Differences in the reporting of harms data in internal sponsored reports versus the corresponding published trial reports: Evaluating the safety reporting of rhBMP-2 in 17 Medtronic sponsored trials (Protocol).

Corresponding author: Alex Hodkinson

Contact details of corresponding author: Department of Biostatistics, Faculty of Health & Life Sciences, University of Liverpool, Shelley's Cottage, Brownlow Street, Liverpool, L69 3GS, UK

Email: ahoddy@liverpool.ac.uk

Authors and affiliations:

Alex Hodkinson, Catrin Tudur-Smith[1], Carrol Gamble[1]

[1]Department of Biostatistics, Faculty of Health & Life Sciences, University of Liverpool, Shelley's Cottage, Brownlow Street, Liverpool, L69 3GS, UK.

Contributions of authors:

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Abstract

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Background

The Food and Drug Administration (FDA) approved Medtronic formulation of recombinant human bone morphogenetic protein 2 (rhBMP-2) in 2002. rhBMP-2 is a single level anterior inter-body lumbar fusion (ALIF) within specific threaded cages and used as an alternative to traditional iliac crest bone graft techniques for spinal fusion surgery. The use of this product in spinal surgery has increased rapidly[1].

Published industry sponsored trials of rhBMP-2 have reported clinical benefits with no adverse events[2]. By 2006, independent studies raised concern over some potential adverse events associated with the use of rhBMP-2 and across all surgical approaches. A subsequent review of publically available data suggests an increased risk of complications and adverse events for patients receiving rhBMP-2 that was 10 to 50 times higher than the original estimates[3].

As of June 2011, amid the controversy between the sponsor (Medtronic) and clinical authors of published articles, the Yale University Open Access (YODA) project[4] reached a landmark agreement to provide full individual participant data (IPD) and internal reports from all their studies of rhBMP-2 in spinal fusion surgery. This enables researchers unrestricted access to the data and the opportunity analyse the adverse event profile of rhBMP-2 which has come under scrutiny.

Objectives

This study has two objectives:

(i) **Reporting:** We aim to compare the quality of reporting of harms data through the comparison of internal reports provided by Medtronic against trial reports published in the medical literature.

(ii) Numerical data: We aim to compare the transparency, accuracy, and completeness of harms data through comparison of internal reports and IPD data for all rhBMP-2 trials provided by Medtronic against harms data presented in trial reports published in the medical literature.

Methods

Criteria for considering trials for this study

We include all patients enrolled and included in the Medtronic randomized control trials (RCTs) of rhBMP-2 undergoing lumber spinal fusion surgery for which there is individual patient data (IPD), internal reports and protocols available for analysis.

Outcome Measures

Objective (i): Detail for quality of harms reporting will be assessed using the CONSORT harm criteria[5] as a benchmark to compare between the internal industry reports and IPD with trial publication.

Objective (ii): Adverse events

Sources for obtaining relevant documents

All 17 protocols, internal research reports, and IPD will be obtained by the YODA project.

Data extraction and management

The review authors (AH, CTS) will independently extract data from the internal reports and publications. We will record all extracted information within an excel spread sheet to make comparisons easier between documents.

Harms data will be assessed by a modified CONOSRT-harms template to assess the important features that the internal reports may have detailed but the publication has not. The template includes the features that would be expected to be found in a published trial report excluding the introduction or discussion sections. The following will be extracted for each trial:

1. **Definition of adverse events** (attention, grading, expected vs. Unexpected events, reference to standardized and validated definitions, and descriptions of new definitions).
2. **Collection of harms data** (mode of collection, timing, attribution methods, intensity of ascertainment, and harms-related monitoring and stopping rules, if pertinent).

3. **Statistical methods** (as detailed with their statistical analysis plan, coding, handling of recurrent events, timing issues, handling of continuous measures, and any statistical analyses).
4. **Participant withdrawals due to harm**
5. **Listing of denominators of AEs**
6. **Rates of outcomes** (scaling and seriousness of the AEs as detailed within the protocol).

One review author will complete data extraction in full. A second review author will check the templates for consistency by selecting the publication at random. A third member of the research team will be consulted for any further disagreements. Four different types of text highlighting will be used in the document:

Yellow: Information is unclear and further discussions maybe required (possibly by consulting the third member).
Red: Only reported in the internal reports (CSR)
Orange: Only reported in a publication
Green: Reported in internal report and full academic publication

Risk of Bias assessment

Data Analysis Plan

Reporting

We will summarize what has been reported and what has not been reported for the internal report and for the trial publication. There will be a measure of agreement between these two in terms of each item on the CONSORT checklist. Our main interest lies within disagreements between reports.

There are two approaches we can consider here; (i) generate a score for each item or scaling system for weak and strong association. E.g. 0-5 0:- being weak and 5:- strong. However this system could prove difficult to resolve when there are major discrepancies in the scoring system between reviewers, (ii) the alternative approach will be yes/no for each of the items then compare these outcomes in descriptive analysis….

Numerical summaries

The second objective was to compare the harms data from the CSR and the publication. So we aim to record all the data recorded within each report separately, and then compare the consistency of their results and make numerical summaries. We may display these summaries as a meta-analysis. E.g. If we have recorded data for say dropout we may graphically depict the proportion of patients included in flow chart. There is another possibility to grade the quality of the harms data reported. In this case we will look to develop a tool with appropriate scaling. But it is important not to overcomplicate this, as to reviewers will need to be able extract and interpreted which grading in applicable.

References

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