Systematic Review and Meta-Analysis of the Safety and Efficacy of Recombinant Human Bone Morphogenetic Protein-2 (rhBMP-2)

PROTOCOL

Background

Human bone morphogenetic protein-2 (rhBMP-2) is used in orthopaedic and spinal surgery to promote fusion. Following 2002 FDA approval for use in anterior lumbar fusion (ALIF) surgery, numbers of spinal procedures using rhBMP-2 grew rapidly, including many in off-label indications. This is despite the fact that the majority of procedures will fuse without use of rhBMP-2 and that in many cases fusion per se is not a pre-requisite for successful surgery. More recently, a number of small studies have raised concern over high rates of adverse events (AE) some of which are potentially life-threatening and which had not been reported in licensing studies. The need for rhBMP-2, its efficacy and its AE profile is therefore under considerable scrutiny and a robust re-evaluation of the research evidence is vital.

In recognition of the importance of this issue, the manufacturers of rhBMP-2 (Medtronic Inc) released all of its clinical research data that are relevant to the use of rhBMP-2 to Yale University for independent scrutiny and review. Yale has contracted two academic groups to carry out independent and unrestricted systematic reviews of the safety and efficacy of rhBMP-2 in spinal fusion, including re-analysis of the individual participant data from Medtronic studies.

This protocol describes the systematic review and associated methodological comparisons to be carried out by the Centre for Reviews and Dissemination (CRD), University of York, UK. The systematic review will consider data from Medtronic studies alongside any non-industry funded clinical research data on rhBMP-2.

In addition to the reviews of benefits and harms described below, the planned research will inform discussions around the comparability of IPD and aggregate data syntheses, and provide objective evidence around data disclosure, selective reporting, industry sponsorship, the availability of individual participant data, and how these might affect the ability to learn about efficacy and adverse events. In
addition, this work will contribute to a wider debate on standards for data disclosure and dealing with potential conflict of interest.

**Objectives**

To evaluate whether rhBMP-2 is more or less effective than standard bone graft therapy (SBGT) in spinal fusion by rigorous systematic review and meta-analysis of relevant studies, including an analysis of individual patient data (IPD), considering

(i) Potential benefits of rhBMP-2, focusing on evidence from randomised controlled trials and on outcomes that are meaningful to patients.

(ii) Potential harms of rhBMP-2 by identifying serious adverse events that have been reported from its use in clinical trials and in general medical practice.

**Methods for synthesis of evidence of clinical effectiveness and safety**

**Inclusion and exclusion criteria**

Two reviewers will independently screen all titles and abstracts retrieved from electronic database and other searches. Full paper manuscripts of any publications that may be relevant will be obtained (where possible) and the relevance of each study assessed by two reviewers according to the criteria below.

Studies that do not meet all of the criteria will be excluded and their bibliographic details listed with reasons for exclusion. Any discrepancies will be resolved by consensus and, if necessary, a third reviewer will be consulted.

**Participants**

Studies including patients undergoing spinal fusion surgery for treatment of degenerative disc disease, spondylolisthesis or any other relevant spinal condition will be included. Although the licensed indication is for use with anterior lumbar interbody fusion, inclusion will not be restricted by operative approach as this will allow evaluation of evidence pertaining to off-label use, particularly with respect to adverse events in cervical and lumbosacral spinal surgery. Anterior lumbar interbody fusion (ALIF), posterolateral lumbar fusion (PLF), posterolateral lumbar interbody fusion (PLIF), transforaminal lumbar
interbody fusion (TLIF), and anterior cervical disectomy and fusion (ACDF) will all be eligible. Inclusion will not be restricted by type of surgery (open, minimally invasive or laparoscopic). Studies of rhBMP-2 use outside spinal fusion surgery (e.g. in long bone fractures) will be excluded, as will all animal and \textit{in vitro} studies. This study will focus only on rhBMP2 and not on other recombinant forms of BMP, such as rhBMP7.

\textit{Interventions}

Studies evaluating rhBMP-2 in spinal fusion will be included in the review, including both Medtronic’s INFUSE/Inductos and AMPLIFY rhBMP-2 carrier/preparations.

\textit{Comparators}

For the evaluation of benefits, studies comparing rhBMP-2 against any standard bone graft techniques (SBGT) will be eligible for inclusion. Studies without a comparator will also be eligible for inclusion in the evaluation of AEs potentially related to the use of rhBMP-2.

\textit{Outcomes}

Inclusion will not be limited by which outcomes are reported. Any studies that are eligible but do not report outcomes of interest will be included and reported as such.

\textit{Study designs}

\textit{Effectiveness}

Only RCTs meeting the above criteria will be included in the review of comparative effectiveness.

\textit{Adverse events}

In accordance with best practice,\(^1\) the review of AEs will not be restricted to RCTs. A decision about which study designs will be included will be taken once we have completed a mapping exercise to determine the volume and scope of studies reporting adverse events, and made a preliminary assessment of the completeness and quality of the available registry data. Attention will be paid to the potential for overlap among identified studies (i.e. the same patients being included in case reports, cohort studies and registries).
Search strategy

A systematic literature search will be performed of the following databases: BIOSIS Previews, Cochrane Central Register of Controlled Trials (Central), the Database of Abstracts of Reviews of Effects (DARE), EMBASE, MEDLINE, MEDLINE in Process and Other Non-Indexed Citations, PubMed, Science Citation Index, TOXLINE, and the FDA website.

The search strategy will be designed to retrieve any studies relevant to the effectiveness or adverse events (AEs) of rhBMP-2 in spinal fusion. Synonyms will be searched for in title and abstract and appropriate indexing/keywords selected. No search filters for specific study designs will be used owing to limitations of searching beyond randomised controlled trials (RCTs) for AEs.² Searches will not be restricted by publication status or date. References of relevant papers will be checked for further relevant studies. Authors of included trials will be asked to notify us of any unpublished studies of which they are aware. A summary of the search strategies used are presented in Appendix 1.

Provision of IPD

Yale University has secured the release of all clinical trial data (published and unpublished), post-marketing surveillance data and spontaneous adverse event data from Medtronic (the manufacturer of rhBMP-2). Yale will make these data available for inclusion in this systematic review.

We will also seek IPD for any additional RCTs identified by the literature searches.

Obtaining Data

Data extraction strategy (for published aggregate data)

A data extraction form will be developed, piloted and adjusted as necessary. Data extracted will include details of study design, setting, and sponsor as well as outcome, trial and patient characteristics.

Data will be extracted into EPPI-Reviewer/Excel. Data extraction will be undertaken independently by two researchers with discrepancies resolved by consensus or recourse to a third researcher if necessary.

Provision of individual patient data

Investigators of trials for which IPD is not supplied by Medtronic will be contacted and asked to participate in the review by providing individual participant data for inclusion and re-analysis. If they
agree to participate, fully anonymised data on all randomised patients relating to the outcomes and trial and patient characteristics described above will be requested.

Data will be accepted in any suitable electronic format, but an example format detailing the recommended coding will be created and offered to all collaborators. Simple checks on the data will be made to ensure data are correctly coded, that missing data are correctly identified and to ensure that the data are consistent with published results. Data from all trials (including Medtronic-sponsored trials) will be incorporated into a single, database with fields that are consistent (as far as possible) across both Medtronic and non-Medtronic trials.

Data storage and confidentiality

All IPD and adverse event data from Medtronic will be transferred to CRD via password-protected memory stick. Data from other investigators will be in a de-identified format and received via secure FTP transfer or encrypted email. All data will be held in a password protected area of the CRD server. Access will be limited to staff working directly on the project. Copying data to laptop computers or memory sticks will be prohibited.

Outcomes

We will consider a range of outcomes and place emphasis on clinical or functional over radiological outcomes, particularly those that are directly meaningful to patients.

Effectiveness outcomes

The outcomes of interest will be:

- disease-specific questionnaires (e.g. Oswestry Disability Index, Neck Disability Index)
- patient QL / functional status questionnaires (e.g. SF-36)
- post-operative pain – surgical site and bone graft donor site
- duration of hospital stay
- operating time
- successful return to work/usual activity
• fusion status
• time to discharge*

Analysis of outcomes marked * are likely to be possible only in the IPD review.

**Adverse event outcomes**

**General**
• heterotopic bone formation
• osteolysis
• infection
• neurological events (new / worse leg pain, sensory disturbance, reflex changes, bladder disturbance)
• cancer
• hardware failure (e.g. cage subsidence, implant breakages)

**Surgery-specific**
• ALIF – major vascular injury, retrograde ejaculation, urinary retention
• ACDF - dysphagia, airway obstruction, neck pain, recurrent laryngeal nerve palsy
• PLIF/TLIF/PLF – leg pain/radiculitis, leg weakness, inflammatory cyst formation

Data on serious adverse events (AEs) will be extracted from relevant observational sources as well as from RCTs (where reported)

**Other data**

In order to investigate how the efficacy and safety of rhBMP-2 might be influenced by trial and patient-level characteristics we will also extract/obtain data on the following, if available:
• spinal location of surgery (eg. cervical or lumbosacral)
• type of surgery (eg. ALIF, PLIF etc.)
• rhBMP-2 dose/volume
• cage type
• nature of spinal condition (e.g., degenerative disc disease, spondylolisthesis)
• comparator treatment
• previous surgical interventions *
• age *
• gender *
• smoking status *

Data marked * may only be available from IPD

Risk of bias (quality) assessment

Critical appraisal of RCTs will be based on trial publications, protocols, and where available on IPD. Risk of bias in RCTs will be assessed using the Cochrane Risk of Bias tool.3 Other study designs will be assessed based on CRD guidance.4 Assessment will be undertaken independently by two researchers with any discrepancies resolved by consensus or recourse to a third researcher if necessary.

All IPD will be subject to detailed checking including examination of patterns of missing data, integrity of randomisation via pattern of randomisation and balance across baseline characteristics, and internal consistency.

Methods of analysis/synthesis

A narrative and tabular summary of key study characteristics will be undertaken. Published main results and quality assessment of individual RCTs will also be tabulated.

Aggregate data from RCTs

Where appropriate (based on clinical similarity of trials and the necessary data being available) aggregate study results (from publications/FDA reports) will be combined in a series of random-effects meta-analyses. Separate analyses will be conducted for each outcome listed above.

It is anticipated that the measures used to assess continuous outcomes will vary between studies, and in these cases standardized mean differences will be calculated where appropriate, and combined in random-effects meta-analyses.
Heterogeneity and inconsistency across trials will be assessed using $\chi^2$ tests and quantified using the $I^2$ statistic.\textsuperscript{5}

**Exploring clinical heterogeneity (subgroup analyses and meta-regression)**

We will investigate how trial-level and (where feasible) patient-level covariates influence the effectiveness of rhBMP-2 therapy. Trials will be grouped by type of surgery as follows: ALIF; PLIF; TLIF; PLF; ACDF. Meta-analyses will be conducted within each surgery subgroup and the results across subgroups compared using tests of heterogeneity to identify differences between surgery types. Similar subgroup analyses and tests for differences across them will be undertaken to identify differences in effectiveness of treatment at differing spinal locations. If feasible, meta-regression will be used to investigate dose-response relationships.

**Individual patient data**

**Two stage modelling**

IPD will be analysed using standard two stage meta-analytic techniques. IPD from each trial will be analysed separately, using the same methods across trials, for each outcome listed above.\textsuperscript{6,7} The resultant summary statistics for each trial will then be combined using random-effects models to give overall estimates of the effect for each outcome explored. For time to event outcomes, we will apply Cox proportional hazards models to each trial, providing the proportional hazards assumption is not clearly violated.\textsuperscript{8}

**Exploring clinical heterogeneity (subgroup analyses)**

Characteristics that vary at the trial level (e.g. comparator type) will be investigated by analysing grouped trials or by meta-regression as described above for aggregate data.

Patient-level characteristics, including underlying condition (degenerative disc disease, spondylolisthesis) age, smoking history, and previous surgery at the same site will be explored (data permitting) in univariate two-stage subgroup analyses.\textsuperscript{9,10}

Characteristics such as type of surgery that may vary between trials (i.e. trials include only one type of surgery) will be analysed using whichever of the above approaches best suits the data.
**One stage modelling**

Time and data permitting, we will also analyse the IPD in a one-stage modelling framework.\(^{11}\) This will enable us to take account of multiple patient characteristics when comparing rhBMP-2 and SBGT (stratified by trial) and also enable simultaneous exploration of multiple potential interactions between treatment and patient or trial-level covariates. For these analyses, we will implement multilevel modelling approaches for binary,\(^ {12}\) continuous,\(^ {13}\) ordinal,\(^ {14}\) and time-to-event\(^ {15}\) outcomes. All IPD analyses will use complete case analysis as imputation of missing data is not feasible within the timescale of this project.

**Combining aggregate and individual participant data**

Where IPD is not available for relevant RCTs we will seek to combine aggregate data and IPD in meta-analyses using two-stage methods as described above and, time-permitting, using more advanced methods which have been described elsewhere.\(^ {16}\) Results from these analyses will be compared to analyses of aggregate data only and of IPD only as a sensitivity analysis.

**Adverse events**

Adverse events will be categorised as described above and results tabulated. Where possible, rates of adverse events in rhBMP-2 surgery and in SBGT will be compared statistically. Where possible, meta-analyses of adverse events will be conducted to compare the incidence and nature of events across trials. Such analyses may be limited given the possible rarity and limited reporting of adverse events in RCTs. The underlying principles of meta-analysis will be applied even where statistical combination is not feasible: specifically, this will include evaluation of consistency of findings, direction and magnitude of effect, and strength of evidence, in addition to considerations of the quality of the evidence.

**Methodological exploration**

**Investigations of bias**

We will investigate possible sources of bias in RCTs and studies of adverse events. In particular we will explore the role of funding source (industry/non industry), publication status (published/unpublished) study design (randomised/non randomised; controlled/uncontrolled; different observational designs) and
components of risk of bias assessments using subgroup meta-analyses and/or meta-regression to compare results from studies that differ by the factor in question.

**Comparing aggregate and IPD approaches**

IPD analyses will be compared with aggregate data analyses. Where results differ we will establish which differences are attributable to data availability (unpublished trials, unreported outcomes, excluded patients) and which are attributable to the methods of analyses.

The summary statistics generated for each trial from the IPD will also be compared with the corresponding published results.

**Data disclosure timeline**

Construction of a timeline of what was reported where and when will provide background information on publication practice and the way that information about efficacy and adverse effects enter the public domain.

**Outputs and dissemination**

A comprehensive report detailing all the analyses described above will be submitted to the coordinating centre by the agreed deadline. This report will meet the requirements of the PRISMA statement for the reporting of systematic reviews and meta-analyses for the appropriate sections of the review.17

We will also disseminate the findings through high-impact journal publications, conference presentations and other relevant channels. We intend that the first publication will coincide with the release of the full report by Yale.

**References**


