Title:

Protocol registration and outcome reporting bias in randomised controlled trials of eczema treatment

Rationale:

As one of the measures to reduce the likelihood of selective reporting bias in RCTs, the International committee of Medical Journal Editors initiated a policy requiring investigators to register their trials into a clinical trial registry before participant enrolment as condition of publication in one of their journals. This policy came into effect in July 1, 2005. [1]

Research Objectives:

1. To assess the proportion of eczema treatment randomized controlled trials (RCTs) with registered protocols.

2. To compare trials with and without registered protocols for differences in risk of bias, sample size, and funding source.

3. To assess the level of outcome reporting bias in eczema treatment trials with properly registered protocols.

Research Hypotheses:

1. Less than half of eczema RCTs will have registered protocols.

2. There are differences in quality of reporting between trials with and without registered protocols.

3. Of the trials with properly registered protocols, there are possible discrepancies between the primary outcome that was registered in the protocol and the primary outcome reported in the published trial report.

Study Design:

Systematic review of published randomised clinical trials of eczema treatment

Methods:

Identifying published eczema trials

We will use the GREAT (Global Resource of Eczema Trials) database to search for published eczema randomised controlled trials.

The GREAT database (http://www.greatdatabase.org.uk) brings together information on all randomized controlled trials of eczema treatments published from the beginning of 2000 to 2011 and is updated every month. [2]

Inclusion criteria:

The review will include all eczema treatment RCTs contained in the GREAT database and published between January 1, 2007 and July 31st, 2011.

Exclusion criteria:

RCTs published as abstracts only without associated full publication. In case we find both an abstract and full paper, only the full paper will be included.

Identifying trial protocols

If the trial protocol ID number is stated in the text of the publication we will use this number to find the protocol.

In cases where the protocol number is not stated, we will search for the protocol in the WHO International Clinical Trials Registry Platform (ICTRP) search platform: http://apps.who.int/trialsearch/ This registry includes registered trials from a number of different trial registries throughout the world. [3]

Two people will search for registered protocols independently (A.B. and H.N.) using a combination of study's key words: "eczema" or "atopic dermatitis" plus keywords describing the trial's interventions such as "pimecrolimus" or "probiotics". All protocols

that meet the search criteria will be reviewed to find the one that matches the published trial using the name of principal investigator, funding source, design, duration, and sample size as appropriate.

Defining trials with "ever-registered" vs. "properly registered" protocols

All trials with registered protocols will be defined as trials that have a registered protocol (referred to as "ever-registered").

In addition, among trials with "ever registered" protocols, we will define a subset of trials with "properly registered" protocols. We defined trials with "properly registered" protocols as being those where:

1. Primary outcome was explicitly stated, and
2. Protocol was registered not later than the end of the study.

In cases where only the start date of participants' enrolment is stated in the protocol, without indication of the end date, we will consider a trial to be properly registered if the protocol was registered within 12 months of the study start date.

Only trials with "properly registered" protocols will be included in the evaluation of outcome reporting bias.

To take into account the amendments and possible changes that could have taken place after initial trial registration, we will use the URL provided on the WHO trial registration webpage to go to the source record in the primary register and look for additional information about the trial.

Comparison between non-registered and ever-registered trials

We will compare ever-registered and non-registered trials on several characteristics including: number of patients randomized, funding, and quality of trial reporting. Quality of trial reporting will be assessed using the Cochrane Collaboration's tool for assessing risk of bias. [4] The risk of bias will be assessed in five different domains: randomization method, allocation concealment, blinding of participants, blinding of outcome assessors, and use of intention-to-treat principle. An assessment of high, low, or unclear risk will be given for each of these domains, for each study.

Comparison of primary outcome between publication and protocol among properly registered trials

For each study with a properly registered protocol, we will review and compare primary outcomes reported in the publication with that stated in the protocol. Both the primary outcome and the time frame for analysis will be recorded.

We will define discrepancies as follows: (1) when the primary outcome in the published report is different to that in the protocol; (2) when the time frame for assessing the primary outcome in the published report is different to that in the protocol.

Sample size estimation:

We estimated that over 100 trials will be needed to estimate proportion of trials with registered protocols with +/- 10% confidence interval.

Statistical analysis

We will use simple count and percentages for categorical variables, and mean with standard deviation (SD) for continuous variables. Proportion will be compared using Chi-square or Fisher exact test. Continuous variables will be compared through t-test. $P<0.05$ (2-tailed) will be considered statistically significant.

Study team:

Helen Nankervis: creating the GREAT database, identifying trials to be included in the study, data extraction from published trials, searching for trial protocols in the WHO ICTRP search platform.

Akerke Baibergenova: searching for trial protocols in the WHO ICTRP search platform, data extraction from published trials and trial protocols, drafting the manuscript.

Kim Thomas and Hywel Williams: concept and design, administrative support, and supervision

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References:

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