
|--------------------|---------|-----------------------------------------------------------------------------|---------------------|----------|
| Recruitment        | 25      | Dates defining the periods of recruitment and follow-up                     | Yes/No              |          |
|                    | 26      | Why the trial ended or was stopped                                          | Yes/No              |          |
| Baseline data      | 27      | A table showing baseline demographic and clinical characteristics for each group | Yes/No              |          |
| Numbers analysed   | 28      | For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups | Yes/No              |          |
| Outcomes and estimation | 29 | For each primary and secondary outcome, results for each group and the estimated effect size and its precision (such as 95% confidence interval) | Yes/No              |          |
|                    | 30      | For binary outcomes, presentation of both absolute and relative effect sizes is recommended | Yes/No              |          |
| Ancillary analyses | 31      | Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory | Yes/No              |          |
| Harms              | 32      | All important harms or unintended effects in each group                     | Yes/No              |          |
| Discussion         | 33      | Trial limitations, addressing sources of potential bias, imprecision and, if relevant, multiplicity of analyses | Yes/No              |          |
| Generalisability   | 34      | Generalisability (external validity, applicability) of the trial findings   | Yes/No              |          |
| Interpretation     | 35      | Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence | Yes/No              |          |
| Other information  | 36      | Registration number and name of trial registry                              | Yes/No              |          |
| Protocol           | 37      | Where the full trial protocol can be accessed, if available                 | Yes/No              |          |
| Funding            | 38      | Sources of funding and other support (such as supply of drugs), role of funders | Yes/No              |          |
### Appendix 4: Risk of Bias tool

| Item                                      | Judgement | Description |
|-------------------------------------------|-----------|-------------|
| Adequate sequence generation?            | Yes       | Quote:      |
|                                           | No        | Comment:    |
|                                           | Unclear   |             |
| Allocation concealment?                  |           |             |
| Blinding of participants and healthcare providers? | |             |
| Blinding of outcome assessors and data analysts? | |             |
| Incomplete outcome data addressed?       |           |             |
| Free of selective reporting?             |           |             |
| Free of other bias?                      |           |             |