**Supplementary digital content 1: Study protocol**

Completeness of reporting in randomized controlled trials of vaccines: adherence to the CONSORT checklist

Protocol

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**Abbreviations**

CONSORT Consolidated Standards of Reporting Trials

Hib Haemophilus influenzae Type B

PCV Pneumococcal conjugate vaccine

PPV Pneumococcal polysaccharide vaccine

RCT Randomized controlled trial

# Background

Randomized controlled trials are frequently conducted in vaccine research, both to obtain licensure and to investigate vaccine related study questions. There are some advantages of randomized controlled trials over observational studies. For example random allocation ensures no systematic differences between intervention groups in factors, known and unknown, that may affect outcome. In addition, blinding ensures that the beliefs and views of participants, clinicians or outcome assessors cannot systematically bias the assessment of outcomes.1

Greenwood and Yule stated already in 1915 conditions for valid inference in vaccine studies:2

1. The persons in each group must be alike

2. The effective exposure of disease must be identical in each group

3. The criteria for receiving the vaccine or not must be independent

All these criteria are met with randomization. In observational studies they would have to examine these criteria carefully to avoid the risk of bias. Studies have shown that bias in RCTs is particularly caused by factors such as inadequate concealment or allocation.3, 4 Trials without adequate concealment tend to show a larger treatment effect.5 Random allocation of patients can be adequately concealed in any trial.4 Conducting meta-analyses of vaccine effects which account for these potential sources of bias is important as studies at low risk of bias might show different results to those at high risk.6 These analyses cannot be conducted if information on risk of bias is not well reported.

Evidence shows that randomized controlled trials (RCTs) are often not optimally reported.5, 7 Inadequate reporting makes it difficult to the reader to evaluate whether a trial is internally and externally valid. To improve reporting quality, the CONSORT (Consolidated Standards of Reporting Trials) statement was developed. This statement was first published in 1996, and has been updated twice in 2001 and 2010. The statement consists of a checklist with 25 items and a flow diagram to help authors reporting an RCT in a standard way.7The quality of reporting has been examined for RCTs in general and in various subject fields,8-11 but, to our knowledge, not for vaccine-related RCTs specifically. We will examine standards of reporting in publications included in 3 systematic reviews which are available to us: pneumococcal polysaccharide vaccine (PPV), pneumococcal conjugate vaccine (PCV) and rotavirus vaccine reviews.

*Streptococcus pneumonia*e (pneumococcus) is an encapsulated bacterium which causes pneumonia, invasive pneumococcal diseases such as meningitis or bacteremia, and otitis media. Risk groups are younger children, elderly persons aged > 65 years and patients with an immunodeficiency. There are two types of pneumococcal vaccine: PPV and PCV. PPV was first used in the 1940’s.12, 13 The surface capsular polysaccharide of *S. pneumoniae* provokes a type-specific protective immune response. As children below the age of 2 years are not able to show proper immune response to polysaccharide vaccine a conjugate vaccine was developed and was first licensed in early 2000.14 A conjugate vaccine is created by attaching the polysaccharide organism to a carrier protein to enhance the immune response. *Haemophilus influenzae* is a bacterium, divided in several serotypes. The most important is *H. influenzae* serotype b (Hib), which causes bacteremia, meningitis and other invasive infections. Younger children are the main risk group. A conjugate vaccine has been available since the early 1990s.

This study will systematically assess the completeness of reporting in RCTs included in reviews of PPV, PCV and rotavirus vaccines by using an adapted CONSORT statement checklist.

# Objective

To assess the standards of reporting of RCTs of pneumococcal vaccine and Hib vaccine.

# Study questions

1) How well are individual items in the CONSORT checklist reported in the RCTs of pneumococcal and Hib vaccines which were included in previous reviews?

2) Has reporting in these RCTs improved since the CONSORT checklist was introduced?

# Methods

## Inclusion criteria

We will include published reports of RCTs that were identified in systematic reviews of PPV, PCV and Hib.6, 15 If any trials are reported in multiple publications, we will only include the primary report. We define the primary report as the first publication in a journal which reports clinical, carriage or immunological outcomes. We will also include trial registry listings from our former reviews.6, 15 If there are more than one trial registry listings we will include the trial registry listing which was submitted first.

Protocol amendment (prior to data collection): Data source

The Hib review will not be used as a source of data as the list of included studies was not finalized prior to the commencement of this study. We will therefore use a recent Cochrane review of rotavirus vaccine.16

Protocol elaboration (prior to data collection): Choice of first publication

We define the primary report as the first publication in a journal which reports clinical efficacy, carriage outcomes or immunological outcomes. If the first articles reporting these outcomes were published in the same or consecutive calendar years, we will choose the article which was first submitted to a journal, or if this is not reported, we will choose the one with the most complete description of randomization methods. If there is in any publication which states that the methods are described elsewhere more in detail, we will use the cited report in our assessment of the completeness of reporting. If a trial has no journal publications listed in the source review, we will search for publications online. We will not search for additional publications if one or more are listed in the source review.

## Exclusion criteria

We will exclude all publications which are not the primary publication and all trial registry listings which were not the first submitted. We will exclude all study designs other than randomized controlled trials.

Protocol amendment (after data collection): Analysis of multiple studies in one publication

To prevent over representation of any single publication be we will exclude all but the first eligible trial reported in a publication. We will consider the first trial to be trial first mentioned in the first table showing results.

## Search strategy

All literature searches have already been conducted for our former systematic reviews (6, 15) and for the review on Hib, which is in progress.

## Databases and Search terms

For the review of PPV the following databases were searched: MEDLINE (1966, to May, 2007), EMBASE (1974 to May, 2007) and the Cochrane Central Register of Trials (CENTRAL) using the key words “pneumococcal vaccine” or “pneumococcal immunization” in combination with “polysaccharide”. For MEDLINE and EMBASE, these key words were combined with terms describing the study design: “randomized controlled trial”, “clinical trial” and “controlled clinical trial”.6

For the review of PCV 12 databases and trial registries were searched from their earliest date. The searches were conducted on August 28th 2009 and the Embase.com search was repeated on March 17th 2010. The following keywords were used: “pneumococcus”, “streptococcus”, “conjugated vaccine”, “immunization” or names of licensed pneumococcal conjugate vaccines.15 The Hib review used a similar search strategy with Hib specific search terms.

## Selection of eligible studies

We will select the primary publications, using the inclusion and exclusion criteria stated above. The lists of articles included in each of the systematic reviews will be independently examined by two suitably qualified reviewers to assess eligibility.

## Data extraction forms

We will develop forms for extracting consistent data about:

* Basic information about the RCT (name of first author, date of publication)
* Information about how well each of the items of the CONSORT-statement checklist is reported, with a focus on information about items related to the risk of bias in the trials
* The agreement of primary outcomes defined in the trial registration with those reported the publication

An extraction guide will be developed to ensure consistent extraction of data.

## Data extraction

Appropriately qualified people will extract and enter data independently and in duplicate from each study. Discrepancies in data extraction will be resolved by consensus. If there is no agreement a third independent reviewer will adjudicate to make a final decision.

## Data analysis

Data will be exported to STATA for analysis.

Primary analysis:

We will calculate the percentage of articles which report adequate the criteria of the CONSORT-statement.

We specify the following primary outcomes:

* C 1a. Does the title identify the study as a randomized trial?
* C 5. For PCV/Hib: Are the intended and actual ages at vaccination reported?
* C 51. For PPV: Are actual ages stated?
* C 6a. Is the primary outcome nominated?
* C 8a. Is it reported how random allocation sequence was generated?
* C 8a1. Was the reported method adequate?
* C 9. Are the mechanisms of allocation concealment described?
* C 91. Were the mechanisms of allocation concealment adequate?
* C 17a2. Are the primary outcomes in the report presented the same as in the trial registry described?
* C 23. Did we find a trial registration?
* C 231. Is the trial registry number reported?

Secondary analyses:

If sufficient data is available we will examine whether reporting of items relating to the risk of bias in RCTs has improved over time. We will conduct 3 analyses:

1. Logistic regression using year of publication as a continuous explanatory variable, and the reporting of each bias related item as a binary outcome. The vaccine examined by each publication will be included as a potential confounder and effect modifier.
2. Logistic regression using year of publication as a binary explanatory variable (1996 and before vs. after 1996), and the reporting of each bias related item as a binary outcome. The vaccine examined by each publication will be included as a potential confounder and effect modifier.
3. Logistic regression using year of publication as a binary explanatory variable (published before CONSORT was adopted by journal in which article published vs. published after CONSORT adopted by journal), and the reporting of each bias related item as a binary outcome. The vaccine examined by each publication will be included as a potential confounder and effect modifier.

## Report writing

An article will be written and will be published in an appropriate journal.

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