Economic evaluation within a factorial-design randomised controlled trial of exercise, manual therapy, or both interventions for osteoarthritis of the hip or knee: study protocol

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ABSTRACT

Introduction: Clinical guidelines for the treatment of hip and knee osteoarthritis recommend non-pharmacological and non-surgical treatments. Exercise treatments are recommended as primary strategies, but specific exercise programme components have not been specified. Early evidence indicates that manual physiotherapy is effective for hip and knee osteoarthritis. The Management of Osteoarthritis (MOA) Trial was designed to evaluate the effectiveness and cost-effectiveness of physiotherapist-led, individualised exercise, manual physiotherapy and a combination of these two interventions in the treatment of adults with hip or knee osteoarthritis. This paper describes the methods that will be used to conduct the economic evaluation of these interventions within the MOA Trial.

Methods and analysis: This comprehensive economic evaluation will assess the incremental cost-effectiveness of physiotherapy plus usual care versus usual care alone from a societal perspective. The authors will conduct a cost-consequences analysis using end-points such as Outcomes Measures in Rheumatology Clinical Trials—Osteoarthritis Research Society International responder criteria and quality-adjusted life years. The evaluation will have a time horizon of 1 year (and so discounting will not be necessary). All costs will be reported in 2009 New Zealand dollars. The authors will address uncertainty via bootstrapping to calculate CIs for the mean incremental cost-effectiveness ratios and by performing sensitivity analyses.

Ethics and dissemination: Ethical approval was granted by the Lower South Regional Ethics Committee of the New Zealand Ministry of Health (ethics reference: LRS/07/11/044). All participants of the MOA Trial provided written informed consent for the capture of their healthcare costs. We will submit the results of the study for publication irrespective of outcome.

Clinical trials registration number: ACTRN1260800130369.

ARTICLE SUMMARY

Article focus

- As osteoarthritis of the hip or knee is one of the most common causes of disability worldwide, the economic burden to health systems and society is high.
- There is a need to establish the economic efficiency of conservative interventions recommended as primary treatments for patients with hip or knee osteoarthritis.
- This protocol paper outlines the methods for investigating and reporting the cost-effectiveness of supervised exercise physiotherapy, manual physiotherapy and a combination of these two interventions, for treating hip or knee osteoarthritis.

Key messages

- This is the protocol for the economic evaluation of two interventions within a randomised controlled trial.
- Economic evaluations within randomised controlled trials provide decision-makers with information about an intervention’s efficiency.
- The results of this trial and the associated economic evaluation will allow stake-holders to make more informed decisions about the optimal allocation of resources for treating hip or knee osteoarthritis.

Strengths and limitations of this study

Strengths

- This protocol paper will ensure the methods used in the economic evaluation are transparent. The economic evaluation is within a pragmatic trial design, thereby enhancing external validity and allowing the intervention’s value for money to be assessed in a real-world scenario.

Limitations

- We applied a definition of disease-related healthcare use in an effort to reduce variability in the cost estimate, and this precluded the estimation of total healthcare costs.
INTRODUCTION

From a public-health viewpoint, hip and knee osteoarthritis (OA) are considered to be the most important musculoskeletal disorders based on their prevalence and associated disability.\(^1\) In New Zealand, 14.8% of adults are diagnosed as having arthritis,\(^3\) and OA is the sixth largest burden of disability.\(^4\) Primary total hip and total knee arthroplasties increased in New Zealand by 14% and 27% respectively between 2004 and 2008.\(^5\) Public hospital inpatient costs related to hip and knee OA were estimated to be $NZ53.8 million in 2005. Direct health-sector costs for 2005 were 0.39% of GDP, and indirect costs were estimated to be up to three times this amount.\(^6\) As New Zealand’s population ages, these estimates are expected to rise.\(^7\)

With the aim of addressing the rising burden of hip and knee OA, treatment strategies and guidelines have been developed.\(^8\) Although joint-replacement surgeries are considered to be good value for money,\(^12\) they are usually only recommended after more conservative treatments have been exhausted.\(^8\) Also, owing to the risk of complications, alternatives to pharmacological treatment are sometimes preferred.\(^14\) Non-pharmacological, non-surgical treatments such as aerobic and strengthening exercises are included in current guidelines as primary treatments; however, the best means of delivering these exercises has not been specified.\(^8\) Promising, but limited, evidence has emerged for the effectiveness of other non-pharmacological, non-surgical treatments such as manual physiotherapy. For patients with hip OA, manual physiotherapy has been shown to be superior to a comprehensive exercise programme.\(^15\) For patients with knee OA, the combination of manual therapy and exercise achieved superior results when compared with a placebo control\(^16\) and a home exercise programme.\(^17\)

The Management of OsteoArthritis (MOA) Trial was designed as a 2×2 factorial randomised controlled trial investigating the effectiveness and cost-effectiveness of both a multimodal, individualised, supervised exercise programme and an individualised manual therapy programme, compared with usual healthcare alone for the management of pain and disability in adults with hip or knee OA.\(^18\) The purpose of this paper is to describe the methods for the economic evaluation conducted in conjunction with the MOA Trial. A detailed description of the MOA Trial and methods for the clinical evaluations are reported elsewhere.\(^18\)

METHODS AND ANALYSIS

Study question

From the viewpoint of (a) society and (b) the New Zealand health system, is a programme of exercise therapy or manual physiotherapy, or a combination of the two, in addition to usual care, cost-effective compared with usual care alone in the treatment of hip or knee OA?\(^2\)

Participants

All MOA Trial participants will be included in this analysis. All participants had OA of the hip or knee as defined by the American College of Rheumatology criteria.\(^19\) They gave signed, informed consent before baseline assessments were undertaken.

Description of interventions

The treatments in the MOA Trial are delivered in addition to usual care. A physiotherapist delivers the interventions as individualised treatments during nine 1 h clinic visits. The treatments include exercise therapy, manual physiotherapy and a combination of these two interventions.\(^18\)

Exercise therapy (Ex) consists of a multimodal programme of warm-up/aerobic, muscle strengthening, muscle stretching and neuromuscular control exercises.\(^18\) A limited list of additional exercises is available to treating physiotherapists for exercises to be individualised to patients based on the findings of physical examinations.\(^18\)

Manual therapy (MT) is defined as the delivery of manually applied forces through procedures intended to modify the quality and range of motion of the target joint and surrounding soft tissues.\(^18\) The primary manual therapy procedures are prescribed from the intervention protocol, and a limited list of secondary procedures is available to treating physiotherapists based on the physical examination findings.

Combination therapy (Ex+MT) consists of a combination of the exercise and manual physiotherapy treatments described above.

The comparator, ‘usual care,’ is defined as the status quo mixture of interventions for treating hip or knee OA found in community practice in the metropolitan region surrounding Dunedin, New Zealand.\(^21\) The benefit of usual care as a comparator is that it has the potential to represent the current real-world situation for decision-makers.\(^21\) The 6-month and 12-month follow-up questionnaires were designed to capture the use of various interventions available to participants in community practice.

Type of economic evaluation

This study is a comprehensive economic evaluation conducted alongside a randomised controlled trial. It is a cost-effectiveness analysis that will follow multiple endpoints (described below), also referred to as a cost-consequences analysis.\(^22\) The main outcomes will be healthcare costs related to OA and a general measure of health-related quality of life (HRQoL) for each intervention compared with usual care, expressed as incremental cost-effectiveness ratios. Clinically relevant criteria, such as the Outcomes Measures in Rheumatology Clinical Trials—Osteoarthritis Research Society International (OMERACT-OARSI) responder criteria, have been suggested for use in economic evaluations of treatments for OA.\(^23\)
Health-related quality of life and quality-adjusted life years

The Medical Outcomes Study-Short Form 12 (SF-12v2) will be used to assess patient health. This general health status measure was converted to a six-dimensional health state classification (SF-6D) by Brazier and Roberts using utility weights from the UK population. The SF-6D allows for the estimation of a single preference-based index, the quality-adjusted life year (QALY), which is recommended as a generic measure of benefit across all cost-effectiveness analyses. A QALY is a year of life experienced with a particular HRQoL as represented on a scale from 0 to 1, where 0 = death and 1 = full health. No negative values indicating health states considered worse than death are possible using the SF-6D. The mean QALYs for each group will be estimated, controlling for baseline utility as recommended by Manca et al.

Responder criteria

The OMERACT-OARSI set of responder criteria considers both absolute and relative changes in pain or function. An individual is considered a responder to a treatment if one of two criteria is met: (1) improvement (≥50% and an absolute change is ≥20%) in pain or function or (2) improvement (≥20% and absolute change ≥10%) in two of the following three areas: pain, function and patient’s global assessment. The MOA Trial captured the pain domain using the numerical pain-rating scale, the function domain using the Western Ontario and McMaster osteoarthritis index, and the patient’s global assessment using the global rating of change.

Perspective

The perspective determines the point of view from which opportunity costs are defined and measured. The societal perspective will be used in this study, as it is the broadest possible and is recommended as the reference case. In addition, we will report direct medical costs and cost-effectiveness from the perspective of the New Zealand health system.

Time horizon

We will use a 1-year time horizon for this analysis. Drummond and colleagues reported that this is a suitable time horizon for symptom-modifying interventions in the treatment of OA. We will also report a 2-year time horizon as a secondary analysis, to investigate assumptions regarding the duration of effects.

Identification of resource use and price weights

The cost of delivering the physiotherapy intervention will be calculated by identifying the number of times each participant, randomised to one of the treatment groups, attended physiotherapy treatment. We will then calculate the cost of this service by applying the unit cost of a single treatment visit ($NZ 64.00) to the number of visits attended. The cost of the home exercise booklets will also be included in the cost of the treatment groups. Because questioning the patient directly about transportation costs for clinic visits would have unblinded the assessor to group allocation (physiotherapy vs usual care), transportation costs will be calculated by multiplying the return distance from the participant’s place of residence using Google Maps, at the University of Otago’s reimbursement rate of $NZ 0.83 per kilometre.

The Osteoarthritis Cost-and-Consequences Questionnaire was designed to capture healthcare use, co-payments and out-of-pocket expenses related to hip or knee OA over the preceding 3-month period. The questionnaire was developed on the basis of existing tools and recommendations with input from experts in public health, health economics, pharmacy and physiotherapy. Healthcare services with the potential to contribute substantially to the cost of OA, such as joint-replacement surgery, were presented in detail to improve recall. The MOA Trial protocol includes administering this questionnaire at baseline and at 6, 12 and 24 months.

Price weights (unit costs) will be applied to the quantity of health services reported. Price weights for public hospital-based inpatient services will be based on New Zealand’s case-mix framework for publically funded hospitals for the fiscal year 2008/2009: the Weighted Inlier Equivalent Separations (WIES), with Amendments for New Zealand from Version 11C to Version WIESNZ, 2008 (WIESNZ08). We will multiply medical and surgical purchase units of $NZ983.33 by inpatient service case-weights to obtain the cost of inpatient services. Emergency visits and specialist visits will be valued according to the hospital’s volume schedule from its funder. Price weights for medical imaging will be calculated as a combination of the relative value unit of the procedure and the reimbursement amount from the imaging contract between the hospital and ACC (Accident Compensation Corporation, New Zealand’s no-fault insurance scheme for work and non-work injury events). Private hospital-based services such as joint-replacement surgery, specialist visits and radiology will be valued at the amount the hospital charges for these services.

Price weights from the New Zealand Pharmaceutical Schedule will be applied to the quantity of medications reported in the questionnaire. This will be done by extrapolating the daily quantities reported for each medication out to 3 months and then multiplying the 3-month quantities by the relevant subsidy as reported in the New Zealand Pharmaceutical Schedule. Over-the-counter medications will be valued at the average market price for each medication from an average of at least three vendors (ie, supermarkets, pharmacies, health food stores) in the area.

Transportation costs will be captured by participant-reported taxi or bus charges incurred. Or, if a private car is used, a cost per kilometre of $NZ0.83 will be applied to the reported/calculated distance travelled. We will ask participants to report their mileage; however, if they are unable to do so, we will ask where they travelled from and the distance will be calculated via Google Maps.
The Osteoarthritis Cost-and-Consequences Questionnaire asks participants to report lifestyle adaptations, aids and adaptations, and the out-of-pocket costs associated with any of these changes. For the societal perspective, we will capture work loss as a result of OA. When quantifying productivity losses, we will use the friction-cost method, which only counts productivity loss for the time it takes to replace a worker.\textsuperscript{36} We will apply a 6-month friction period to a participant’s loss of productivity during the MOA Trial.\textsuperscript{57} In the questionnaire, participants also report their absences from work during the past month due to OA and the total work time lost as a result of OA-related interventions such as total joint replacement. We will apply individual participant wage rates to lost time.

Because follow-up will be limited to 1 year, discounting (to recognise the differential timing of costs and benefits) will not be necessary for this economic evaluation. The quantity of resources used for each cost domain will be reported separately from the cost. All costs in this study will be expressed in 2009 New Zealand dollars ($NZ) exclusive of government goods and services tax; in 2009 $NZ1 = £0.43.

**Study boundaries**

This study will include the impact on family members and friends of helping participants cope with their OA. Family members’ and friends’ travel costs and lost productivity from accompanying participants for OA-related healthcare visits, and any other costs incurred helping participants (provided the assistance is OA-related), will be derived from asking participants to estimate these amounts. Only OA-related costs will be used for the analysis of the MOA Trial due to the comorbidities that are abundant in the OA population,\textsuperscript{38} and the variance that is likely to be produced within the cost estimate as a result of including comorbidities. Participants will be encouraged to define a GP or hospital visit as OA-related if it is a follow-up for their hip or knee complaints, if a significant part of the visit is devoted to their hip or knee complaints, or if the doctor renews OA-related prescriptions. In addition, visits that are a result of complications from OA-related management will also be captured; for example, visits to a gastroenterologist because of gastrointestinal complaints while on non-steroidal anti-inflammatory medications will be counted as ‘OA-related.’

**Willingness-to-pay thresholds**

Countries such as New Zealand have been observed to use funding-decision thresholds that are close to twice the GDP per capita.\textsuperscript{39} However, agreed-upon maximum willingness-to-pay thresholds can vary from one to three times GDP per capita.\textsuperscript{21, 40} Hence, one, two and three times GDP per capita will be used as policy-relevant willingness-to-pay thresholds in our analyses.

**Statistical analysis**

The comparison of costs between the physiotherapy groups and usual care will be carried out using both univariate and multivariable analysis. The univariate analysis of cost data will be conducted using one-way analysis of variance. If our cost data violate the assumptions of parametric statistics, non-parametric methods of analysing group means will be used.\textsuperscript{41} Non-parametric bootstrapping will be used for comparing means and calculating CIs of cost data that violate parametric assumptions.\textsuperscript{25, 42} Multivariable analysis of cost data will be performed in an attempt to improve the power for tests of difference between groups by explaining variation owing to other causes.\textsuperscript{25, 43} The multivariable analysis will include baseline costs and effects as covariates in the model and these prespecified potential confounding factors: age, body mass index, baseline pain intensity, duration since first diagnosis, quadriceps muscle strength, mental health and self-efficacy.\textsuperscript{18} A variety of statistical models can be used for the multivariable analysis of cost data; each has its strengths and weaknesses depending on the distribution of costs in the study.\textsuperscript{43} If no single model appears most appropriate, the results from a number of different models will be reported.\textsuperscript{45}

Missing data will be addressed by a multiple imputation approach to reflect the uncertainty present when replacing missing data. We will consider censored data if more than 10% of data are lost to follow-up owing to any cause other than a participant’s death. We will calculate the percentage of censored data based on the number of censored assessments relative to the total number of potential assessments. If censored data need to be addressed, the censoring mechanism will be defined (missing completely at random, missing at random or missing not at random) and the appropriate statistical method used.\textsuperscript{25, 43}

Summary measures will be presented along with sampling uncertainty to describe the best estimate of the costs and effects of the treatment groups in relation to the comparator. We will calculate the incremental cost-effectiveness ratios by dividing the incremental cost by the incremental health benefit (ie, \(\frac{\text{Costs}_{\text{PT}} - \text{Costs}_{\text{UC}}}{\text{Effects}_{\text{PT}} - \text{Effects}_{\text{UC}}}\)) for the combined physiotherapy (PT) groups and usual care (UC), and for each physiotherapy treatment group, Ex, MT and MT+Ex versus UC. The incremental differences between these groups will be reported. CIs will be calculated for the incremental cost-effectiveness ratios, and cost-effectiveness acceptability curves will be calculated to determine the likelihood that physiotherapy will be considered cost-effective using one, two and three times GDP per capita as policy-relevant willingness-to-pay thresholds.

**Sensitivity analysis**

Although uncertainty will be addressed through the use of robust imputation procedures, calculation of CIs and calculation of cost-effectiveness acceptability curves, assumptions also need to be considered in sensitivity analyses. Price weights used in our analyses will combine weights that are generalisable to the New Zealand population and others that are peculiar to the Dunedin...
metropolitan area. Medical products, appliances and equipment costs that are peculiar to the Dunedin metropolitan area will be decreased by 2.5% to 28% to reflect the difference in cost for these services in different regions in New Zealand based on 2007 and 2010 health-expenditure data from Statistics New Zealand.44 The cost of outpatient services, including our physiotherapy interventions, will be increased by 33.6% and decreased by 12.3% to reflect the difference in outpatient costs between different regions in New Zealand.44

Uncertainty can also arise from the choice of model for the multivariable analysis of costs.33 We will develop several multivariable models to assess this effect on the cost estimate. If model choice leads to a significant variation in results, multiple models for the analysis of costs will be presented.

Summary of findings
Findings will be summarised as pattern 1, 2 or 3 findings as presented by Glick et al.43 Pattern 1 and 2 findings will result in a range of values for which a statement of cost-effectiveness can be made about the intervention with 95% certainty. Pattern 3 findings will necessitate a downgrade of the level of confidence with which our results can be considered (eg, from 95% confidence to 80% confidence). In the event of a pattern 3 finding, we will calculate the largest definable CI that will indicate the highest level of confidence we can have about the difference in economic value between the physiotherapy and usual care groups.43

Ethics and dissemination
This paper describes the methods for evaluating the cost-effectiveness of physiotherapy treatments within the MOA Trial. The HRC and Lottery Grants Board peer-reviewed the grant application, and the Lower South Regional Ethics Committee of the New Zealand Ministry of Health approved the MOA Trial (ethics reference: LRS/07/11/044).

Data and safety monitoring was initially referred to the Data and Safety Monitoring Board of the Health Research Council of New Zealand. The Board considered the risks low or the recruitment period short, and referred responsibility back to the MOA Trial Team. We set up a panel comprising the co-investigators, selected international advisors, and an independent member to which the principal investigator reports regularly.

We will submit the results of the trial for publication irrespective of outcome.

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Acknowledgements
We acknowledge the support of the School of Physiotherapy, University of Otago and the MOA Trial team members.18

Funding
The MOA Trial was supported (in part) by contracts from the Health Research Council of New Zealand (HRC ref. 07/199 and 07/200) and a grant-in-aid from the New Zealand Lottery Grants Board (MR212664).

Competing interests
None.

Patient consent
Obtained.

Ethics approval
Ethical approval was granted by the Lower South Regional Ethics Committee of the New Zealand Ministry of Health (ethics reference: LRS/07/11/044).

Contributors
JHA conceived the study. DP led the design and coordination of the economic evaluation and wrote the manuscript. All authors participated in the study design, commented on drafts of this paper, and read and approved the final manuscript.

Provenance and peer review
Not commissioned; peer reviewed for ethical and funding approval prior to submission.

Data sharing statement
We welcome data sharing; policies and procedures are in place governing the access and use of these data; these will be administered by Dr Abbott, the principal investigator of the MOA Trial. The technical appendix, statistical code and dataset are available to researchers from haxby.abbott@otago.ac.nz. Informed consent for data sharing was not obtained from participants a priori, but the presented data are anonymised; risk of identification is low, and the potential benefits of sharing these data outweigh the potential harms.

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