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Incremental clinical effectiveness and cost effectiveness of providing supervised physiotherapy in addition to usual medical care in patients with osteoarthritis of the hip or knee: 2-year results of the MOA randomised controlled trial

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SUMMARY

Objective: To investigate the clinical- and cost-effectiveness at 2-year follow-up of providing individual, supervised exercise physiotherapy and/or manual physiotherapy in addition to usual medical care.
Method: People with hip or knee osteoarthritis meeting the American College of Rheumatology clinical diagnostic criteria were randomised (1:1, concealed, assessor-blinded) to four groups: usual medical care; supervised exercise physiotherapy; manual physiotherapy; or combined exercise and manual physiotherapy. Physiotherapy group participants were provided 10 50-min treatment sessions including booster sessions at 4 and 13 months, in addition to usual care. The primary outcome at 2-year follow-up was incremental cost-utility ratio (ICUR) of each physiotherapy intervention in addition to usual care, compared with usual care alone, from the health system and societal perspectives. To allow interpretation of negative ICURs, we report incremental net benefit (INB). The primary clinical outcome was the Western Ontario and McMaster Osteoarthritis Index (WOMAC).
Results: Of 206 patients, 186 (90·3%) were retained at 2-year follow-up. Exercise physiotherapy and manual physiotherapy dominated usual care, demonstrating cost savings; combined therapy did not. Exercise therapy had the highest incremental net benefits (INBs), statistically significant at all willingness-to-pay (base-case: societal New Zealand (NZ)$6,312, 95%CI 334 to 12,279; health system NZ$8,065, 95%CI 136 to 15,994). Clinical improvements were superior to usual care only in the exercise physiotherapy group (−28.2 WOMAC points, 95%CI -49.2 to −7.1). No serious adverse events were recorded.
Conclusion: Individually supervised exercise therapy is cost-effective and clinically effective in addition to usual medical care at 2-year follow-up, and leads to cost savings for the health system and society.
Trial registration: Prospectively registered with the Australian NZ Clinical Trials Registry, reference ACTRN12608000130369.

Introduction

Hip and knee osteoarthritis (OA) are typically characterized by a long period of progressively increasing morbidity between the first development of clinical symptoms and, in many cases, the eventual need for joint replacement surgery[1–3]. During this time, clinical guidelines generally recommend the use of conservative non-

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surgical, non-pharmacological treatment options, primarily exercise therapy, as first-line treatments[4], however such therapies are under-utilized.[5]

The aims of the Management of Osteoarthritis (MOA) trial were to investigate the incremental clinical- and cost-effectiveness of an exercise therapy programme and/or a manual therapy programme informed by the best available evidence, delivered in addition to usual medical care, compared to usual medical care only for the management of hip and knee OA[6]. We hypothesised that such interventions may provide incremental benefits over usual medical care alone in terms of clinical outcomes and value for money. The pre-planned primary outcome at the 2-year endpoint of this trial was cost-effectiveness of the physiotherapy programmes compared with usual care[6]. This study reports on the cost-effectiveness and clinical outcomes of the MOA trial interventions using 2-year follow-up data to investigate the long-term economic and health gains attributable to providing individual, supervised physiotherapy in addition to usual medical care.

Methods

Study design and participants

The MOA trial was a factorial randomised controlled trial of exercise therapy and manual therapy, in addition to usual medical care, for patients with knee or hip OA. Pre-specified protocols for both the trial and the economic evaluation have been published[6,7]. The primary outcome at 2-year follow-up (specific aim 3[6]) was a parallel group economic evaluation of each intervention compared with usual care only.

Details of participant recruitment, eligibility and exclusion criteria, and participant flow have been reported previously[6,8]. Briefly, patients with suspected hip or knee OA were recruited via two sources: a) patients attending general medical practitioners (GPs) in Dunedin, New Zealand (NZ); and b) patients referred by their GP to attend a first specialist consultation by an orthopaedic surgeon at the Department of Orthopaedic Surgery outpatient clinic (Dunedin Hospital, New Zealand) for assessment of hip or knee OA, but not meeting the priority threshold for offer of joint replacement surgery.

Consenting participants were required to meet the American College of Rheumatology clinical criteria for hip or knee OA[9], have no previous history of rheumatoid arthritis or previous hip or knee joint replacement surgery at the time of study enrolment, no recent (within 30 days) initiation of opioid or corticosteroid intervention, and able to complete the proposed course of intervention and follow-up.

Randomisation and masking

To ensure allocation concealment, a research manager (non-clinician) randomly assigned participants, using the TENALEA online computer-generated randomisation service[10], after baseline assessment and enrolment by the outcome assessors. Randomisation was stratified by joint affected (hip or knee), in equal ratio and randomly varying block sizes[6], to one of four intervention groups: usual care only; physiotherapist-delivered exercise therapy in addition to usual care; physiotherapist-delivered manual therapy in addition to usual care; and a combination of both the exercise therapy and manual therapy in addition to usual care. Assessments were conducted by one of 3 study assessors blinded to group allocation. Physiotherapy interventions were provided by physiotherapists not involved in outcome assessment. GPs and orthopaedic surgeons were blinded to patients' group allocation.[6,8]

Procedures

In each of the three treatment groups, participants attended seven physiotherapy sessions of approximately 50 min each over a 9-week programme, as well as two additional 'booster' sessions at week 16, and a final booster session at week 54. The treatment protocols have been reported earlier (Web Appendix 1).[8,11]

The usual care control group received no trial physiotherapy. We measured, by participant self-report questionnaire, all medical and other healthcare services consumed by all participants during the trial, including any reported access to non-trial physiotherapy. Each participant's GP, blinded to group allocation, was requested to avoid referral to physiotherapy within the 9-week intervention phase, to avoid contamination, but we did not require physiotherapy be withheld throughout the follow-up period of the trial. All participants recruited from secondary care continued to receive their usual care by consultant orthopaedic surgeons blind to group allocation. Participation in the trial had no bearing on patients' prioritisation for, or access to, joint replacement surgery. All participants continued to receive the usual routine care offered by their own GP and other healthcare providers throughout the trial and follow-up. In this way, the trial evaluates the effectiveness of physiotherapy care in addition to usual care, and provides a real-world, policy-relevant comparator on which to base value-for-money decisions regarding health services provision.

Outcomes

Assessors administered patient-reported outcome questionnaires and performed clinical assessments at baseline, 9 weeks, 6 months, 1 year, and 2 years. Economic variables were self-reported by patients at baseline and at 6 months, 1- and 2- years.

The primary outcome at the 2-year endpoint of this trial was incremental cost-effectiveness of the physiotherapy programmes[6]. The primary effectiveness outcome for the economic evaluation was the quality-adjusted life years (QALYs) experienced over the 2-year follow-up period, assessed using the SF-6D, a six-dimension health-related quality of life (HRQoL) instrument derived from the 12-item Medical Outcomes Study-Short Form 12 (SF-12v2). Utility weights derived from the UK general population were applied to SF-6D profiles to estimate QALYs[12]. We calculated QALYs by using time-weighted averages at the beginning and end of each of the 6-month, 1-year, and 2-year measurement periods. QALYs and costs from the second year of follow-up were discounted by an annual rate of 3.5 percent.[13]

Total OA-related costs were estimated from both the health system and societal perspectives. Healthcare costs, other related expenditures, and lost productivity resulting from OA to participants and their friends and family members was collected using the Otago Costs and Consequences Questionnaire (OCC-Q) instrument validated for use in the OA population[14]. Total joint replacements were verified against the NZ National Joint Register. Resource use within the healthcare sector was valued using 2009 unit costs derived from various sources (see Web Appendix 2). All costs are expressed in 2009 NZ dollars, exclusive of Goods and Services Tax.

Productivity losses associated with inability to work due to OA were valued using the friction cost method, applying a 6-month friction period, and are reported separately. Individual participant wage rates were applied to time lost.

The primary clinical outcome was change in the composite Western Ontario and McMaster osteoarthritis index (WOMAC) between baseline and 2-year follow-up. Secondary outcome measures included measures of pain, physical function, and global rating of change. Participants were classified as responders or non-responders according to the Outcome Measures in Rheumatoid

Arthritis Clinical Trials – Osteoarthritis Research Society International (OMERACT-OARSI) responder criteria at 2 years: ≥50% improvement in pain or function and an absolute improvement of ≥20; or ≥20% improvement and an absolute improvement of ≥10 in at least two out of three of pain, function, and global assessment[15], using the WOMAC pain and function subscales and the global rating of change instrument. Adverse events were recorded and classified.

Statistical analysis

All data analyses were done in Stata (Station, TX, USA) version 14.2 by a health economist (RW) not involved in the trial design or conduct. As pre-specified in the trial protocol, all analyses were conducted according to intention-to-treat, and results are reported separately for the full sample of participants and for those participants who did not receive the potentially confounding, non-study intervention of hip or knee replacement during the trial and follow-up period.[6]

Both item-level data missingness and censoring due to loss to follow-up were addressed via multiple imputation using the MI package in Statav14.2. Data were treated as missing at random (MAR). Patterns of missing data and the distribution of responses were examined to determine appropriate imputation equations for each variable. Data from three participants who died during the follow-up period were treated as complete cases with known costs and effects in the economic analysis, and excluded from the analysis of clinical outcomes at 2-year follow-up. Thirty-six imputed data sets were created, and variable distributions examined against observed data.

We calculated incremental cost-utility ratios (ICURs) and incremental net benefits (INBs) at the willingness to pay thresholds of one, two, and three times GDP per capita (NZ$42,981, NZ$85,962, and NZ$128,943, respectively)[16]. incremental net benefit (INB) analysis, not included in the initial protocol[7], was added to solve difficulties with the interpretation of ambiguous negative ICURs, and as such is a best-practice recommendation[17]. INB represents the value of an intervention in monetary terms given a willingness-to-pay threshold for the unit of benefit (i.e., QALY), and is calculated as [incremental benefit x threshold] minus incremental cost. Confidence intervals (CIs) around INB estimates were calculated around sample mean incremental costs and QALYs[18]. Confidence ellipses were constructed on the cost-effectiveness plane to illustrate the impact of sample uncertainty on the cost-effectiveness of each intervention relative to usual care. All analyses were undertaken from both the societal and health system perspectives. Results were adjusted for age, sex, primary OA joint (hip or knee), body mass index, number of years since symptom onset, and baseline WOMAC score, quadriceps muscle strength, mental health, self-efficacy, and SF-6D score, as pre-specified in the analysis protocol[6]. Additional sensitivity analyses were conducted by (1) restricting the sample to complete cases only, to evaluate the impact of the imputation of censored data; and (2) excluding productivity losses from the analysis from the societal perspective.[7]

The primary clinical outcome analysis investigated firstly the main effects of the factorial design and interaction, and secondly the between-group treatment effect, compared with usual care, of each of the three interventions on change in the WOMAC composite score between baseline and 2-year follow-up[6]. Both adjusted and unadjusted analyses were undertaken; adjusted analyses were primary, performed using analysis of covariance controlling for the same set of covariates (except baseline SF-6D value) as the economic analysis. Secondary clinical outcomes are reported as means and 95% CIs of the change from baseline to 2-year follow-up, by intervention group. Analyses were adjusted for the same set of confounding variables as above, using linear (pain, physical function, and global change) and logistic (OMERACT-OARSI response) regression models.

Results

206 participants aged between 37 and 92 years (mean 66 years) were recruited (Fig. 1) between 23 March 2008 and 30 March 2009, and are described in Table I as previously[8]. 203 were surviving at 2-year follow-up. All 206 participants completed the OCC-Q and SF-12 questionnaires at baseline, 192 (93·2%) at 6-months, 192 (93·2%) at 1-year, and 186 (90·3%) at 2-years. 180 (87·4%) completed the questionnaires at all three follow-up points. Seventy-one participants (34·5%) received either a hip or knee joint replacement during the 2-year follow-up period.

From the perspective of the NZ health system, the programme of manual therapy in addition to usual care had a mean incremental cost over 2 years of $1,011 relative to usual care only, while the combined manual and exercise therapy had an incremental cost of $1,635 (Table II). The exercise therapy intervention was cost-saving relative to usual care (-$935 per patient). From the societal perspective, both manual therapy and exercise therapy were cost-saving (incremental costs of -$2,184 and -$3,530 respectively). Combined therapy had an incremental cost of $210 relative to usual care only. Excluding productivity costs from the societal perspective, only exercise therapy was cost-saving relative to usual care (-$1795; Table II).

Restricting the sample to complete cases only ($n = 183$), manual therapy and exercise therapy were cost-saving from the health system perspectives, while all interventions were cost-saving from the societal perspective. Among those without joint replacement surgery during the trial ($n = 135$), exercise therapy and combined therapy were cost-saving from both the health system and societal perspectives, while manual therapy was cost-saving from the societal perspective only.

All three physiotherapy interventions produced clinically significant gains in QALYs lived over the 2-year follow-up compared with usual care (Table II)[19]. Exercise therapy produced the largest gains (0·15 QALYs), while manual therapy and combined therapy both produced gains of 0·07 QALYs. Results were similar for both the complete cases sub-sample and the sample of participants without joint replacement surgery during the trial.

Cost-utility analyses revealed that all three interventions were cost-effective relative to usual care only at willingness to pay thresholds of one, two, and three times GDP per capita (Table III). After adjusting for covariates, both exercise therapy and manual therapy dominated usual care from both the societal and health system perspectives. Exercise therapy had the highest probability of cost-effectiveness in almost all scenarios (Fig. 2).

INBs were positive for all three physiotherapy interventions at all willingness to pay thresholds (Table III). Exercise therapy had the highest INBs, with 95% CIs strictly greater than zero at all willingness to pay thresholds. Manual therapy had INBs significantly greater than zero at the 2×GDP per capita (health sector perspective) and the 2×GDP per capita (societal perspective) thresholds, while INBs for combined therapy did not reach statistical significance.

In the subgroup without joint replacement during the trial, all three MOA trial interventions were highly cost-effective relative to usual care from both the societal and health system perspectives; exercise therapy again dominated usual care from both the societal and health system perspectives, while manual therapy dominated usual care from the societal perspective only. Exercise therapy was again the intervention with the highest INBs, which were significantly greater than zero, at the 95% confidence level, at all

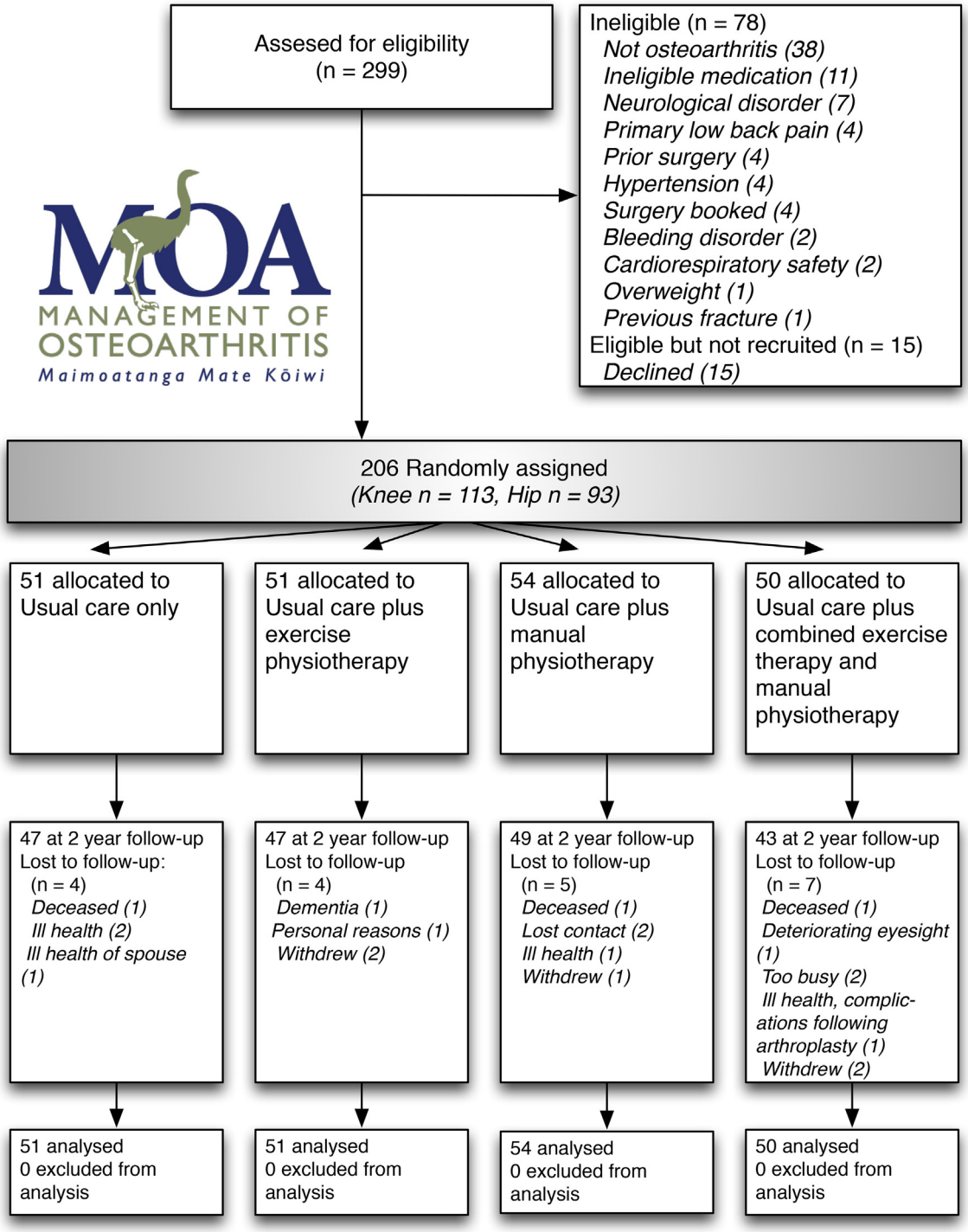

Fig. 1. Profile of the Management of Osteoarthritis (MOA) trial.

willingness to pay thresholds. Manual therapy and combined therapy had similar INBs in this sub-sample; however these were significantly greater than zero from the societal perspective only, at the 1×(combined therapy) and 2×(manual therapy) GDP per capita thresholds and above.

Sensitivity analyses showed that, in the complete case analysis, the INBs were generally slightly higher than the base case analysis. Both the manual therapy and exercise therapy interventions had INBs statistically significantly greater than zero at all willingness-to-pay thresholds, from both the societal and health system perspectives. The combined therapy intervention remained cost-effective, but did not reach statistical significance.

Excluding productivity costs from the societal perspective slightly reduced the cost-effectiveness of all three interventions. All interventions, however, remained highly cost-effective relative to usual care only, with INBs significantly greater than zero for exercise therapy (at all willingness-to-pay thresholds) and manual therapy (at the 2×GDP per capita threshold and above).

Table I
Characteristics of participants at entry to the trial

	Usual care control ($n = 51$)	Usual care plus manual therapy ($n = 54$)	Usual care plus exercise therapy ($n = 51$)	Usual care plus combined exercise + manual therapy ($n = 50$)
Demographic				
Men, *n* (% of group)	26 (51.0)	26 (48.1)	19 (37.3)	21 (42.0)
Women, *n* (% of group)	25 (49.0)	28 (51.9)	32 (62.7)	29 (58.0)
Age (years)	66.1 (10.7)	67.3 (10.2)	66.9 (8.2)	66.0 (8.9)
Body mass index (kg/m^2)	29.5 (5.8)	29.2 (5.9)	29.3 (6.0)	30.1 (5.4)
Clinical				
WOMAC score (range 0–240, lower scores represent less pain, stiffness and disability)	93.8 (52.8)	114.8 (56.3)	95.5 (57.3)	99.1 (48.8)
Timed up and go test (s)	7.69 (3.26)	7.68 (3.07)	7.50 (3.14)	6.88 (2.33
30-s sit to stand test (no. of stands):	9.65 (4.29)	9.80 (4.54)	10.39 (4.37)	10.60 (3.79)
40 m self-paced walk time (s):	33.21 (12.42)	33.67 (10.18)	33.42 (11.14)	30.93 (8.37)
Pain intensity score (range 0–10, higher scores represent more pain)	3.1 (2.0)	4.2 (2.3)	3.5 (2.0)	4.0 (2.1)
Quadriceps muscle strength (kg/kg body mass)	0.21 (0.12)	0.20 (0.09)	0.20 (0.07)	0.20 (0.08)
Duration since first diagnosis of osteoarthritis (years)	2.8 (1.3)	2.5 (1.4)	2.6 (1.4)	2.9 (1.3)
Mental health (depression screening test) score indicates low risk of depression, *n* (% of group)	26 (51.0)	27 (50.9)	27 (52.9)	28 (56.0)
Hip osteoarthritis, *n* (% of group)	23 (45.1)	24 (44.4)	22 (43.1)	21 (42.0)
Knee osteoarthritis, *n* (% of group)	28 (54.9)	30 (55.6)	29 (56.9)	29 (58.0)
Both hip and knee osteoarthritis, *n* (% of group)	13 (25.5)	12 (22.2)	10 (19.6)	17 (34.0)

Values are mean (SD) unless specified otherwise. WOMAC= Western Ontario and McMaster osteoarthritis index.

Table II
Mean (SD) costs and health outcomes through 2 years in base case and sensitivity analyses*

	Usual care control		Usual care plus manual therapy		Usual care plus exercise therapy		Usual care plus combined exercise + manual therapy	
Cost outcomes								
MOA trial programme	0	(0)	486	(204)	503	(185)	507	(187)
Public health system costs	7,410	(12,239)	9,047	(14,915)	6,851	(10,572)	7,248	(10,600)
Private health system costs	1,863	(6,600)	752	(2,655)	984	(3,648)	3,154	(7,899)
Costs to patient, family, and friends	1,477	(2,968)	806	(1,146)	618	(583)	929	(1,206)
Productivity costs	4,620	(13,212)	2,096	(6,184)	2,884	(9,853)	3,742	(9,793)
Total New Zealand health system costs	9,273	(13,957)	10,284	(14,840)	8,338	(10,976)	10,908	(11,875)
Complete cases only ($n = 183$)	9,777	(14,419)	9,444	(14,255)	8,266	(10,820)	10,888	(11,977)
No hip or knee replacement ($n = 135$)	3,299	(6,936)	4,904	(14,606)	1,281	(2,588)	2,669	(7,415)
Total societal costs	15,370	(20,447)	13,187	(16,808)	11,840	(17,336)	15,580	(18,102)
Complete cases only ($n = 183$)	15,551	(20,521)	12,183	(16,223)	11,564	(17,270)	15,433	(18,134)
Excluding productivity costs	10,750	(14,281)	11,090	(15,228)	8,955	(11,113)	11,837	(12,352)
No hip or knee replacement ($n = 135$)	9,689	(18,425)	6,586	(15,871)	2,748	(6,778)	4,327	(9,497)
Health outcomes								
QALYs	1.31	(0.286)	1.39	(0.210)	1.46	(0.234)	1.38	(0.186)
Complete cases only ($n = 183$)	1.31	(0.292)	1.40	(0.208)	1.44	(0.221)	1.40	(0.173)
No hip or knee replacement ($n = 135$)	1.32	(0.315)	1.39	(0.224)	1.51	(0.231)	1.41	(0.186)

* All participants ($n = 206$); QALYs = quality-adjusted life years.

The clinical outcomes of all three treatment groups showed clinically significant reductions of >28 WOMAC points from baseline to 2-year follow-up (Table IV, Fig. 3(a)). In the factorial analysis, exercise therapy was superior to no exercise therapy (−28·2 WOMAC points, 95% CI -49·2 to −7·1), manual therapy was not significantly better than no manual therapy (−6·3, WOMAC points, 95% CI -28·1 to 15·5) in the main intention-to-treat analysis, with a non-significant detrimental interaction effect (+13·7 WOMAC points, $p = 0·368$). Compared with usual care only, exercise therapy provided a clinically-significant gain in WOMAC (Table IV), while manual therapy and combined therapy did not. Improvement over time was observed in the usual care only group, however this did not reach the clinical significance threshold (−22·5 WOMAC points, 95% CI -37·5 to −7·5), and disappeared after eliminating the effects of joint replacement surgery (Table IV). The number needed to treat (NNT) to gain one additional OMERACT-OARSI responder, compared with usual care only, was 5 (2.6–73.7) for exercise therapy and 5 (2.4–23.8) for combined exercise- and manual therapy. For manual therapy the NNT was equivocal, at 7 with a lower 95% confidence bound of 2.0 extending to a number needed to harm of 22.2.

For the sample of participants without joint replacement surgery during the trial, the usual care group showed a non-significant worsening of WOMAC points over the period (+6.8 WOMAC points, 95% CI -7·2 to 20·8) [Fig. 3(b)]. In the factorial analysis, exercise therapy was superior to no exercise therapy (−30·8 WOMAC points, 95% CI -53·5 to −8·0), manual therapy was not significantly better than no manual therapy (−19·6, WOMAC points, 95% CI -43·8 to 4·6), with a large but marginally non-significant detrimental interaction effect (+33·6 WOMAC points, $p = 0·054$). Compared with usual care only, exercise therapy again provided a clinically-significant gain in WOMAC (Table IV), while manual therapy and combined therapy did not. The change in WOMAC scores in each treatment group was similar for those with hip OA and those with knee OA (Web Appendix 3).

In secondary analyses, the physical performance tests showed non-significant worsening in the usual care group, consistent improvements in the exercise therapy group, and inconsistent

Table III
Incremental cost-utility ratios and incremental net monetary benefits for manual therapy, exercise therapy, and combined therapy relative to usual care only, base case and sensitivity analyses*

	Manual therapy relative to usual care		Exercise therapy relative to usual care		Combined exercise + manual therapy relative to usual care	
Incremental cost-utility ratio						
Base case						
NZ health system perspective	−7,138	†	−3,657	†	35,566	
Societal perspective	−43,475	†	−16,616	†	20,832	
No hip or knee replacement						
NZ health system perspective	11,932		−9,753	†	−3,876	†
Societal perspective	−34,075	†	−39,637	†	−55,233	†
Complete cases only						
NZ health system perspective	−20,135	†	−10,225	†	32,513	
Societal perspective	−50,501	†	−20,628	†	22,658	
Excluding productivity costs						
Societal perspective	−14,789	†	−10,068	†	27,709	
Incremental net benefit (95% CI)						
Base case						
NZ health system perspective						
1×GDP/capita	4,480	(-1,595 to 10,554)	6,312	(344 to 12,279)	464	(-5,695 to 6,624)
2×GDP/capita	8,322	(224 to 16,419)	12,128	(4,137 to 20,119)	3,156	(-5,049 to 11,362)
3×GDP/capita	12,163	(1,542 to 22,785)	17,945	(7,440 to 28,449)	5,848	(-4,912 to 16,609)
Societal perspective						
1×GDP/capita	7,728	(-494 to 15,949)	8,065	(136 to 15,994)	1,387	(-6,673 to 9,447)
2×GDP/capita	11,570	(1,739 to 21,400)	13,882	(4,324 to 23,440)	4,079	(-5,674 to 13,833)
3×GDP/capita	15,411	(3,402 to 27,421)	19,698	(7,947 to 31,449)	6,771	(-5,244 to 18,787)
No hip or knee replacement						
NZ health system perspective						
1×GDP/capita	3,422	(-3,334 to 10,179)	8,144	(1,800 to 14,489)	4,621	(-2,618 to 11,860)
2×GDP/capita	8,160	(-1,663 to 17,983)	14,783	(5,374 to 24,192)	8,860	(-1,488 to 19,208)
3×GDP/capita	12,898	(-471 to 26,267)	21,421	(8,494 to 34,347)	13,099	(-909 to 27,106)
Societal perspective						
1×GDP/capita	8,494	(-1,043 to 18,030)	12,760	(4,019 to 21,501)	9,686	(234 to 19,138)
2×GDP/capita	13,231	(1,411 to 25,052)	19,398	(8,312 to 30,484)	13,925	(1,961 to 25,888)
3×GDP/capita	17,969	(3,140 to 32,798)	26,036	(11,905 to 40,168)	18,163	(2,953 to 33,374)
Complete cases only						
NZ health system perspective						
1×GDP/capita	6,330	(17 to 12,644)	6,890	(775 to 13,004)	645	(-5,764 to 7,054)
2×GDP/capita	10,641	(2,181 to 19,102)	12,455	(4,202 to 20,709)	3,294	(-5,260 to 11,848)
3×GDP/capita	14,952	(3,834 to 26,071)	18,021	(7,135 to 28,907)	5,943	(-5,281 to 17,166)
Societal perspective						
1×GDP/capita	9,376	(1,124 to 17,628)	8,237	(202 to 16,271)	1,252	(-7,070 to 9,574)
2×GDP/capita	13,687	(3,644 to 23,730)	13,802	(3,995 to 23,610)	3,901	(-6,216 to 14,018)
3×GDP/capita	17,998	(5,590 to 30,406)	19,368	(7,224 to 31,511)	6,550	(-5,946 to 19,046)
Excluding productivity costs						
Societal perspective						
1×GDP/capita	5,164	(-1,053 to 11,380)	7,179	(1,068 to 13,290)	957	(-5,339 to 7,252)
2×GDP/capita	9,005	(784 to 17,227)	12,996	(4,880 to 21,112)	3,649	(-4,679 to 11,976)
3×GDP/capita	12,847	(2,118 to 23,576)	18,812	(8,200 to 29,425)	6,341	(-4,528 to 17,209)

Results are adjusted for age, sex, primary OA joint, baseline WOMAC score, baseline SF-6D HRQoL, body mass index, symptom duration, quadriceps muscle strength, depression, and self-efficacy.

* All participants ($n = 206$).

† Treatment dominates usual care only.

changes in the other intervention groups (Table V). Exercise therapy provided significant gains over usual care at 2 years follow-up in the Timed Up-and-Go test and 40 m fast-paced walk test. Pain intensity scores improved over time in all three intervention groups; in the usual care group, scores improved within the full sample, but worsened slightly for those without a joint replacement during the follow-up period. The proportion of OMERACT-OARSI responders was higher in all three intervention groups than in the group receiving usual care only, and statistically significant in the exercise therapy and combined therapy groups (full sample only) compared with usual care alone.

The number of joint replacement surgeries was significantly greater in the combined therapy group compared with usual care (Table V). No serious adverse events associated with trial interventions were recorded.

Discussion

This study has shown that providing physiotherapist-delivered, individualised programmes of exercise therapy and/or manual therapy in addition to usual care for the treatment of hip and knee osteoarthritis was cost-effective relative to usual care only, from both the societal and the narrower health system perspectives. In particular, the programme of exercise therapy was found to be cost-saving to the health system and society over 2 years, resulted in the largest health utility gains, and provided INBs significantly greater than zero at 95% confidence levels, in the base case and all sensitivity analyses, at all willingness to pay thresholds. These results imply that if health systems were to provide access to high-quality, individually supervised exercise physiotherapy intervention programmes in addition to usual care, cost savings

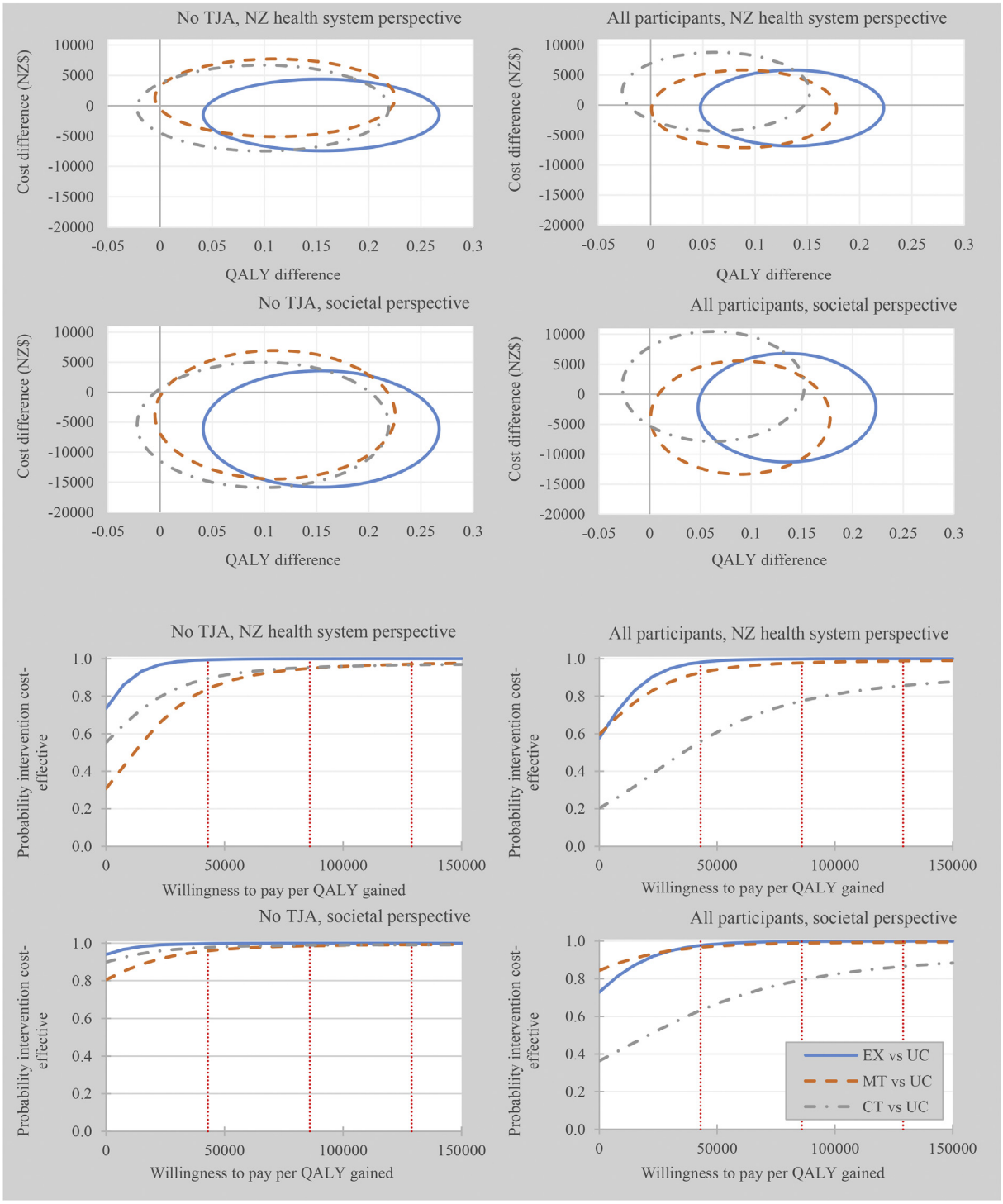

Fig. 2. Cost-effectiveness plane (95% Confidence intervals (CIs)) and cost-effectiveness acceptability curves for the MOA physiotherapy treatments relative to usual care in terms of cost per QALY gained from the perspectives of the New Zealand (NZ) health system and society for participants without joint replacement surgery during the trial ($n = 135$) and all participants ($n = 206$).

may be reaped through reduced healthcare consumption and raised productivity.

The main strengths of this trial were its pragmatic design, utilizing a real-world comparison of usual, GP-led medical care, and its adequate sample size and statistical power, low loss to follow-up, comprehensive cost data, and the informativeness of the long-term (2-year) follow-up. This allowed an externally-valid investigation of the incremental effects and value-for-money of providing ancillary health services in addition to usual care. A limitation of economic evaluations alongside clinical trials is that sample size is typically calculated for the primary clinical outcome, leaving the economic evaluation underpowered. Our study turned out to be sufficiently powered to find statistical significance at the 95% confidence level of INBs for the most clinically effective

Table IV
Mean (SD) WOMAC scores at 2-year follow-up and change in score from baseline*

	Usual care control ($n = 50$)		Usual care plus manual therapy ($n = 53$)			Usual care plus exercise therapy ($n = 51$)			Usual care plus combined exercise + manual therapy ($n = 49$)		
Unadjusted					Between-group diff. (95%CI)			Between-group diff. (95%CI)			Between-group diff. (95%CI)
WOMAC score at 2 years											
All participants ($n = 203$)	76.7	(62.1)	74.2	(58.4)	−2.4 (−25.0 to 20.1)	48.9	(45.2)	−27.8 (−50.1 to −5.5)	58.9	(51.7)	−17.7 (−40.9 to 5.5)
No hip or knee replacement ($n = 132$)	93.3	(62.8)	84.7	(57.3)	−8.6 (−36.9 to 19.7)	54.7	(47.5)	−38.6 (−66.0 to −11.2)	77.9	(54.0)	−15.4 (−45.5 to 14.8)
Within-group change in WOMAC score from baseline											
All participants ($n = 203$)	−17.8	(66.0)	−42.4	(63.5)	−24.7 (−49.9 to 0.5)	−45.6	(58.7)	−27.8 (−52.9 to −2.7)	−38.5	(58.4)	−20.7 (−46.6 to 5.2)
No hip or knee replacement ($n = 132$)	11.8	(46.0)	−20.7	(48.9)	−32.5 (−56.8 to −8.1)	−20.4	(43.9)	−32.2 (−55.6 to −8.8)	−11.4	(50.2)	−23.2 (−49.2 to 2.8)
Adjusted											
WOMAC score at 2 years											
All participants ($n = 203$)	78.5	(51.5)	72.2	(53.8)	−6.3 (−28.1 to 15.5)	50.3	(43.0)	−28.2 (−49.2 to −7.1)	57.7	(47.8)	−20.7 (−43.0 to 1.5)
No hip or knee replacement ($n = 132$)	94.4	(43.2)	74.8	(42.7)	−19.6 (−43.8 to 4.6)	63.6	(37.5)	−30.8 (−53.5 to −8.0)	77.6	(45.2)	−16.8 (−42.9 to 9.4)
Within-group change in WOMAC score from baseline											
All participants ($n = 203$)	−22.5	(51.5)	−28.7	(53.8)	−6.3 (−28.1 to 15.5)	−50.6	(43.0)	−28.2 (−49.2 to −7.1)	−43.2	(47.8)	−20.7 (−43.0 to 1.5)
No hip or knee replacement ($n = 132$)	6.8	(43.2)	−12.8	(42.7)	−19.6 (−43.8 to 4.6)	−24.0	(37.5)	−30.8 (−53.5 to 8.0)	−10.0	(45.2)	−16.8 (−42.9 to 9.4)

* Of participants surviving at 2 year follow-up ($n = 203$ of 206, 98.5%). Negative change represents improvement. Adjusted results: linear regression model adjusting for age, sex, primary OA joint, baseline WOMAC score (scale 0–240), body mass index, symptom duration, quadriceps muscle strength, depression, and self-efficacy. WOMAC= Western Ontario and McMaster osteoarthritis index.

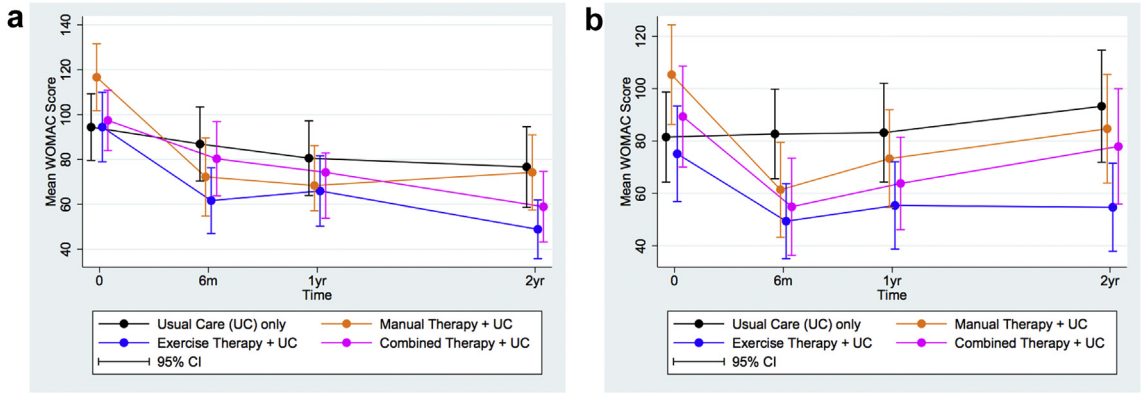

Fig. 3. Course of outcomes by group from baseline through 2-year follow-up. 3a = Primary intention-to-treat analysis ($n = 206$); 3b = subgroup analysis of participants who did not undergo joint replacement surgery during follow-up ($n = 132$). Bars represent time-specific estimates with 95% confidence intervals, adjusted for age, sex, primary OA joint, baseline WOMAC score, body mass index, symptom duration, quadriceps muscle strength, depression, and self-efficacy. WOMAC= Western Ontario and McMaster osteoarthritis index (scale 0–240).

intervention, that was robust to all sensitivity analyses. Other limitations included the fact that joint replacement surgery was non-randomised co-intervention that has the potential to bias the effects of the trial interventions; to clarify this, we planned *a priori* to conduct secondary subgroup analyses of participants who did not undergo joint replacement surgery[6]. The observation of higher rates of joint replacement surgery in the combined therapy group after adjusting for covariates (not significant in the other two physiotherapy groups) was unexpected and may be due to chance, given that GPs and orthopaedic surgeons were blinded to group allocation, but as surgery is the highest cost item this had the potential to bias the results. Any bias in regard to cost-effectiveness would, however, have been in favour of the usual care group, which was shown in the results to be dominated by the three intervention groups. The healthcare costs collected were restricted to only OA-related utilisation; given that costs relating to other comorbidities were not accounted for, this approach likely provides only a limited perspective, which may have resulted in underestimation of cost-effectiveness. Generalizability of cost-effectiveness results between countries is limited by six key threats: demography and epidemiology of the disease; clinical practice patterns and conventions; healthcare provision; relative price levels; opportunity costs of resources; and consumer health state valuation preferences.[20] We consider these threats as minimal in regard to osteoarthritis among British Commonwealth health systems, and we used UK preference weightings for calculation of QALYs from the SF-6D.[12]

Other evidence of the cost-effectiveness of manual or exercise therapy for the treatment of hip and knee OA is scarce[21,22]. The results reported here for the exercise therapy intervention are consistent with two recent studies that assessed the cost-effectiveness of a physiotherapist-delivered class-based exercise programme and a water exercise programme delivered by qualified swimming instructors, both of which found lower costs and incremental QALY gains relative to usual care comparators[23,24]. The findings extend our previously published analyses of 1-year follow-up data from the MOA trial[25]. At 1 year, manual therapy and exercise therapy were both found to be cost-effective relative

Table V
Changes in secondary outcomes from baseline to 2-year follow-up.* Mean (SD) unless specified otherwise

	Usual care control	Usual care plus manual therapy	Between-group diff. (95%CI)	Usual care plus exercise therapy	Between-group diff. (95%CI)	Usual care plus combined exercise + manual therapy	Between-group diff. (95%CI)
Timed up and go test (s)†							
No hip or knee replacement ($n = 132$)	1.32	1.07	−0.26	−0.81	−2.14	0.09	−1.24
	(0.35 to 2.30)	(0.02 to 2.12)	(-1.74 to 1.23)	(-1.77 to 0.14)	(-3.52 to −0.78)	(-1.07 to 1.25)	(-2.78 to 0.31)
All participants ($n = 203$)	0.53	0.44	−0.09	−1.37	−1.89	0.01	−0.52
	(-0.31 to 1.36)	(-0.39 to 1.26)	(-1.28 to 1.10)	(-2.17 to −0.57)	(-3.05 to −0.73)	(-0.85 to 0.86)	(-1.72 to 0.69)
30s sit to stand test (no. of stands)‡							
No hip or knee replacement ($n = 132$)	−0.50	−0.17	0.33	1.65	2.15	1.29	1.79
	(-2.12 to 1.12)	(-1.87 to 1.53)	(-2.08 to 2.75)	(0.04 to 3.23)	(-0.18 to 4.47)	(-0.65 to 3.23)	(-0.82 to 4.40)
All participants ($n = 203$)	−0.08	0.36	0.44	0.43	0.50	1.39	1.47
	(-1.48 to 1.33)	(-1.04 to 1.76)	(-1.59 to 2.46)	(-0.93 to 1.78)	(-1.46 to 2.46)	(-0.06 to 2.84)	(-0.57 to 3.51)
40 m self-paced walk time (s)†							
No hip or knee replacement ($n = 132$)	4.20	−0.24	−4.44	−3.85	−8.04	1.17	−3.02
	(-0.05 to 8.44)	(-4.97 to 4.50)	(-10.87 to 2.00)	(-8.11 to 0.42)	(-14.17 to −1.92)	(-4.00 to 6.35)	(-9.88 to 3.83)
All participants ($n = 203$)	1.27	−1.48	−2.75	−6.77	−8.04	−0.85	−2.12
	(-2.20 to 4.74)	(-5.01 to 2.05)	(-7.74 to 2.23)	(-10.11 to −3.42)	(-12.88 to −3.20)	(-4.54 to 2.84)	(-7.24 to 2.99)
Pain intensity score (range 0–10, negative scores indicate reduced pain)							
No hip or knee replacement ($n = 132$)	0.19	−1.07	−1.26	−0.89	−1.07	−0.37	−0.55
	(-0.58 to 0.95)	(-1.91 to −0.24)	(-2.42 to −0.10)	(-1.66 to −0.12)	(-2.18 to 0.03)	(-1.29 to 0.56)	(-1.79 to 0.68)
All participants ($n = 203$)	−1.01	−1.65	−0.63	−1.92	−0.91	−1.78	−0.77
	(-1.66 to −0.36)	(-2.29 to −1.00)	(-1.57 to 0.30)	(-2.55 to −1.29)	(-1.83 to 0.01)	(-2.45 to −1.10)	(-1.72 to 0.19)
OMERACT-OARSI responders, no. (% of group)			Odds ratio (CI)				
No hip or knee replacement ($n = 132$)	9 (26.9%)	15 (48.3%)	2.85 (0.87 to 9.36)	17 (48.3%)	2.85 (0.89 to 9.07)	12 (38.9%)	1.84 (0.53 to 6.45)
All participants ($n = 203$)	21 (44.4%)	30 (51.5%)	1.39 (0.57 to 3.37)	33 (66.4%)	2.80 (1.12 to 6.98)	32 (67.1%)	2.91 (1.14 to 7.41)
Joint replacement surgeries, no. (% of group)							
All participants ($n = 203$)	13 (27.3%)	19 (29.3%)	1.14 (0.41 to 3.11)	17 (35.4%)	1.66 (0.61 to 4.52)	22 (47.0%)	3.18 (1.14 to 8.87)
Complete cases ($n = 183$)	13 (28.3%)	15 (31.9%)	1.19 (0.49 to 2.89)	15 (32.6%)	1.22 (0.51 to 2.99)	19 (43.2%)	1.93 (0.80 to 4.63)

Results (except for counts of OMERACT-OARSI respondents and joint replacement surgeries) are adjusted for age, sex, primary OA joint, baseline WOMAC score, body mass index, symptom duration, quadriceps muscle strength, depression, and self-efficacy.

* Of participants surviving at 2 year follow-up ($n = 203$ of 206, 98.5%).

† Negative times represent shorter time to complete, indicating improvement.

‡ Positive values represent more repetitions, indicating improvement.

to usual care only from both perspectives, and manual therapy cost-saving from the societal perspective, while combined therapy was cost-effective only from the societal perspective. This update shows that these gains are maintained and extended over 2 years, in particular for the exercise therapy intervention. To our knowledge, no previous studies have assessed the cost-effectiveness of a programme of supervised exercise physiotherapy or of manual physiotherapy in addition to usual care for the treatment of hip or knee OA[21]. The external validity of this study, establishing the long-term effectiveness of this highly generalizable intervention, compared with a real-world comparator, is a strength of this study.

Trials assessing the long-term clinical effectiveness of conservative therapies are also scarce; the little available evidence indicates absence of long-term effect[26–29]. The 2-year follow-up of this trial shows that the treatment effect of exercise therapy can strengthen compared with usual care. Although we observed diminishment of the treatment effects of the physiotherapy interventions over time in this subgroup [Fig. 3(b)], notably, we observed deterioration in the subgroup of usual care patients who did not receive joint replacement surgery (11·8 WOMAC points, 95% CI -3·2 to 26·8, unadjusted). This finding bears consideration when interpreting long-term follow-up data of studies with alternative comparison populations. Our 2-year follow-up shows that the gains from exercise therapy were maintained and extended over 2 years, compared with usual care, while those of manual therapy were not, likely due to the active, self-efficacious nature of exercise therapy. Maintenance and enhancement of the modest but significant treatment effect of conservative therapies is an important new area of study. Building on very thin systematic review evidence[28], data from our trials and collaborations indicate that providing 'booster sessions' intended to reinforce patient adherence and enhance treatment effects are an effective[30] and cost-effective[31] strategy when the clinical effectiveness of exercise therapy is modest, but equivocal when the exercise therapy effect is stronger or follow-up shorter[32,33]. The results also corroborate evidence from our 1-year follow-up that, within a limited treatment session time, single interventions result in better outcomes than combined interventions[8]. These results are consistent with previous evidence that attempting to deliver too many modes of therapy in a restricted timeframe may compromise the effective dose delivered of each component[34], and provide no greater effect than an attentive therapist delivering placebo and advice.[35]

Conclusions

Our findings indicate that the MOA trial exercise therapy intervention programme resulted in substantial health gains to patients over 2 years of follow-up, was cost-effective at conventional willingness-to-pay thresholds, and was cost-saving relative to usual care only from both the health system and societal

perspectives. These findings suggest that if health systems were to provide access to high-quality, individually supervised exercise physiotherapy intervention programmes in addition to usual care, cost savings may be reaped through reduced healthcare consumption and raised productivity.

Patient consent

Obtained.

Ethics approval

The trial was approved by the Lower South Regional Ethics Committee of the NZ Ministry of Health (LRS/07/11/044), and complied with the Helsinki Declaration. All participants provided informed consent to take part in the trial.

Data sharing

The research team will consider reasonable requests for sharing of deidentified patient level data. Requests should be made to the corresponding author. Consent for data sharing was not obtained but the presented data are anonymised and risk of identification is low. The original protocols are available from the corresponding author on request.[6,7]

Contributions

JHA conceived the trial, was the principal investigator, led the study design and conduct, led the literature search, funding applications, and wrote the second and final drafts of the manuscript. He is guarantor. RW analysed the reported data, produced the tables and graphs, and wrote the first draft of the manuscript. RW and JHA had full access to all data and take responsibility for the integrity of the data. JHA, AAW, DP and CC designed the intervention programmes and data collection tools and acquired the data. All authors had access to the trial data and approved the final paper. The contributions and affiliations of the MOA Trial team are outlined in Web Appendix 4. The late AJC (deceased), MCR (retired), GDB, and JCT contributed to design and monitoring of the trial. JCT also contributed to recruitment.

Competing interests

We declare no competing interests.

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Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.joca.2018.12.004.

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