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The Need, Value and Affordability of First-line Treatments for Hip and Knee Osteoarthritis in Alberta

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The Need, Value and Affordability of First-line Treatments for Hip and Knee Osteoarthritis in
Alberta

by

Darren Randell Mazzei

A THESIS

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Abstract

Clinical guidelines have recommended exercise and education as first-line treatments for hip and knee osteoarthritis (OA) for 25 years, but these proven treatments are underused globally. In Alberta, joint replacements are publicly funded. Meanwhile, first-line treatments are funded with private insurance or out-of-pocket which reduces access. We sought to inform the policy-making process in Alberta by addressing three objectives: 1) Describe “usual care” (UC) patterns of education, exercise, weight management, pain medication and other nonsurgical treatments for knee OA in a cohort of people recommended for nonsurgical care by an orthopaedic surgeon; 2) Estimate the real-world incremental net monetary benefit (INMB) of a standardized education and exercise therapy program (GLA:D®) compared to usual care for people managing hip and/or knee OA; 3) Estimate the budget impact of funding GLA:D® for people with hip and knee OA waiting for total joint replacement (TJR) consultation in a universal publicly insured healthcare system. We surveyed 250 people over the telephone and found that only 20% of people used treatments consistent with international clinical guidelines during a three-to-six-year period after an orthopaedic surgeon recommended nonsurgical care. Our prospective matched cohort study (GLA:D® n=127, UC n=127) showed that GLA:D® had a positive INMB compared to UC from the Ministry of Health perspective over 12-months. The INMB of GLA:D® was still positive but less certain over a lifetime as well as when out-of-pocket and private insurance costs were considered. Our budget impact analysis model showed that publicly funding GLA:D® for everyone waiting for TJR consultation could be an affordable solution to avoid surgeries, improve equitable access to evidence-based treatments and save more than the program costs. Our research shows that publicly funding GLA:D® would increase use of first-

line treatments in Alberta by filling an important care gap, offer more equitable access to evidence-based care, reduce significant out-of-pocket expenses for people living with OA and improve health system performance.

Keywords: Health economics, Economic evaluation, Cost-effectiveness analysis, Budget impact analysis, Osteoarthritis, Hip, Knee, Education, Exercise therapy

Preface

Three manuscripts were published in preparation of this doctoral thesis and two are currently under review. Darren Mazzei led the study design, data collection and data analysis with critical input from his supervisor (Dr. Deborah Marshall), thesis supervisory committee (Dr. Jackie Whittaker, Dr. Peter Faris and Tracy Wasylak) and other co-authors. Here are the citations of our published work:

Mazzei DR, Ademola A, Abbott JH, Sajobi T, Hildebrand K, Marshall DA. Systematic review of economic evaluations investigating education, exercise, and dietary weight management to manage hip and knee osteoarthritis: Protocol. Systematic Reviews. 2020, 9(1), 229. DOI: 10.1186/s13643-020-01492-6

Mazzei DR, Ademola A, Abbott JH, Sajobi T, Hildebrand K, Marshall DA. Are education, exercise and diet interventions a cost-effective treatment to manage hip and knee osteoarthritis? A systematic review. Osteoarthritis and Cartilage. 2021 Apr;29(4):456-470. DOI: 10.1016/j.joca.2020.10.002

Mazzei DR, Whittaker JL, Kania-Richmond A, Faris P, Wasylak T, Robert J, Hawker G, Marshall DA. Do people with knee osteoarthritis use guideline-consistent treatments after an orthopaedic surgeon recommends nonsurgical care? A cross-sectional survey with long-term follow-up. Osteoarthritis and Cartilage Open 2022 4(2). DOI: 10.1016/j.ocarto.2022.100256

Mazzei DR, Faris P, Whittaker JL, Wasylak T, Marshall DA. Real-world cost-effectiveness of a standardized education and exercise therapy program for hip and knee osteoarthritis compared to usual care. Under review at Osteoarthritis & Cartilage.

Mazzei DR, Whittaker JL, Faris P, Wasylak T, Marshall DA. Estimating the budget impact of implementing a standardized education and exercise therapy program for hip and knee osteoarthritis in a publicly insured healthcare system. Under review at Osteoarthritis & Cartilage.

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Dedication

This work is dedicated to every patient that told me they could not afford physiotherapy.

Cailynn and Oslo, thanks for supporting me. I can't wait to spend more time with you.

Contributions of Authors

In the systematic review (Chapter Two), Darren Mazzei and Dr. Deborah Marshall developed the study concept. Darren Mazzei and Ayoola Ademola developed the study protocol with Dr. Haxby Abbott, Dr. Tolulope Sajobi, Dr. Kevin Hildebrand, and Dr. Deborah Marshall providing critical input. Darren Mazzei and Ayoola Ademola executed the search strategy with subject matter expert advice provided by Dr. Haxby Abbott, and Dr. Deborah Marshall. Data extraction, synthesis, risk of bias assessment, manuscript preparation, and interpretation were performed by Darren Mazzei and Ayoola Ademola. All authors provided input on final manuscript.

In the first manuscript (Chapter Three), Darren Mazzei, Dr. Jackie Whittaker, Dr. Peter Faris, Tracy Wasylak, and Dr. Deborah Marshall developed the study concept. Darren Mazzei and Dr. Deborah Marshall developed the study protocol with Dr. Jackie Whittaker, Dr. Ania Kania-Richmond, Dr. Peter Faris and Tracy Wasylak providing critical input. Data analysis was conducted by Darren Mazzei with input by Dr. Peter Faris, and Dr. Deborah Marshall. Results were interpreted by Darren Mazzei, Dr. Peter Faris, and Dr. Deborah Marshall with critical feedback provided by all other authors. Manuscript draft preparation was performed by Darren Mazzei. All authors provided input on the final manuscript.

In the second manuscript (Chapter Four), all authors developed the study concept. Darren Mazzei developed the study protocol with critical input from Dr. Peter Faris, Dr. Jackie Whittaker, Tracy Wasylak, and Dr. Deborah Marshall. Recruitment and data collection was conducted by Darren Mazzei. Data analysis was conducted by Darren Mazzei with input from

Dr. Peter Faris. Results were interpreted by Darren Mazzei with critical feedback provided by all other authors. Manuscript draft preparation was performed by Darren Mazzei. All authors provided input on the final manuscript.

In the third manuscript (Chapter Five), all authors developed the study concept. Darren Mazzei developed the study protocol, built the model, and performed the analysis with critical input from Dr. Peter Faris, Dr. Jackie Whittaker, Tracy Wasylak, and Dr. Deborah Marshall. Results were interpreted by Darren Mazzei with critical feedback provided by all other authors. Manuscript draft preparation was performed by Darren Mazzei. All authors provided input on the final manuscript.

Table of Contents

Abstract	ii
Preface	iv
Acknowledgement	vi
Dedication.....	vii
Contributions of Authors	viii
Table of Contents	x
List of Figures.....	xiv
List of Tables	xv
List of Abbreviations	xvii
1 INTRODUCTION	1
1.1 Osteoarthritis	2
1.2 Osteoarthritis Services in Alberta.....	5
1.3 Using Insurance Coverage to Optimize Resources in Publicly Insured Healthcare Systems	7
1.4 Applying Economic Theory and Methods to Health	8
1.4.1 Quantifying Cost Inputs.....	9
1.4.2 Quantifying Health Outputs.....	11
1.4.3 How to Determine an Intervention is an Efficient Use of Resources	12
1.4.4 Methodological Issues in Economic Evaluations of First-Line Osteoarthritis Treatments	13
1.5 Research Program Overview.....	14
2 ARE EDUCATION, EXERCISE AND DIET INTERVENTIONS A COST-EFFECTIVE TREATMENT TO MANAGE HIP AND KNEE OSTEOARTHRITIS? A SYSTEMATIC REVIEW	16
2.1 ABSTRACT	17
2.2 INTRODUCTION	18
2.3 METHODS	19
2.3.1 Eligibility criteria.....	19
2.3.2 Literature search and study selection	19
2.3.3 Data Extraction and Synthesis	20
2.3.4 Synthesis of Results	21
2.3.5 Risk of Bias Assessment	21
2.4 RESULTS	22
2.4.1 Exercise Interventions	25

2.4.2	Exercise and Education Interventions	26
2.4.3	Exercise and Diet Interventions	26
2.4.4	Diet Interventions	27
2.4.5	Education Interventions	27
2.4.6	Subgroup Analysis	28
2.4.7	Risk of Bias Assessment	28
2.5	DISCUSSION	29
2.5.1	Policy Implications.....	34
2.5.2	Strengths and Limitations	34
2.5.3	Recommendations for Future Research	36
2.5.4	Conclusion	37
3	DO PEOPLE WITH KNEE OSTEOARTHRITIS USE GUIDELINE-CONSISTENT TREATMENTS AFTER AN ORTHOPAEDIC SURGEON RECOMMENDS NONSURGICAL CARE? A CROSS-SECTIONAL SURVEY WITH LONG-TERM FOLLOW-UP	38
3.1	ABSTRACT	39
3.2	INTRODUCTION	40
3.3	METHODS	41
3.3.1	Study and Design	41
3.3.2	Participants	42
3.3.3	Data Collection	42
3.3.4	Outcomes.....	43
3.3.5	Sample Size	44
3.3.6	Statistical Methods.....	45
3.4	RESULTS	47
3.5	DISCUSSION	54
3.5.1	Conclusions	59
4	REAL-WORLD COST-EFFECTIVENESS OF A STANDARDIZED EDUCATION AND EXERCISE THERAPY PROGRAM HIP AND KNEE OSTEOARTHRITIS COMPARED TO USUAL CARE	60
4.1	ABSTRACT	61
4.2	INTRODUCTION	62
4.3	METHODS	63
4.3.1	Study Design	63
4.3.2	Participants.....	64
4.3.3	Recruitment.....	64

4.3.4	Data collection.....	64
4.3.5	Health Outcomes.....	66
4.3.6	Costs.....	66
4.3.7	Sample Size	68
4.3.8	Statistical Analysis	69
4.3.9	Missing Data and Outliers	69
4.3.10	Cost-Utility Analysis over 12-months	69
4.3.11	Cost-Utility Analysis over Lifetime.....	71
4.4	RESULTS	75
4.4.1	Participants.....	75
4.4.2	Health Outcomes.....	76
4.4.3	Costs.....	79
4.4.4	Cost-Utility over 12-Months	81
4.4.5	Cost-Utility over Lifetime	82
4.5	DISCUSSION	85
4.5.1	Policy Implication	88
4.5.2	Strengths and Limitations	88
4.5.3	Recommendations for Future Research	89
4.5.4	Conclusion	90
5	ESTIMATING THE BUDGET IMPACT OF IMPLEMENTING A STANDARDIZED EDUCATION AND EXERCISE THERAPY PROGRAM FOR HIP AND KNEE OSTEOARTHRITIS IN A PUBLICLY INSURED HEALTHCARE SYSTEM.....	91
5.1	ABSTRACT	92
5.2	INTRODUCTION	93
5.3	METHODS	95
5.3.1	Model Design.....	95
5.3.2	Data Sources	96
5.3.3	Population Estimate	97
5.3.4	Cost Estimate	98
5.3.5	Sensitivity Analysis	100
5.3.6	Scenario Analysis	101
5.4	RESULTS	102
5.4.1	Base Case Analysis.....	102
5.4.2	Sensitivity Analysis	103

5.4.3	Scenario Analysis	105
5.5	DISCUSSION	105
5.5.1	Policy Implications.....	109
5.5.2	Strengths, Limitations and Future Research	110
5.5.3	Conclusion	111
6	SUMMARY	112
6.1	Summary of Key Findings.....	112
6.2	Strengths and Limitations	113
6.3	Policy Implications.....	113
6.4	Implementation.....	115
6.5	Contributions to the Research Field	118
6.6	Knowledge Translation	119
6.7	Future Research.....	120
	Appendix A. Comparison of Structured Osteoarthritis Management Programs Implemented in Healthcare Systems.....	121
	Appendix B. PRISMA Checklist.....	122
	Appendix C. Systematic Review Search Criteria.	125
	Appendix D. Economic Evaluations of Education, Exercise and Dietary Weight Management to Manage Hip and Knee Osteoarthritis Summary Tables.	137
	Appendix E. Telephone Questionnaire Used in Chapter Three.	150
	Appendix F. CHEERS Checklist.....	116
	Appendix G. Cost-Questionnaire Used in Chapter Four.	120
	Appendix I. 12-Month Linear Regression Performance from Cost-Effectiveness Analysis in Chapter Four.....	132
	Appendix J. Lifetime Markov Model Convergence Testing from Cost-Effectiveness Analysis in Chapter Four.....	141
	REFERENCES.....	142

List of Figures

Figure 1. Prisma flow diagram of study selection.

Figure 2. Cost-effectiveness plane representing intervention compared to control.

Figure 3. Authors' risk of bias assessment using the CHEC list.

Figure 4. Participant flow diagram.

Figure 5. Incremental net monetary benefit formula.

Figure 6. Depiction of the Markov model used to evaluate lifetime horizon.

Figure 7. Participant flow diagram.

Figure 8. Incremental net monetary benefit at a range of willingness to pay thresholds (Ministry of Health perspective, Complete cases).

Figure 9. Probabilistic incremental cost-effectiveness ratio of GLA:D® compared to UC over lifetime time horizon (Ministry of Health, All cases, No surgery).

Figure 10. Cost-effectiveness acceptability curve comparing GLA:D® to UC at willingness to pay thresholds ranging from \$0-\$100,000 (Ministry of Health, All cases, No surgery).

Figure 11. Budget impact analysis formula.

Figure 12. Annual budget forecast of publicly funding GLA:D® compared to status quo.

Figure 13. Change in budget impact estimates based on parameter uncertainty.

List of Tables

Table 1. Methods used in cost-effectiveness research.

Table 2. Participant characteristics.

Table 3. Use of nonsurgical treatments over three to four years post consult.

Table 4. Relationship between participant characteristics and use of nonsurgical treatments.

Table 5. Relationship between participant characteristics and use of first-line treatments.

Table 6. Relationship between participant characteristics and use of guideline-inconsistent treatments.

Table 7. Markov model parameters and transition probabilities (Ministry of Health perspective, All cases, No surgery).

Table 8. Participant demographics.

Table 9. Health outcomes over 12-months for participants with complete data.

Table 10. *Unadjusted costs for the GLA:D® and usual care cohorts by service type over 12-months.*

Table 11. Summary of incremental net monetary benefit over 12-months from the Ministry of Health and healthcare perspective.

Table 12. Probabilistic sensitivity analysis over lifetime from the Ministry of Health and healthcare perspective.

Table 13. Parameters used in the budget impact analysis model.

Table 14. Estimates used in the sensitivity analysis to examine parameter uncertainty.

Table 15. Scenario analysis population estimates.

Table 16. Budget impact for publicly funding GLA:D®.

Table 17. Scenario analysis for publicly funding GLA:D® in select subpopulations.

List of Abbreviations

Abbreviation	Description
AHCIP	Alberta Healthcare Insurance Plan
AHS	Alberta Health Services
BIA	Budget impact analysis
BJH SCN™	Bone and Joint Health Strategic Clinical Network™
CEA	Cost-effectiveness analysis
CHEC	Consensus on Health Economic Criteria
CHEERS	Consolidated Health Economic Evaluation Reporting Standards
ESCAPE	Enabling Self-Management And Coping With Arthritic Knee Pain through Exercise
EQ-5D	European Quality of Life 5-Dimension
GRADE	Grading of Recommendations Assessment, Development and Evaluation
GLA:D®	Good Life with Osteoarthritis in Denmark®
ICER	Incremental cost-effectiveness ratio
ICUR	Incremental cost-utility ratio
ISPOR	International Society of Pharmacoeconomics and Outcomes Research
HIIS	Health Innovation, Implementation and Spread
HOOS	Hip Injury and Osteoarthritis Outcome Score
KOOS	Knee Injury and Osteoarthritis Outcome Score
MCID	Minimally important clinical difference

NICE	National Institute for Health and Care Excellence
OA	Osteoarthritis
OARSI	Osteoarthritis Research Society International
PROM	Patient-reported outcome measure
QALY	Quality adjusted-life years
QOL	Quality of life
RCT	Randomized controlled trial
TJR	Total joint replacement
WTP	Willingness to pay

1 INTRODUCTION

Medicare is celebrated as one of the primary symbols of Canadian identity¹. Canadian medicare was established in 1957 when the federal government started providing all provinces and territories conditional funding to deliver medically necessary hospital-based and physician services to all citizens². Canadians are proud of our universal publicly insured healthcare system because it provides care based on need instead of ability to pay. However, gaps in care remain. Approximately 30% of healthcare services in Canada remain privately insured or paid out-of-pocket³. Community-based healthcare treatments like medications, dentistry, optometry, and outpatient rehabilitation fall outside of medicare's basket of services which means access is based on ability to pay instead of need. Healthcare in the 1950's primarily managed acute episodic care with physicians as the sole provider². Today, Canadians manage numerous chronic diseases which primarily require community-based services from many specialized healthcare professionals². Insurance models would typically invest in low cost services before committing to high cost care, but provincial health insurance plans across Canada force people living with chronic diseases like osteoarthritis (OA) to pay out-of-pocket for first-line treatments (accepted as the initial treatment in standard clinical practice) like exercise therapy while offering 100% coverage for publicly funded, resource-intensive surgical total joint replacements (TJR)⁴. Governments often face chronically long wait times for TJR surgery, but first-line treatments for managing OA are rarely considered in the policy debate. This doctoral thesis seeks to inform the policy-making process by exploring the need, value, and affordability of first-line treatments for managing hip and knee OA in Alberta, Canada.

1.1 Osteoarthritis

Osteoarthritis impacts about 15% of the population and is the second most common chronic disease in Canada, after hypertension^{5,6}. Canada's provinces and territories collectively spend \$10.2 billion dollars annually managing OA. Budgets are forecasted to reach \$550 billion by 2040 when 25% of the population is expected to be living with OA⁵. Only 30% of people with knee OA and 14% of people with hip OA will have a TJR in their lifetime⁷. However, the high prevalence of OA makes hip and knee replacement the second and third most common surgeries in Canada⁸. Increased demand for OA services is driven by a growing and aging population coupled with the increased prevalence of obesity⁶. Health systems must adapt to meet the growing demand for OA services.

Osteoarthritis (OA) pathology and symptoms are caused by a complex mixture of inflammatory, metabolic, and mechanical factors^{9,10}. People living with OA can experience chronic joint pain, tenderness, stiffness, crepitus, restricted range of motion, bony enlargement, and intermittent warmth^{5,11}. Cyclical pain is often associated with movement which leads to activity restrictions, mobility decline, functional limitations, and reduced quality of life (QOL)⁶. People living with OA also experience acute episodes of increased pain caused by synovitis, an acute inflammatory response in a joints' synovial membrane¹¹. Structural joint changes appear as chondral integrity deteriorates and a maladaptive remodeling process creates tissue hypertrophy, increased vascularity, subchondral bone lesions and osteophyte formation^{11,12}. However, clinical signs and symptoms rarely follow the pathoanatomical disease progression¹³. Patient-reported pain only has a small association with bone marrow lesions or synovitis that is present on diagnostic

imaging¹¹. The OA population is also heterogenous, showing large variability in disease progression and response to treatment¹¹. Current research attempts to identify clinical phenotypes, but phenotypes cannot accurately predict disease progression or treatment response at this time¹⁴.

There is no cure for OA so international clinical guidelines recommend a stepped treatment approach focused on symptom management¹⁵. Everyone diagnosed with hip and knee OA, regardless of disease severity or co-morbidity, is recommended education and exercise therapy as first-line treatment^{15,16}. Education should include self-management techniques and information about the disease¹⁵. Structured exercise therapy consisting of strengthening, cardiovascular, and/or neuromuscular balance exercises are safe, effective, and appropriate¹⁵. Clinical guidelines recommend overweight or obese people with hip or knee OA use dietary weight management to attempt losing 5-10% of bodyweight¹⁵. Adjunct therapies like aquatic therapy, gait aids, and cognitive behavioural therapy are recommended on a case-by-case basis. Pharmacological pain management may be included as an adjunct therapy if first-line treatments do not alleviate symptoms, although risks and co-morbidities must be considered¹⁵. People with severe, end-stage OA are recommended TJR when an adequate trial of first-line treatments fail to manage OA symptoms¹⁷.

International clinical guidelines have recommended first-line treatments for 25 years¹⁸, but underuse of first-line treatments with overuse of medications and surgery is a global phenomenon. In the United States, more people with OA are prescribed pain medications than

referred to physiotherapy or provided with lifestyle advice¹⁹. Less than half of a sample in Australia used exercise to manage their OA²⁰. In Canada, only one quarter of survey respondents with hip and knee OA reported receiving advice about exercise or weight loss²¹. Joint replacement is effective for the right patient, but adverse events like infection, deep vein thrombosis, stiffness requiring manipulation under anesthetic, and fracture were experienced by 14% of people undergoing surgery²². After receiving a TJR, between 15-30% of people also report dissatisfaction or little to no symptom improvement²³. Given the risks and suboptimal outcomes experienced by some people, it seems reasonable for publicly insured healthcare systems to encourage the optimal use of first-line treatments prior to undertaking a costly TJR.

Many structured OA management programs incorporating education and exercise have been developed and implemented in healthcare systems to improve uptake of proven first-line treatments (Appendix A)²⁴. “Enabling Self-Management and Coping with Arthritic Knee Pain through Exercise (ESCAPE)-pain” was developed, evaluated, and then implemented across the United Kingdom (UK) to deliver best-practice self-management education and exercise therapy to over 12,000 participants with hip and knee OA in a structured six-week long group program²⁵. In Sweden almost 135,000 people living with hip, knee, shoulder, and hand OA have participated in the “Better Management of Patients with Osteoarthritis” program which provides education and a six- or seven-week group or home exercise program²⁶. Danish researchers developed an eight-week standardized group exercise and education program called “Good Life with osteoArthritis in Denmark (GLA:D®)” for hip and knee OA^{27,28}. GLA:D® consists of two education sessions and twelve supervised neuromuscular exercise sessions

delivered twice per week²⁷. GLA:D® education sessions provide basic OA knowledge, treatment guidelines and self-management tips while neuromuscular exercises use sensorimotor inputs to improve movement quality and movement efficiency^{27,29}. GLA:D® has been implemented in the Danish healthcare system and reports similar effectiveness to previously conducted RCTs by the same Danish research team^{22,27,28,30,31}. Bone and Joint Canada identified the lack of programs for nonsurgical management of hip and knee OA in Canada then worked with Danish researchers to adapt GLA:D® to fit the Canadian context and supported its spread across the country³². GLA:D® has continued to spread internationally²⁸. Approximately 85,000 GLA:D® participants from ten countries have reported decreased pain intensity, less pain medication use, better function, and higher QOL after the program³³. Implementing structured education and exercise therapy has shown benefits in other countries around the world.

1.2 Osteoarthritis Services in Alberta

Approximately 680,000 Albertans are currently living with OA and 1.25 million will be diagnosed by 2040^{34,35}. The average age of OA diagnosis is 55; approximately 60% will live with OA for 9 years before seeking specialty care and 40% will manage their disease for the rest of their life^{36,37}. Little is known about the community-based services people use to manage their OA from the time they are diagnosed until they have a TJR consultation. However, 40% of Albertans have not used first-line treatments prior to undergoing TJR³⁸ even though attempting first-line treatments is one criteria for appropriate use of TJR¹⁷. In 2017, the Alberta Health Services (AHS) Bone and Joint Health Strategic Clinical Network™ (BJH SCN™) identified a lack of evidence-based first-line OA treatment programs in the province and began piloting GLA:D®.

However, payment model disparities were identified as a key barrier when implementing GLA:D® at private and publicly funded facilities across the province³⁹.

Osteoarthritis services in Alberta are funded by a mixture of public and private payment models. In Alberta, the Canada Health Act is operationalized through the Alberta Healthcare Insurance Plan (AHCIP) which provides 100% publicly funded coverage for medically necessary care to all Alberta residents except Indigenous peoples, members of military, and people who opt out of coverage⁴⁰. Osteoarthritis services covered by the AHCIP include physician consultations, diagnostic imaging, hospital stays, surgical interventions, inpatient medication, inpatient rehabilitation, and some outpatient rehabilitation delivered at rural hospitals⁴¹.

Physicians are private, independent contractors who mostly deliver care to patients through a fee-for service business model with the government paying amounts set out in the schedule of medical benefits⁴². Alberta's Ministry of Health, known as Alberta Health (AH), provides funding as a global budget for Alberta Health Services (AHS) to deliver hospital-based services and some community-based care. Alberta Health Services offers the Alberta Health Living Program which includes education classes about OA self-management. Albertans 65 years of age or older have access to publicly-insured medication coverage through Alberta Blue Cross. Alberta Health also provides full or partial public funding for home supports and medical devices like walking aids and knee braces depending on age and/or income through the Alberta Aids to Daily Living program⁴⁰. Meanwhile, exercise therapy has primarily been funded by private insurance or out-of-pocket. Exercise therapy was delivered exclusively at private community rehabilitation clinics until the BJH SCN™ start piloting GLA:D® in 2017. A few Primary Care Networks (PCNs), which

are a patient's publicly funded medical home in Alberta, recognized this care gap and recently employed kinesiologists to deliver GLA:D® and exercise prescription for other diseases. Some rural hospitals have also started offering the GLA:D® program. GLA:D® is now being delivered at 45 privately funded community rehabilitation clinics, 5 out of 40 PCNs, and 18 out of 106 AHS facilities⁴³. Private funded facilities are primarily concentrated in urban centers. The 5 publicly funded PCNs operate in suburban Edmonton and Calgary. Meanwhile, all 18 AHS facilities are in rural communities. The mixture of public and private funding creates geographic and cost-related inequitable access to publicly funded exercise therapy programs across Alberta.

1.3 Using Insurance Coverage to Optimize Resources in Publicly Insured Healthcare Systems

User fees and insurance coverage affect healthcare service use⁴⁴. People with higher co-payments and contribution limits tend to seek less medical care⁴⁵. Uninsured and underinsured Canadians are more likely to report not taking prescribed medications due to cost⁴⁶. There was an 18% reduction in outpatient physiotherapy use when the Ontario Ministry of Health defunded rehabilitation services in 2005⁴⁷. Costs are consistently reported as a barrier to accessing rehabilitation services across Canada^{48–50}. Patients and clinicians in Alberta report that private insurance and out-of-pocket payment reduce access to first-line OA treatments³⁹.

Alberta Health could fund first-line OA treatments, thereby reducing or removing user fees to incentive use, but decision-makers must consider the resource implications and policy tradeoffs of funding a new intervention. Decision-makers in publicly insured healthcare systems must make difficult decisions to balance trade-offs between access, effectiveness, and affordability

to deliver appropriate care to the insured population. Alberta Health and its partners who deliver care (i.e. AHS and PCNs) aim to provide a sustainable, high-performing healthcare system that maximizes value for money⁵¹. Improving value for money means Alberta Health would allocate resources for its partners to deliver effective and efficient interventions, known as high-value care, while divesting from low-value care. These difficult resource decisions can be informed by health economics methodology.

1.4 Applying Economic Theory and Methods to Health

Using healthcare resources efficiently maximizes the health benefits gained by society.

Health economists attempt to transparently evaluate opportunity costs, meaning what is given up when limited resources are allocated to one intervention instead of another⁵².

Extra-welfarism is the theoretical foundation of health economics methodology which combines traditional welfare economics with additional characteristics⁵³. Welfare theory assumes individual preferences, shown by a person's willingness to pay for something, is the best way to quantify value⁵⁴. Welfare theory uses dollars to measure the inputs and outputs in a cost-benefit calculation⁵⁴. Methods such as cost-benefit analysis and cost-minimization analysis fall under this theoretical paradigm (Table 1). However, welfare theory has notable limitations when applied to health. Decision-makers and the public have historically been hesitant to allocate healthcare resources based solely on income and free market principles⁵⁴. Most people in society believe a rich person's health should not be more valuable than a poor person's, although the rich person could spend more⁵⁵. Some academics have suggested

healthcare should be government subsidized and allocated equally because health is a necessary foundation for all members of society to maximize their own capabilities^{56–58}. A cost-benefit calculation rooted in welfarist theory only considers the consumption of healthcare goods and services, ignoring the value of experiences like pain, happiness, autonomy, movement, and social relationships that affect everyone’s health⁵³. Extra-welfarist theory addresses these limitations by including the intangible value of health in the cost-benefit calculation by measuring inputs as dollars and outputs in units of health⁵³. Cost-effectiveness analysis and cost-utility analysis fit within the extra-welfarist paradigm because they compare the incremental difference in cost and health outcomes between two or more interventions⁵².

Table 1. Methods used in cost-effectiveness research.

Method	Input Unit	Output Unit	Output Example
Cost-benefit analysis	Monetary	Monetary	Dollars
Cost-minimization analysis	Monetary	Monetary	Dollars saved
Cost-effectiveness analysis	Monetary	Disease-specific health outcome	Dollars per increased unit of function
Cost-utility analysis	Monetary	Generic health outcome	Quality-adjusted life years

1.4.1 Quantifying Cost Inputs

Which costs are included in an economic evaluation depends on the perspective, as in whose point of view is taken when making a resource decision. The publicly funded healthcare payers perspective is recommended by the Canadian Agency for Drugs and Technologies in Health (CADTH) for economic evaluations conducted in Canada⁵⁹. However, section 1.2 describes that the AH only funds some services for OA management while most first-line treatments are

funded by private insurance and out-of-pocket. Experts in OA economic evaluations recommend collecting all relevant costs to manage the disease⁶⁰. In Alberta, this means it might be worthwhile to conduct economic evaluations from a broader perspective by also collecting costs funded by private insurance and out-of-pocket to capture all services being used to manage OA.

Costs can be measured with patient-reported questionnaires, cost diaries or administrative data. Cost-questionnaires are easily administered but accuracy, response rates, selection bias and recall bias are potential concerns⁶¹. Tan cross-referenced patient-reported physiotherapy visits with medical records and found 11% of participants accurately reported their attendance while 52% overreported and 38% underreported the number of physiotherapy sessions they attended⁶². Petrou et al. found patient-reported resource use was 90% accurate for hospital inpatient admissions, hospital-delivered outpatient services, and adverse events but 30% accurate for community-based care⁶¹. However, bias can be reduced by using validated patient-reported cost-questionnaires with a three-month recall period which was shown to produce accurate cost estimates compared to administrative data in sample of participants with hip and knee OA in New Zealand⁶³. Cost diaries may produce more reliable results but are more onerous to complete⁶⁴. Rather than relying on memory, many researchers use administrative data to collect healthcare resource use because it is a more robust method when the data is available^{65–70}. Canada has high quality administrative data for publicly funded services. However, a combination of data collection methods may be required if researchers wish to consider all services being used to manage OA funded publicly and privately.

1.4.2 Quantifying Health Outputs

Health can be measured in a variety of ways. Health economists prefer a generic health measure that is comparable across diseases which includes both quantity and quality of life (QOL)⁷¹. Quality adjusted-life years (QALY) capture these principles and are the most common health measure used in economic evaluations. QALYS are calculated by collecting patient-reported outcome measure (PROMS) in a sample over time.

Generic and disease-specific PROMs are routinely used by health economists to measure health-related QOL⁷². Generic PROMS ask overarching questions which can be applied to any condition while disease-specific measures ask narrow questions highly focused on the disease experience. Health economists prefer generic PROMs because they allow more accurate comparisons between different types of diseases although disease-specific PROMs allow a more sensitive comparison between interventions within the same disease⁷². The International Society for Pharmacoeconomics and Outcome Research (ISPOR) recommends collecting both generic and disease-specific PROMS when calculating cost-effectiveness^{59,73}.

The most popular generic PROM is the European Quality of Life 5-Dimension (EQ-5D)⁷⁴. EQ-5D five level version (EQ-5D-5L) evaluates five domains (self-care, usual activity, mobility, pain/discomfort, and anxiety/depression) with 5 response levels producing 3125 possible health states⁷⁴. EQ-5D-5L improves on the ceiling effects observed with the previous three-level version and is validated in the OA population in Alberta⁷⁵. Health-related QOL scores from generic PROMs like EQ-5D-5L are used to define health states. Each health state then has a

health utility weight ranging from 0.148 (worse than death) to 0.949 (maximum health) applied to it from the general population^{76,77}. Health utility is used to calculate QALYs by adding the time spent in each health state using an area under the curve calculation where a line is drawn between the health states at each time point⁵². QALYs gained or lost as costs are incurred can then be compared to the opportunity cost of different interventions in any disease.

Disease-specific PROMs such as the Knee Injury and Osteoarthritis Outcome Score (KOOS) and the Hip Injury and Osteoarthritis Outcome Score (HOOS) are recommended by Osteoarthritis Research Society International (OARSI) for OA research^{72,73}. KOOS and HOOS are validated disease-specific PROMs that can produce subscale scores for symptoms, function and QOL⁷⁸. Health economists could calculate the cost per incremental improvement in symptom or function subscales, but these estimates would only be comparable to other interventions for hip and knee OA.

1.4.3 How to Determine an Intervention is an Efficient Use of Resources

Cost-effectiveness describes the investment required for additional health gains⁵².

Theoretically, allocating resources to cost-effective interventions allows the funder to maximize the health benefit achieved with finite resources. However, it is possible for an intervention to be cost-effective, but unaffordable. A scenario may arise where a cost-effective intervention has a high price and large patient population which strains the budget of a publicly insured healthcare system. Affordability can be assessed with budget impact analysis methods to estimate the patient population and changes in healthcare expenditures over a budget cycle from implementing a new service^{79–81}. Cost-effectiveness investigates efficiency, while budget

impact analysis evaluates affordability. The combination of cost-effectiveness and budget impact analysis results produces comprehensive economic evidence that can be used to inform decision-making when a healthcare system considers adopting a new intervention.

1.4.4 Methodological Issues in Economic Evaluations of First-Line Osteoarthritis Treatments

In 2011, a systematic review of cost-effectiveness studies evaluating nonpharmacological and nonsurgical interventions for hip and knee OA synthesized 11 economic evaluations in the research field⁸². Pinto et al. found limited evidence supporting the cost-effectiveness of conservative treatments as well as poor methodological quality such as inconsistent comparators, time horizon, health outcome measures, costs and perspective⁸². They recommended conducting more high-quality economic evaluations by collecting generic PROMs to calculate QALYs, capturing all disease-related costs, measuring cost and effects for at least 1 year and comparing interventions to usual care⁸². In 2013, an expert panel released a consensus statement calling for better adherence to guidelines⁸³. The expert panel subsequently published a reference case which outlines standardized recommendations for population, perspective, comparators, time horizon, preferred health outcome, treatment effect measurement, and cost measurement to frame the boundaries of high-quality economic evaluation of OA interventions⁶⁰. In 2013, ISPOR also released the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) which is a 24 item checklist designed to improve the transparency of reporting characteristics of economic evaluations⁸⁴. Numerous economic evaluations of first-line OA treatments have been published since 2011, but a systematic review has not been conducted to synthesize the current literature in the research field and evaluate whether standardized methods impacted results.

1.5 Research Program Overview

International evidence shows that first-line OA treatments are underused. Implementing structured OA programs has helped increase use of first-line treatments in healthcare systems globally. The AHS BJH SCN™ supported GLA:D® implementation in Alberta since 2017, but the complex mixture of funding sources was identified as a barrier that produces cost-related inequitable access to the program^{39,85}. Equitable access to publicly funded care is a core value at AH with the organization seeking to reduce inequitable service variation across the province⁸⁶. Determining an equitable funding model for GLA:D® is a strategic priority as the BJH SCN™ seeks to scale the program across Alberta^{39,87}. This thesis seeks to develop a body of evidence that can help decision-makers identify a funding model that provides equitable access to GLA:D® in Alberta.

This body of research includes four major components that were written for an international audience and submitted to international peer-review publications. We conducted a systematic review (Chapter Two) as preliminary work to understand the methods researchers used to evaluate the cost-effectiveness of first-line treatments in other healthcare systems around the world. In Chapter Three we attempted to define usual care (UC), the standard nonsurgical treatments used by people with OA, then compared these findings to international evidence-based OA clinical guidelines. Chapter Four presents our cost-effectiveness analysis where we compared patient-level cost and outcomes between GLA:D® and UC to calculate the ‘value for money’ of structured education and exercise therapy. Since user fees are known to impact use of healthcare resources, we built a budget impact analysis (BIA) model to estimate the fiscal

implications if the AH publicly funded GLA:D® as people wait for TJR consultation in Alberta (Chapter Five). Together, this collection of manuscripts reports the need, value, and affordability of GLA:D® in Alberta, Canada.

2 ARE EDUCATION, EXERCISE AND DIET INTERVENTIONS A COST-EFFECTIVE TREATMENT TO MANAGE HIP AND KNEE OSTEOARTHRITIS? A SYSTEMATIC REVIEW

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Our systematic review presented in this chapter was completed as preliminary work to understand the methods used when evaluating the cost-effectiveness of first-line OA treatments in other healthcare systems around the world. Our systematic review helped us understand the methodological challenges and assess the transferability of results from other jurisdictions to the Canadian context. There are six threats to the transferability of cost-effectiveness results between countries: 1) general population health-state preferences, 2) epidemiology of the disease, 3) practice patterns, 4) health system characteristics, 5) relative prices and 6) opportunity costs of resource use^{88,89}. Osteoarthritis epidemiology is similar in western countries where economic evaluations have been produced but local practice patterns, health system characteristics, prices, and opportunity costs of resource use differ substantially between previously reported trial-based economic evaluations and the Canadian context. We used our systematic review's findings to develop the study design reported in Chapter Four.

2.1 ABSTRACT

Objective: To identify research gaps and inform implementation we systematically reviewed the literature evaluating cost-effectiveness of core treatments (education, exercise, and diet) for the management of hip and/or knee OA.

Methods: We searched Medline, Embase, Cochrane Central Register of Controlled Trials, National Health Services Economic Evaluation Database, and EconLit from inception to November 2019 for trial-based economic evaluations investigating hip and/or knee OA core treatments. Two investigators screened relevant publications, extracted data, and synthesized results. Risk of bias was assessed using the Consensus on Health Economic Criteria list.

Results: Two cost-minimization, five cost-effectiveness and 16 cost-utility analyses evaluated core treatments in six health systems. Exercise therapy with and without education or diet was cost-effective or cost-saving compared to education or physician-delivered usual care at conventional willingness to pay (WTP) thresholds in 15 out of 16 publications. Exercise interventions were not more cost-effective than physiotherapist-delivered usual care in three studies at conventional WTP thresholds. Education interventions were not cost-effective compared to usual care or placebo at conventional WTP thresholds in three out of four publications.

Conclusions: Structured core treatment programs were clinically effective and cost-effective, compared to physician-delivered usual care, in five healthcare systems. Providing education about core treatments was not consistently cost-effective. Implementing structured core treatment programs into funded clinical pathways would likely be an efficient use of healthcare system resources and enhance physician-delivered usual primary care.

2.2 INTRODUCTION

Hip and knee osteoarthritis (OA) pose a substantial burden to individuals and health systems⁹⁰. International guidelines recommend education, exercise, and dietary weight management (if appropriate) as core treatments for hip and knee OA regardless of disease severity and co-morbidity¹⁵. Core treatments are safe, appropriate, and effective but uptake of these proven treatments remains low⁹¹. Evaluating cost-effectiveness can support implementation of core treatments in healthcare systems and reimbursement plans⁹².

Economic evaluations allow decision-makers to understand the consequences of resource allocation decisions by comparing cost and health outcomes of two or more interventions⁵². A cost-effective treatment provides additional health benefit at additional cost but within the decision-makers' willingness to pay (WTP) for those health benefits⁵². A previous systematic review of cost-effectiveness research for nonsurgical and nonpharmacological OA treatments found limited studies that used poor quality methodology⁸². Since then, a reference case was published to outline minimum criteria for economic evaluations of OA treatments⁶⁰. Evaluating and synthesizing the current literature will identify research gaps and inform appropriate implementation. We systematically reviewed the literature evaluating cost-effectiveness of core treatments (education, exercise, and dietary weight management) for management of hip and/or knee OA.

2.3 METHODS

We followed the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines and specific recommendations for systematic reviews of economic evaluations^{93–96}.

Our PRISMA checklist is in Appendix B. We prospectively registered our protocol with PROSPERO (Registration Number CRD42020155964; accepted 28/04/2020).

2.3.1 Eligibility criteria

We included full economic evaluations conducted alongside randomized or nonrandomized clinical trials of people with hip and/or knee OA receiving education, exercise, and dietary weight management interventions compared to any control. Education was defined as any formal instruction about OA and self-management techniques¹⁵. We defined exercise as any prescribed activity requiring muscular contraction¹⁵. Dietary weight management was defined as any type of intervention with the goal of caloric restriction¹⁵. Full trial-based economic evaluations compare two or more comparators using a cost-utility analysis (CUA), cost-effectiveness analysis (CEA), cost-benefit analysis (CBA) or cost-minimization analysis (CMA)⁵². Publications were excluded if they did not have a comparator or evaluated surgical, pharmaceutical, or nutraceutical interventions.

2.3.2 Literature search and study selection

We modified published search filters⁹⁷ to develop the search strategy in Appendix C. Medline, Embase, Cochrane Central Register of Controlled Trials (CENTRAL), National Health Services Economic Evaluation Database, and EconLit were searched from inception to November 2019 without restriction in year or language. PubMed was not included because Medline records are

almost identical. Search quality was evaluated by ensuring a list of known economic evaluations were included in the retrieved records.

All retrieved records were imported to Covidence, a web-based data management tool designed for synthesizing healthcare evidence⁹⁸. Two authors (DRM and AA) used a pre-defined screening process to independently review titles and abstracts. Conflicts were resolved by consensus or a content matter expert (JHA and DAM). Full-text articles were screened using a similar process. During full-text review we contacted authors of study protocols and conference abstracts when a subsequent published manuscript was not found. Authors were given 8 weeks to respond. Alerts were set up in each database to notify DRM if additional publications met our inclusion criteria. May 27, 2020 was our final cut-off date for including publications.

2.3.3 Data Extraction and Synthesis

Two authors (DRM and AA) split data extraction. Twenty-six items from the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist were extracted⁸⁴. CHEERS outlines best practice for reporting economic evaluations⁸⁴. We also extracted country, model of delivery, resource use assumptions, inflation rate, health outcomes, intervention costs, and the conclusion about cost effectiveness made by the authors. The primary outcome in an economic evaluation is the incremental difference in cost and outcomes between interventions and control. A CUA produces an incremental cost-utility ratio (ICUR) reported as cost per quality-adjusted life year (QALY), whereas a CEA produces an incremental cost-effectiveness ratio

(ICER) reported as cost per health outcome. DRM reviewed all extracted data to ensure accuracy.

2.3.4 Synthesis of Results

A meta-analysis was not attempted because methods for pooling cost-effectiveness estimates do not currently exist⁹⁹. Subgroup analysis was attempted to identify common themes producing a cost-effective recommendation. We used these subgroups: randomized versus nonrandomized study designs, type of treatment received, type of comparator, country, and OA population based on inclusion criteria.

2.3.5 Risk of Bias Assessment

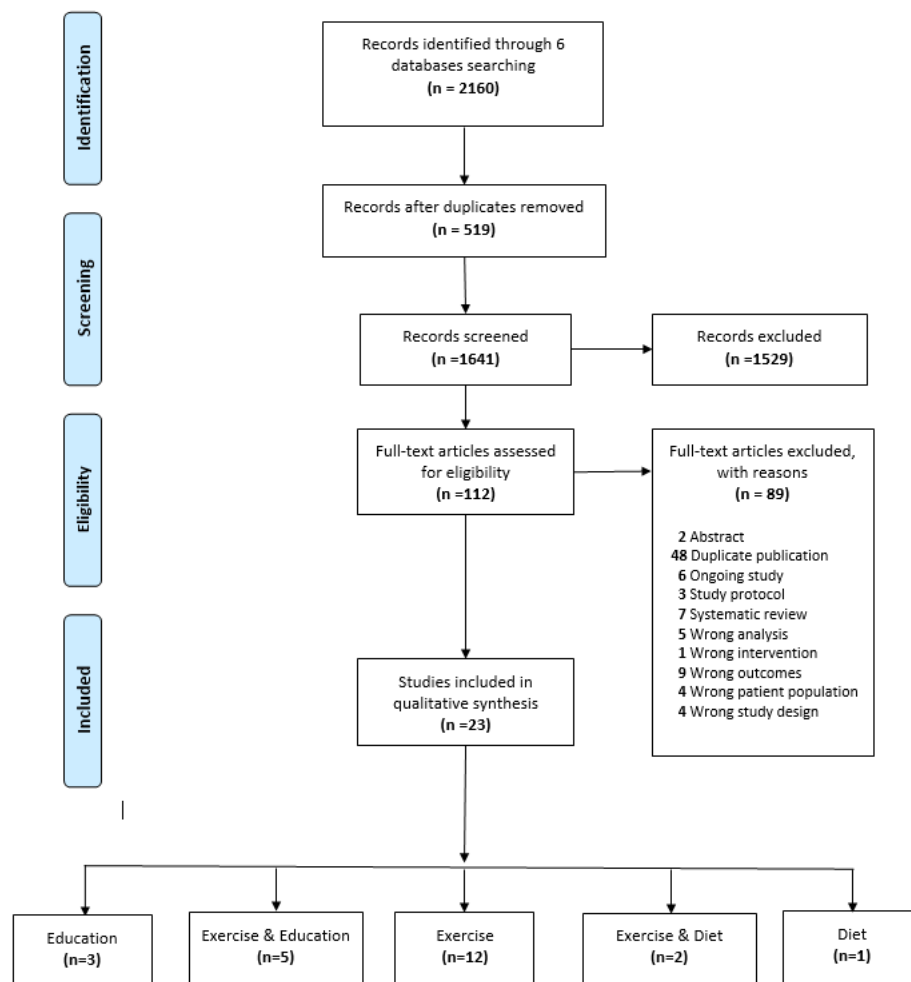
Two authors (DRM and AA) independently assessed risk of bias using the Consensus on Health Economic Criteria (CHEC) list¹⁰⁰. CHEC list is a validated risk of bias tool with 19 yes-or-no questions¹⁰⁰. CHEC list was designed and is recommended for systematic reviews of trial-based economic evaluations^{94,100,101}. Like Odnoletkova et al., we added one additional question to assess model-based analyses because two publications met our inclusion criteria but modelled outcomes over longer time horizons than the observational time period^{66,69,102}. We followed the CHEC list instructions, recording “yes” when study authors appropriately considered the characteristic and “no” when characteristics were not reported, justified, and adequately considered¹⁰³. We added an intermediate category, “unclear,” to differentiate from “no” when authors reported a characteristic but did not adequately consider or provide justification. A cumulative quality score was not reported because the CHEC list does not have a quality scoring

scheme. Whether current instruments can discriminate between high- and low-quality economic evaluations is also up for debate¹⁰⁴.

2.4 RESULTS

We obtained 2,160 relevant records, 1,641 titles and abstracts were screened, 122 articles were reviewed, and 23 publications met our inclusion criteria (Figure 1). One author contributed preliminary results to our review¹⁰⁵.

Figure 1. Prisma flow diagram of study selection.

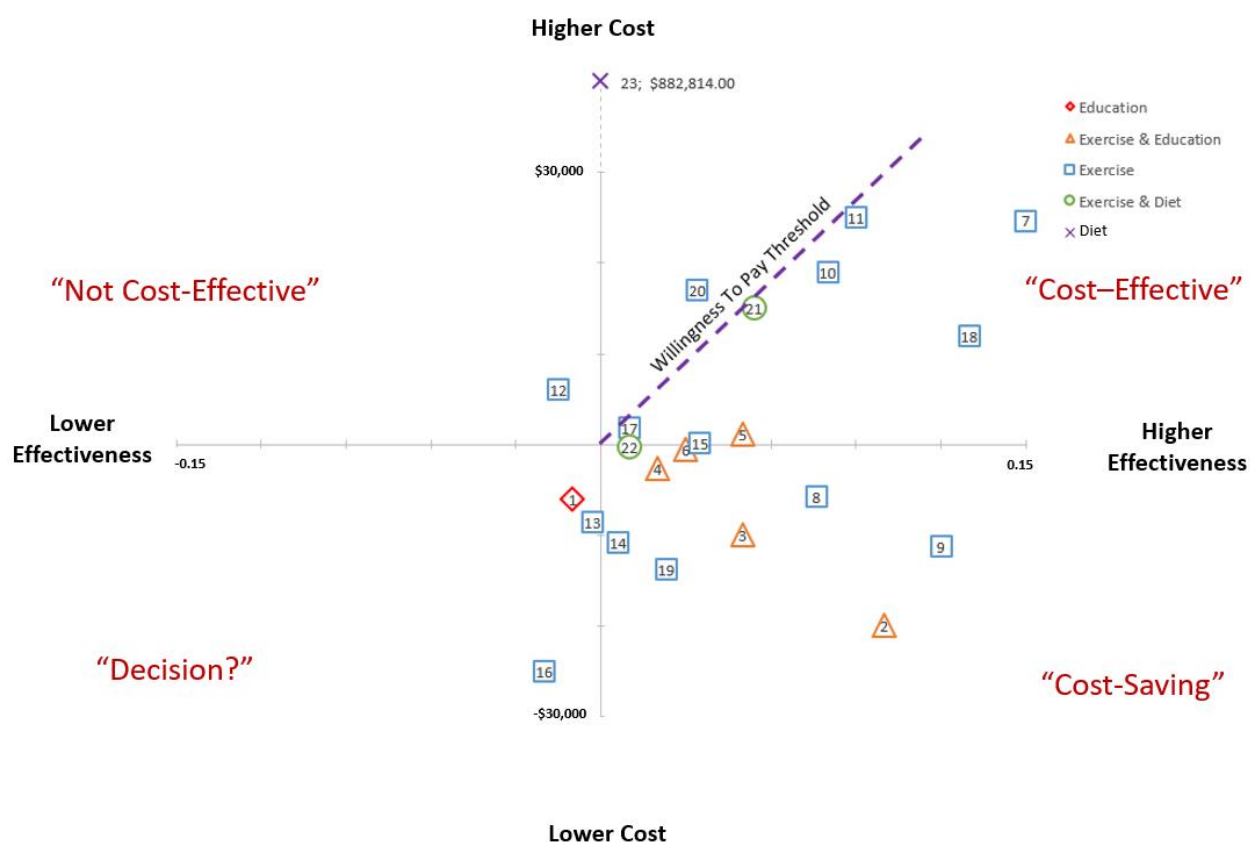


We included two cost-minimization¹⁰⁶, five cost-effectiveness^{107–111} and 16 cost-utility analyses^{62,64–68,105,112–120}, characteristics of each study are described in Appendix D, Table 1. Authors reported a societal^{64,66,115,121}, healthcare payer^{67,68,109,110,119,120} or both perspectives^{62,65,66,105,106,106–108,111–114,116,118}. One author did not explicitly report a chosen perspective¹¹⁷. European Quality of Life 5-Dimension (EQ-5D) was the most common generic patient-reported outcome measured (PROM) used to calculate health utility. Three publications collected patient-level data then modelled two year⁶⁶, five year¹⁰⁵, and lifetime horizons¹¹³.

We classified studies reporting lower incremental costs and improved outcomes as cost-saving (no ICUR is reported in these cases)⁵². Seven studies concluded interventions were cost-saving^{62,70,108,110,115,117,121}, nine studies concluded interventions were cost-effective^{66,67,105,107,111–113,116,119} and seven studies concluded interventions were not cost-effective compared to the control^{64,65,68,106,114,118} (Appendix D, Table 2). Converted to 2019 US dollars using purchasing-power-parity exchange rates, 16 CUA's produced an ICUR ranging from cost-saving to \$882,814/QALY^{62,64–68,105,112–121}. Fifteen out of 19 exercise interventions with and without education and diet adjunct therapies reported cost-effective or cost-saving results compared to control on the cost-effectiveness plane while two diet and education interventions were not cost-effective compared to control (Figure 2). Two CMAs were not included in the figure but reported conflicting results^{70,106}. Three studies observed ceiling effects using EQ-5D three-level version (EQ-5D-3L) to calculate health utility^{64,119–121}. Four studies suggested cost-questionnaire recall bias may impact cost estimates^{62,66,68,109}. Three studies cautiously interpreted results

because sample sizes were underpowered for economic evaluation^{65,115,117}. Including surgical costs modified results in four studies^{62,68,112,116}.

Figure 2. Cost-effectiveness plane representing intervention compared to control.



Number Legend

1: Patel, 2009	2: Hurley, 2012	3: Jessep, 2009
4: Hurley, 2007	5: Fernandes, 2017	6: Bennell, 2016
7: Abbott, 2019	8: Abbott, 2019 (5yr obs)	9: Abbott, 2019 (LT model)
10: Bove, 2018 (2 yr obs)	11: Bove, 2018 (5 yr model)	12: Kigozi, 2018
13: Kloek, 2018	14: Tan, 2016	15: Pinto, 2013
16: Coupe, 2007	17: Thomas, 2005*	18: Cochrane, 2005
19: Richardson, 2004	20: Sevic, 2009*	21: Losina, 2019 (LT model)
22: Sevic, 2000*	23: O'Brien, 2018	

*= Cost-Effectiveness Analysis, yr = Year, obs = Observed, LT = Lifetime

Note: All costs converted to 2019 US Dollars

Note: CMA were not included in this figure

Note: This figure illustrates the position of each study relative to the axes and willingness to pay threshold. Comparing the relative position of studies is not recommended, as it does not account for different comparators and health care system characteristics.

2.4.1 Exercise Interventions

Twelve studies evaluated exercise interventions compared to either physician-delivered usual care^{62,105,112,116,121,121}), physiotherapist-delivered usual care^{64,65,68}, exercise^{66,119,120}, or education^{110,111}. Three publications evaluating the Management of OsteoArthritis (MOA) trial showed a three-month physiotherapy supervised multimodal exercise program with and without adjunct manual therapy was cost-effective or cost-saving compared to physician-delivered usual care over one, two and five years at a WTP threshold of NZ\$42,981 (one times 2009 gross domestic product per capita) in New Zealand (NZ)^{105,112,116}. Bove et al. observed a similar supervised multimodal exercise program with booster sessions were cost-effective at a US\$100,000/QALY WTP threshold compared to exercise only in the United States (US)⁶⁶. Sevick et al. also observed a three-month supervised exercise program, and 15-month home exercise program would reduce healthcare utilization and improve OA symptoms compared to education in the US¹¹⁰. In the Netherlands (NL), Tan et al. found exercise therapy was cost-effective at €20,000/QALY WTP threshold compared to physician-delivered usual care, but Coupe et al. showed a comparable exercise intervention had negligible difference in cost and outcomes compared to usual care delivered by a physiotherapist^{62,64}. Klok et al. found a supervised exercise session with an online platform to monitor exercise dosage and symptoms was not cost effective at €10,000/QALY WTP threshold compared to physiotherapist-delivered usual care in NL as well⁶⁵. Four studies evaluating exercise interventions in the United Kingdom (UK) found class-based exercise had lower ICERs compared to physician-delivered usual care or

a home exercise program but exercise therapy with 8-12 sessions was a similar ICER compared to exercise therapy with four sessions^{68,111,119–121}.

2.4.2 Exercise and Education Interventions

Five studies evaluated exercise and education interventions compared to either physician-delivered usual care^{107,108}, physiotherapist-delivered usual care¹¹⁷ or education, physiotherapist-delivered usual care¹¹⁷ or education^{67,115}. In the UK, the Enabling Self-Management and Coping with Arthritic Knee Pain through Exercise (ESCAPE-pain) program, a self-management education and progressive exercise program, was cost-effective at one year and cost-saving over 30-months compared to physician-delivered usual care at £0 and £6,000 WTP thresholds^{107,108}. ESCAPE-pain was adapted into a community-based format delivering a standardized six-week group program producing more QALYs and costing less than physiotherapist-delivered usual care¹¹⁷. The MEDIC study consisting of education and 12-week group exercise program was cost-effective compared to an education pamphlet for people with knee OA receiving pre-surgical consultation in Denmark at conventional WTP thresholds⁶⁷. In Australia (AU), Bennell et al. used frequentist statistics to report combined exercise therapy and pain coping skills training led to small QALY improvements for marginally less costs compared to pain coping skills training alone, but findings were not statistically significant¹¹⁵.

2.4.3 Exercise and Diet Interventions

Two studies in the US evaluated the combination of exercise and diet compared to physician-delivered usual care or a healthy lifestyle education program^{109,113}. Sevvick et al. used a CEA to show an intensive 18-month diet and exercise intervention with the goal of 5% weight loss

would likely be an efficient use of healthcare resources compared to a healthy lifestyle control¹⁰⁹. Losina et al. used a validated OA model to perform a CUA showing an intensive 18-month Intensive Diet and Exercise for Arthritis (IDEA) intervention was cost-effective at US\$50,000/QALY WTP threshold compared to physician-delivered usual care over a lifetime horizon¹¹³. The IDEA trial aimed for 10% weight loss using a structured intensive daily caloric restriction program with an 18-month facility or home-based exercise intervention completed three times per week¹²².

2.4.4 Diet Interventions

O'Brien et al. showed telephone-delivered weight loss consultations to individually tailor national dietary and physical activity guidelines did not produce a clinical benefit and cost more compared to physician-delivered usual care for participants with knee OA waiting for a surgical consultation in AU¹¹⁴.

2.4.5 Education Interventions

Three studies evaluated education interventions compared to either physician-delivered usual care¹⁰⁶ and education¹¹⁸ or placebo⁷⁰. Mazzuca et al. conducted a CMA in the US, which assumes health outcomes were the same, and reported health system cost-savings from an intervention with an arthritis educator nurse recommending exercise, pain management, and joint protection⁷⁰. Lord et al. also conducted a CMA showing the nurse-led group education in the UK increased costs compared to physician-delivered usual care in the UK¹⁰⁶. Patel et al. used a more rigorous CUA to determine group education produced fewer QALYS and cost less compared to an education booklet in the UK health system¹¹⁸.

2.4.6 Subgroup Analysis

Eight exercise interventions were considered either cost-saving or cost-effective compared to controls. An additional seven studies found structured exercise therapy with education or diet as an adjunct to exercise therapy were cost-saving or cost-effective compared to controls. No trends were observed in the subgroup analysis for intervention, country, or inclusion criteria. There were not enough nonrandomized studies to conduct a subgroup analysis compared to randomized studies.

2.4.7 Risk of Bias Assessment

Methodological quality has improved since the previous systematic review and reference case were published (Figure 3)^{60,82}. Twelve additional studies have been reported since the previous systematic review and 10 studies since the reference case was published. Identification of costs were insufficient when all costs in the chosen perspective were not identified^{66,109,110,115,121}. Supported by evidence from Petrou et al. we defined cost-questionnaires with longer than three-month recall insufficient for accurately measuring costs^{61,66,68,107,108,110,114,117,121}. We considered outcomes to be valued inappropriately if justification was not provided for using population weights from a different country^{64,106,108–112,114–117,121}. Economic evaluations over a period of longer than one year did not use a discount rate^{64,68,110} or used 3%^{66,113}, 3.5%, and 5%^{109,111}. Discount rates were not included over one year^{64,67,68,110} and appropriate justification was not provided for studies under one year^{62,70,106,115,117}. Eight authors did not sufficiently explore the generalizability of their findings to the decision-making context^{62,64,70,110,111,113,114,117,118}. Only three publications provided sufficient ethical

considerations related to the distribution of treatment benefits within the general population^{116,118,121}.

Figure 3. Authors' risk of bias assessment using the CHEC list.

Study	Patient Population	Competing Alternatives	Research Question	Economic Study Design	Time Horizon	Perspective	Costs Identified	Costs Measured	Costs Valued	Outcomes Identified	Outcomes Measured	Outcomes Valued	Incremental CE Analysis	Discounting	Uncertainty Analysis	Conclusions	Generalizability	Conflict of Interest/Funding	Ethical Issues/Distribution	Modelling
Abbott et al. 2019												?							N	N/A
Losina et al. 2019																	?		N	
Bove et al. 2018							N	?											N	
Kigozi et al. 2018						?		?						N					N	N/A
Kloek et al. 2018																			?	N/A
O'Brien et al. 2018					N			?				?					?		N	N/A
Fernandes et al. 2017						?								N					N	N/A
Bennell et al. 2016							N					?		?	?			N	N	N/A
Tan et al. 2016														?			?		N	N/A
Pinto et al. 2013.												?								N/A
Hurley et al. 2012								?		N		N						N	N	N/A
Jessep et al. 2009						N		?				N	N	?	N	N	N	N	N	N/A
Patel et al. 2009																	N			N/A
Sevick et al. 2009						?	N					N			N	?		N	N	N/A
Coupe et al. 2007												?	N	N				N		N/A
Hurley et al. 2007					N			?							?	?		N	?	N/A
Richardson, 2006						?													N	N/A
Cochrane et al. 2005						?	?	?				?	?		?					N/A
Thomas et al. 2005	?					N				N		N					N	N	N	N/A
Sevick et al. 2000						?	N	N				N		N	N	?	N	N	N	N/A
Lord et al. 1999												N	N	?					N	N/A
Mazzuca et al. 1999				N		N								?	N		?	?	N	N/A

Reference case published in 2014

Yes, appropriately considered by authors

?, Unclear, not appropriately considered or justified by authors

N, No, not appropriately reported, considered or justified by authors

N/A, Not Applicable, not required in this article

Note: Risk of bias assessment was not conducted on preliminary results from Abbott, 2019¹⁰⁵.

2.5 DISCUSSION

Exercise interventions with or without education and diet adjunct therapies compared to physician-delivered usual care or education appear to be cost-effective or cost-saving at

conventional WTP thresholds in numerous healthcare systems. We found 15 out of 16 publications concluded exercise interventions (four with education and two with diet) were cost-effective or cost-saving compared to education or physician-delivered usual care at conventional WTP thresholds while three publications reported exercise interventions compared to physiotherapist-delivered usual care were not cost-effective at conventional WTP thresholds. Cost-effectiveness of core treatments seems to depend on the effectiveness of the intervention, the comparator, and healthcare system characteristics.

More structured interventions appear to be clinically effective and cost-effective while less structured interventions are not. Highly structured programs such as MOA, ESCAPE-pain, MEDIC, and IDEA produced significant clinical benefits and were cost-effective compared to physician-delivered usual care at conventional WTP thresholds^{105,107,108,112,113,116}. Meanwhile providing only education about appropriate self-management, exercise, and diet for OA did not consistently produce incremental health benefits at or below conventional WTP thresholds compared to physician-delivered usual care or placebo^{70,106,114,118}. Similar findings were observed in a recent publication showing physician and nurse teams providing education and medication review aligning with National Institute for Health and Care Excellence (NICE) clinical guidelines is not an adequate intervention for people with hand, hip, knee, and spine OA¹²³. Structured programs might improve clinical effectiveness and cost-effectiveness by encouraging treatment adherence. Kigozi et al. found treatment adherence was an effect modifier impacting clinical effectiveness and cost-effectiveness results when evaluating specific exercise programs compared to physiotherapist-delivered usual care⁶⁸. Structured programs are also expected to

produce incremental health benefits for multiple years after the intervention has been completed^{66,105,113}. Although more costly to deliver, a structured supervised program may improve treatment adherence thereby enhancing clinical effectiveness and making the program a worthwhile investment at conventional WTP thresholds.

‘Usual care’ was the most common comparator although 10 publications used physician-delivered usual care and four publications evaluated usual care delivered by a physiotherapist. Usual care provided by a primary care physician and physiotherapist are markedly different which may have led to different conclusions. Participants receiving usual care from a physiotherapist are likely being prescribed exercises whereas physician-delivered usual care may include general physical activity recommendations but specific exercise prescription would be unlikely. The incremental treatment difference between a specific exercise program and usual care delivered by a physiotherapist is likely smaller than evaluating an exercise program compared to physician-delivered usual care. The incremental difference between intervention and control arms is likely to show different cost-effectiveness conclusions when usual care is delivered by a physician or physiotherapist. Our results suggest that adding structured programs delivering core treatments into healthcare systems where OA is managed by primary care physician without physiotherapist support would likely produce incremental treatment effects within the cost decision-makers are willing to pay for those greater health benefits.

Optimizing care by integrating core treatments into clinical pathways would likely deliver clinically effective and cost-effective care to people managing OA. Previous systematic reviews

show surgical and pharmacological interventions are also cost-effective for the appropriate person living with OA^{15,124–126}. Marra et al. found a pharmacist-led optimized care intervention was cost-effective compared to physician-delivered usual care at conventional WTP thresholds in Canada¹²⁷. The pharmacist led intervention included a medication review, communication with the primary care physician, referral to a structured education and exercise intervention delivered by a physiotherapist, and follow-up pharmacist consultations¹²⁷. Cost-effectiveness of optimized primary care interventions may also be underestimated if nonsurgical OA management programs delay or avoid surgery. A recent trial-based economic evaluation of total knee arthroplasty observed 68% of surgical candidates randomized to an exercise therapy intervention had not proceeded to surgery two years after the study period¹²⁸. This exercise and education program would pay for itself if 8% of people with knee OA avoided a total joint replacement¹²⁹. An integrated pathway aligning with OA clinical guidelines would be cost-effective in multiple healthcare systems but could be cost saving if total joint replacement were avoided.

Our results contribute several notable observations since the previous systematic review produced by Pinto et al.⁸². Many authors have conducted trial-based economic evaluations over one year or longer, consistently applied discount rates and compared interventions to usual care since Pinto et al. recommended these methodological improvements. Cost-utility analyses are also the primary type of full economic evaluation being conducted. Most recent studies have reported both a societal and healthcare payer perspective which aligns with ISPOR good practice guidelines, the reference case, and CHEC List^{60,72,103}. Healthcare payer perspectives are

being produced at the same time which continue to align with national regulatory guidelines^{59,84,100}.

Although study quality has improved, some methodological challenges persist.

Only one publication in this systematic review collected EQ-5D five-level version (EQ-5D-5L)⁶².

To address the limitations of the EQ-5D-3L, the EQ-5D-5L was developed in 2011 and has been validated in the OA population^{75,130,131}. General population preference weights are available in numerous countries, so it remains unclear why authors continue to use EQ-5D-3L for OA populations when the EQ-5D-5L accounts for well-reported ceiling effects^{75,131}.

Collecting resource use with cost-questionnaires was highly variable and impacted methodological quality in several papers. Cost-questionnaires are easily administered but recall bias is a concern⁶¹. Tan cross-referenced patient-reported physiotherapy visits with medical records and found 11% of participants accurately reported their attendance while 52% overreported and 38% underreported the number of physiotherapy sessions they attended⁶². Petrou et al. found patient-reported resource use was 90% accurate for hospital inpatient admissions, hospital-delivered outpatient services and adverse events but 30% accurate for community-based care⁶¹. Cost diaries may produce more reliable results but are more onerous to complete⁶⁴. Rather than relying on memory, administrative data was a more robust method used by six publications for collecting healthcare resource^{65–68,70,113}. Abbott and Pinto validated the Osteoarthritis Cost and Consequences Questionnaire showing patient-reported cost-

questionnaires can produce a good cost estimate as an alternative to collecting administrative data in NZ⁶³.

2.5.1 Policy Implications

Integrating core treatments into clinical pathways and healthcare payment plans would likely be a worthwhile investment at conventional WTP thresholds. Overall healthcare system performance would likely improve if healthcare systems providing physician-delivered usual care implemented structured OA management programs which include exercise therapy with or without diet and education. Healthcare systems currently delivering core treatments in clinical pathways must carefully consider the added benefit and cost of adjunct therapies to encourage long-term treatment adherence and behavior change.

2.5.2 Strengths and Limitations

Our review focused on trial-based economic evaluations because methodological differences limit comparability of model and trial-based studies, trials are more common than models in this research field, and trial-based economic evaluations allow for a more robust comparison by collecting patient-level cost and outcomes^{83,94,101,132,133}. Data for all characteristics in the CHEERS checklist was extracted but we did not use CHEERS to assess risk of bias because it is designed to assess quality of reporting instead of quality of conducting an economic evaluation⁸⁴. Although reporting and conducting are related, checklists such as the CHEC list have been developed specifically for assessing methodological quality⁸⁴.

Study designs and healthcare system characteristics continue to limit comparability between trial-based economic evaluations. Limited comparability and absence of meta-analysis techniques to pool cost-effectiveness estimates limit the ability of systematic reviews of economic evaluations to draw strong conclusions like systematic reviews of clinical trials. Our multi-purpose systematic review was conducted to critically appraise the literature so we did not take the additional step of assessing the clinical trials risk of bias using Grading of Recommendations Assessment, Development and Evaluation (GRADE) which is recommended when the purpose of systematically reviewing economic evaluations is to inform clinical practice guidelines^{95,134}. Lastly, assessing risk of bias in economic evaluations will include some level of subjectivity based on authors' knowledge and biases. We attempted to reduce bias by independently applying the CHEC list and strictly adhering to the assessment instructions¹⁰³. When our interpretation of instructions differed a content matter expert (DAM) would resolve conflicts. Disagreements and final decisions were documented to create decision rules which were uniformly applied across all studies.

2.5.3 Recommendations for Future Research

Analysts can assess whether the studies reported in this systematic review are transferrable to inform local decisions. Modelling techniques or additional trial-based economic evaluations might be needed if these publications cannot inform local decisions. Analysts can also support local decisions by conducting budget impact analyses to estimate the affordability of implementing core treatments into clinical pathways. Future research should develop and evaluate a feasible diet intervention. Integrating a cost-effective and affordable diet intervention into clinical pathways would benefit many people living with OA and may have additional health benefits for people living with multimorbidity. Whether core treatments reduce the risk of surgical intervention is an outstanding question. Evaluating long-term follow-up (i.e. 5 or 10 years) of previously published randomized controlled trials of core treatment may identify whether core treatments modify risk of surgical interventions.

Future economic evaluations of OA interventions should align methods with the reference case and take additional steps to collect high-quality data using administrative data, validated cost-questionnaires, and the most current PROMs⁶⁰. Administrative data is preferred for collecting health resource use. Patient-borne costs can be collected using validated cost-questionnaires in three-month time periods or less to limit recall bias. If authors use the EQ-5D, we also recommend the five-level version instead of the three-level to mitigate ceiling effects observed in OA populations^{75,131}. Lastly, treatment adherence and surgical costs should be evaluated in sensitivity analyses for all future studies evaluating cost-effectiveness of core treatments for OA. Measuring adherence will enable analysts to conduct sensitivity analysis to evaluate how adherence impacts cost-effectiveness results.

2.5.4 Conclusion

Exercise interventions with or without education and diet as adjunct therapies appear to be cost-effective in numerous health systems although variability in study designs limit comparability. These findings suggest healthcare system performance would likely benefit from integrating high quality, supervised exercise programs into funded or insured clinical pathways.

3 DO PEOPLE WITH KNEE OSTEOARTHRITIS USE GUIDELINE-CONSISTENT TREATMENTS AFTER AN ORTHOPAEDIC SURGEON RECOMMENDS NONSURGICAL CARE? A CROSS-SECTIONAL SURVEY WITH LONG-TERM FOLLOW-UP

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Mazzei DR, Whittaker JL, Kania-Richmond A, Faris P, Wasylak T, Robert J, et al. *Do people with knee osteoarthritis use guideline-consistent treatments after an orthopaedic surgeon recommends nonsurgical care? A cross-sectional survey with long-term follow-up*. *Osteoarthritis and Cartilage Open* 2022: 100256.

Ample research shows first-line OA treatments are underused globally¹³⁵, but more evidence was needed to understand the Alberta context. Previous research showed that 40% of Albertans had not used first-line OA treatments prior to undergoing TJR³⁸. However, 30% of people receiving a TJR consultation are not recommended joint replacement. This presented an opportunity for our research team to understand what community-based services people use to manage their OA when recommended nonsurgical care.

3.1 ABSTRACT

Objective: Describe “usual care” patterns of education, exercise, weight management, pain medication, and other nonsurgical treatments for knee osteoarthritis (OA) in a cohort of people recommended for nonsurgical care by an orthopaedic surgeon.

Methods: We used a telephone-administered questionnaire to capture treatments people with knee OA used over the three to six years after an orthopaedic surgeon recommended nonsurgical care in Alberta, Canada. The primary outcome, guideline-consistent nonsurgical treatments, was an aggregate measure defined as using education, exercise, weight management, and at least one recommended medication. Secondary outcomes were first-line (education, exercise, and weight management) and guideline-inconsistent treatments (joint protection, opioids, hyaluronic acid, platelet rich plasma, and stem cell therapy). Multivariable robust Poisson regression assessed the association between participant characteristics and use of guideline-consistent, first-line, and guideline-inconsistent treatments.

Results: 479 people were invited and 250 participated (52%). Participants were 58% female with a mean age 66.2 (+/- 1.01) years. Participants received education by a healthcare professional (64%), exercised regularly (74%), used weight management (38%), and used recommended pain medications (91%). All guideline-consistent nonsurgical treatments were used by 19% of participants, 19% of participants used first-line treatments, and 42% used guideline-inconsistent treatments. Over six years, 34% had another consult then underwent arthroplasty. Older participants were less likely to use any treatment. People with post-secondary education were more likely to use first-line treatments, and males were more likely to use guideline-inconsistent treatments.

Conclusions: Nonsurgical usual care for people with knee OA in Alberta, Canada was not consistent with international clinical guidelines.

3.2 INTRODUCTION

Rising incidence of knee osteoarthritis (OA) creates significant burden on individuals and health systems^{90,136}. International clinical guidelines recommend knee OA be treated with a stepped approach focused on symptom management¹⁵. Education, exercise, and weight management are recommended as first-line treatments¹⁵, meaning the primary treatment in standard clinical practice⁴, for everyone with knee OA. Pharmaceutical pain management is provided as an adjunct when first-line treatments do not adequately relieve symptoms⁴. Total joint replacement (TJR) is appropriate when nonsurgical (first-line and pharmaceutical) treatments are not sufficient for symptom management¹⁷.

International evidence suggests first-line treatments for knee OA are underused while pharmaceutical and surgical treatments are overused^{19,91,137,138}. Previous research investigated use of nonsurgical treatments over short periods^{19,91,137,138}, but knee OA is a chronic disease and long-term use of these services are unknown. In addition, prior research has focused on evaluating nonsurgical treatment use before being referred to the orthopaedic surgeon, not the people with knee OA who attend an initial orthopaedic consultation regarding TJR who are not surgical candidates (approximately 40 percent of those referred³⁸. First-line and pharmaceutical treatments would typically be recommended to manage symptomatic knee OA for people who are not surgical candidates, but the actual use of these services after consultation is unknown.

We sought to fill this knowledge gap by evaluating long-term use of nonsurgical treatments after an orthopaedic surgeon consultation.

Understanding what treatments people choose and how these strategies align with international clinical guidelines can help decision-makers close evidence-practice gaps by designing and implementing new services for people with symptomatic knee OA who are not currently eligible for TJR. This study describes “usual care” patterns (the mixture of treatments currently being used) in a cohort with knee OA who were not surgical candidates and identifies the participant characteristics associated with nonsurgical treatment use.

3.3 METHODS

We followed the guidelines for reporting cross-sectional studies¹³⁹.

3.3.1 Study and Design

This cross-sectional study was nested within a prospective cohort study (BEST-Knee)^{140,141}.

Participants attended a TJR consultation at a high-volume bone and joint central intake clinic with 25 orthopaedic surgeons in Edmonton, Alberta, Canada between October 27, 2014 and September 30, 2016. An orthopaedic surgeon confirmed knee OA as the primary diagnosis but did not recommend TJR during this initial consultation. Participants were re-engaged between October 28, 2019, and February 3, 2020, to capture the nonsurgical (education, exercise, weight management, and pharmaceutical) treatments used to manage their OA symptoms since the initial orthopaedic consultation.

3.3.2 Participants

Participants were enrolled if they previously consented to participate in the BEST-Knee Study^{140,141}, had an orthopaedic surgeon diagnosis of knee OA, were deemed inappropriate for surgical intervention during the initial orthopaedic consultation, were ≥ 30 years of age, had the ability to read and comprehend English, and understand and provide written consent to participate.

3.3.3 Data Collection

We designed a telephone-administered questionnaire in REDCap, a secure web-based application designed to support data capture for research studies¹⁴² (Appendix E). The questionnaire asked about socio-demographics, comorbidities, health professional visits, and OA treatments used after their initial orthopaedic consultation. Comorbidities were identified by answering yes or no to the following list of conditions: “heart disease”, “heart attack (myocardial infarction)”, “high blood pressure”, “high cholesterol or lipids”, “stroke”, “asthma”, “chronic bronchitis”, “emphysema or chronic obstructive pulmonary disease”, “diabetes”, “kidney disease”, “liver disease”, “intestinal or stomach ulcer”, “rheumatoid arthritis”, “depression”, “low back pain”, and “other physical impairment which limits your activity”. Participants were contacted in chronological order starting with the person with the most recent orthopaedic surgeon consultation.

3.3.4 Outcomes

The primary outcome, guideline-consistent nonsurgical knee OA treatment use (yes or no), was an aggregate measure defined as having used education, exercise, weight management (if body mass index ≥ 25 kg/m²), and at least 1 recommended medication (oral or topical anti-inflammatory, acetaminophen, or corticosteroid injection) unless gastrointestinal or cardiovascular contraindications were reported. The guideline-consistent treatment definition was developed using the 2014 Osteoarthritis Research Society International (OARSI) guidelines for nonsurgical treatment of knee OA¹⁵ to align with the evidence-based recommendations that existed during the participant's initial orthopaedic consultation. Our guideline-consistent treatment definition also aligned with the 2019 OARSI guidelines because education, exercise, weight management, and pharmaceutical recommendations did not change from 2014 to 2019. If statements with Boolean operators (and/or) were used to create the conditional expressions for the primary outcome and coding was verified by visually inspecting the dataset. Participants had guideline-consistent education if they reported that a registered healthcare professional (orthopaedic surgeon, family doctor, physiotherapist, chiropractor, naturopath, or other registered health professional) provided formal instruction about OA and self-management techniques. Guideline-consistent exercise was defined as the participants' self-reported use of any amount of any exercise requiring muscular contraction for the purpose of health benefits or managing knee OA symptoms. Two definitions were also used to define an adequate dose of exercise. A minimum exercise dosage to maintain physical function was defined as 55 minutes or more of moderate-to-vigorous intensity physical activity per week which aligns with

evidence suggesting this dosage best predicts disability-free status over four years in people with knee OA¹⁴³. A minimum exercise dosage for general health maintenance was defined as 150 minutes or more of moderate-to-vigorous intensity physical activity per week which aligns with current Canadian Society of Exercise Physiologist guidelines^{144,145}. Guideline-consistent weight management was defined as attempted weight management reported by people with body mass index ≥ 25 kg/m². All people < 25 kg/m² were defined as receiving guideline-consistent weight management if they did or did not report attempting weight management.

Secondary outcomes evaluated prior use of first-line treatments and guideline-inconsistent treatments. First-line treatments are a subset of the primary outcome measure and defined as education, exercise, and weight management (if body mass index ≥ 25 kg/m²). Guideline-inconsistent treatments are defined as joint protection, opioid use, and injections (hyaluronic acid, platelet rich plasma, and stem cell therapy) because 2014 guidelines suggested these interventions lacked evidence, were of limited efficacy, and/or had an unfavourable risk profile (2019 guidelines made a similar statement). Joint protection was included in the definition for guideline-inconsistent treatments because biomechanical interventions were the only intervention included in the 2014 guidelines¹⁴⁶, but were removed in 2019 guidelines¹⁵ due to inadequate efficacy and poor-quality evidence.

3.3.5 Sample Size

King et al. found 39% of participants in the BEST-Knee study had not attempted all nonsurgical treatments prior to surgical referral to centralized clinics³⁸. We estimated that a sample size of

250 participants would provide 90% power to detect a minimum difference of 0.2 in participant characteristics between those who used and did not use guideline-consistent nonsurgical treatments if 40% of our sample used nonsurgical treatments and p-value was set at < 0.05 .

3.3.6 Statistical Methods

Participant characteristics were summarized using frequencies, medians, and interquartile ranges or means and standard deviations, as appropriate. Continuous variable distributions were assessed for normality. Characteristics for respondents/non-respondents, the entire sample, and those who used or did not use guideline-consistent nonsurgical treatments, first-line treatments, and guideline-inconsistent nonsurgical treatments were compared using the Chi-square test, Fisher's exact test, or Student's t-test, as appropriate.

This study evaluates the combination of sex and gender using the term sex because pre-consult questionnaires did not include questions that separated gender (i.e., man, woman, and gender diverse people) from sex at birth (i.e., male or female). A race-based analysis was not possible because 91% of the sample identified as Caucasian.

We used robust Poisson regression models as these enabled us to express associations between participant characteristics and health outcomes as relative risks¹⁴⁷ (RR)(the risk of a health event in one group divided by the risk of a health event in another group¹⁴⁸). The following variables were assessed individually for association with the primary and secondary outcomes: sex, age, level of education (post-secondary vs less), household income ($>$ and $<$

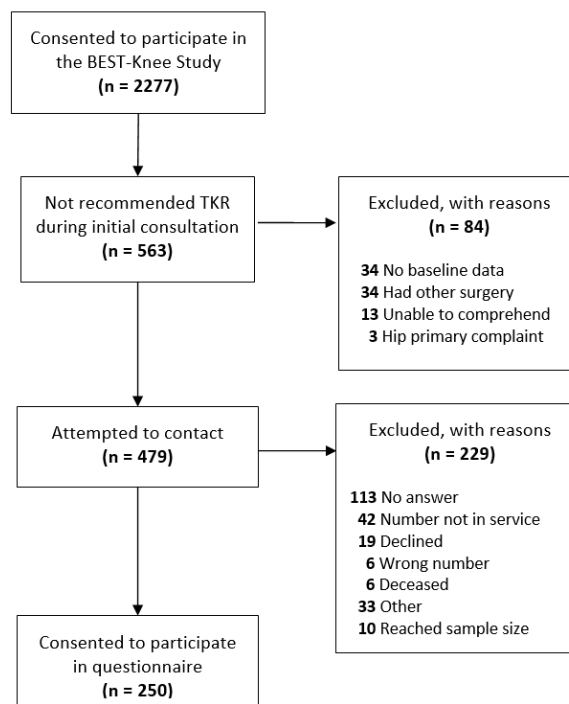
\$60,000/ year), marital status (married vs divorce/separated/widowed), living arrangement (living alone vs living with spouse/family/relatives), specific comorbidities (yes/ no), number of comorbidities (0, 1, 2, and 3+), reason for nonsurgical recommendation reported by the orthopaedic surgeon (symptoms not severe enough, patient declined surgery, another treatment should be tried first and other reason), and whether the participant proceeded to surgery at a later date. Specific comorbidities were evaluated as some (i.e., heart disease, kidney disease, and gastrointestinal disease) may contraindicate use of guideline-consistent pharmaceuticals. The number of comorbid conditions was assessed to evaluate the overall burden of comorbidity. Variables were excluded from the model if sample size in either group was below 10. Robust Poisson regression models were built with all hypothesized variables and variables with statistically significant (p -value <0.05) association in univariate analysis. Variables were entered in the model using stepwise selection based on p -value (low-to-high). Likelihood ratios were assessed to determine which nested model performed best. Models produced similar results, so we reported models with all hypothesized variables. All RR in the robust Poisson regression are presented with 95% confidence intervals (CI) and a two-sided p -value of 0.05 was considered statistically significant. A small fraction (4%) of our data was missing. We are reporting observed data only because we cannot conclude that our data was missing at random and exploratory multiple imputation made no appreciable difference to the primary outcome results.

Statistical analyses were performed using STATA (v15.1. College Station, Texas, USA). The study was approved by the Research Ethics Boards at the Universities of Calgary (REB 14-1294).

3.4 RESULTS

Of 563 people who were not candidates for surgical intervention during the initial orthopaedic consultation, we attempted to contact 479, and 250 agreed to participate (52% response rate) (Figure 4). All participant characteristics in Table 2 were similar between respondents (58% female, mean age 66.2 years, 95% CI, 65.1 to 67.2) and non-respondents (61% female, mean age 64.1 years, 95% CI, 62.7 to 65.4) except the orthopaedic surgeon selected "other" as the reason for not recommending TJR in significantly fewer respondents than non-respondents ($n=11$ vs $n=36$, $p=0.001$). We could not identify a pattern in the written responses that accompanied the "other" classification.

Figure 4. Participant flow diagram.



Participants were 58% female, with a mean age of 66.2 years (95% CI, 65.1 to 67.2) and 55% had attended post-secondary education (Table 1). The primary reason orthopaedic surgeons did not recommend TJR during the initial consultation was because symptoms were not severe enough (56%), recommendation to try another treatment first (20%), co-morbidities made the risks of surgery outweigh the benefits (14%), patient declined surgery (6%), and other reason (4%). Over 6 years, 34% of participants in our sample proceeded to TJR (these participants were included in the analysis and reported use of nonsurgical treatments between the initial and second orthopaedic consultation).

Table 2. Participant characteristics.

	Overall n=250	Use of recommended nonsurgical treatments		
		Used All n=46	Did Not Use All n=191	p-value
Demographics				
Female	146 (58.4)	34 (73.9)	112 (58.0)	0.047 *
Age, years, mean (SD) [†]	66.2 (8.3)	63.3 (7.8)	66.9 (8.3)	0.008 *
Working	48 (19.2)	13 (28.3)	34 (17.6)	0.103
Retired	178 (71.2)	29 (63.0)	140 (72.5)	0.297
Post-secondary	137(54.8)	33(71.7)	104(54.5)	0.033 *
Annual income > \$60,000	157 (62.8)	27(58.7)	124(64.3)	0.265
Married	172 (68.8)	28 (60.9)	136 (70.5)	0.171
Living w/ spouse	166(66.4)	32(69.6)	126(65.3)	0.426
Proceeded to surgery at later date	85 (34.0)	18 (39.1)	64 (33.2)	0.443
Co-Morbidities				
BMI, kg/m ² , mean (SD) [†]	33.5 (6.7)	34.7 (7.3)	33.2 (6.6)	0.252 7

BMI \geq 25 kg/m² (overweight or obese)[†]	221 (88.4)	37 (80.4)	184 (95.4)	0.213
Heart disease	43 (17.2)	5 (10.9)	37 (19.2)	0.280
Hypertension	136 (54.4)	21 (45.7)	109 (56.5)	0.192
High cholesterol	87 (34.8)	11 (23.9)	73 (37.8)	0.087
Stroke	5 (2.0)	-	5 (2.6)	0.586
Asthma	18 (7.2)	8 (16.7)	10 (5.2)	0.001 *
Lung disease	18 (7.2)	2 (4.2)	16 (8.4)	0.538
Diabetes	55 (22.0)	12 (26.1)	42 (21.8)	0.558
Kidney disease	11 (4.4)	-	10 (5.2)	0.216
Liver disease	4 (1.6)	-	4 (2.1)	1.0
Gastrointestinal disease	11 (4.4)	1 (2.2)	8 (4.2)	1.0
Rheumatoid arthritis	4 (1.6)	1 (2.1)	3 (1.6)	0.577
Depression	35 (14.0)	9 (19.6)	23 (11.9)	0.226
Low back pain	123 (49.2)	17 (35.4)	100 (52.4)	0.032 *
Other physical impairment	67 (26.8)	12 (26.1)	51 (26.4)	0.963
Number of Co-Morbidities				
0	34 (13.6)	9 (19.6)	24 (12.4)	
1	61 (24.4)	14 (30.4)	43 (22.3)	0.246
2	50 (20.0)	9 (19.6)	40 (20.7)	0.861
3+	105 (42.0)	14 (30.4)	86 (44.6)	0.081
Missing	11(4.4)			
Reason for Non-Surgical Diagnosis				
Symptoms are not severe enough	140 (56.0)	27(58.7)	110 (57.0)	0.834
Another treatment should be tried first	50 (20.0)	8 (17.4)	40 (20.7)	0.612
Co-morbidity	35 (14.0)	6 (13.0)	26 (13.5)	1.00
Patient declined surgery	14 (5.6)	2 (4.3)	10 (5.2)	0.816
Other	11 (4.4)	3 (6.5)	7 (3.6)	
Missing	11(4.4)			

Note: values represent n (%) unless otherwise stated. Thirty-four different univariate analyses with p-value of 0.05 suggests there is an 83% chance that a statistically significant finding is a false positive.

*= p-value < 0.05 when evaluating participant characteristic between those who used and did not use guideline-consistent nonsurgical treatments

[†]= during initial orthopaedic consultation

Guideline-consistent nonsurgical treatments were used by 19% of participants following their initial orthopaedic consultation (Table 3). Among these participants, 64% received education by a health professional, 74% exercised regularly, 38% used weight management techniques, and 91% used guideline-consistent pain medications. Participants reported learning about OA from their orthopaedic surgeon (40%), family doctor (31%), physiotherapist (8%), chiropractor (2%), naturopath (0.4%), education class (6%), friends (10%), internet (10%), other source (9%), or had not learned anything about OA (20%). Participants reported regularly exercising by walking (52%), biking (18%), strength training (12%), taking the GLA:D® program²⁷ (4%) swimming (6%), aquacise (7%), deep water workouts (1%), and other (9%). The average active person reported exercising for 343 minutes per week (95% CI, 299.5 to 386.8) over 3.7 days per week (95% CI 3.0 to 4.3). Participants reported taking acetaminophen (46% non-prescription and 8% prescription), topical non-steroidal anti-inflammatory (NSAIDs) (8% non-prescription and 18% prescription), oral NSAIDs (23%), opioids (10%), disease modifying anti-rheumatic drugs (0%), anti-depressants (7%), capsaicin (0%), chondroitin (3%), diacerein (0%), risedronate (0.4%), rosehip (0%), and other (12%). Medications were taken as needed (48%), daily (44%), weekly (6%), monthly (1%), or other (1%). Participants spoke with their family doctor about weight management (4%), saw a dietitian (11%), followed the Canada Food Guide¹⁴⁹ (2%), attended a weight loss program (4%), ate less (16%), and other (10%). People were 3% less likely to use guideline-consistent treatments for each additional year of age (RR 0.97, 95% CI 0.94 to 0.99) (Table 4). Of the people who reported exercising, 16% did not meet the minimum dosage to maintain their functional status and 37% did not meet the minimum dosage to maintain overall health.

Table 3. Use of nonsurgical treatments over three to four years post consult.

	Overall n=250
All guideline-consistent treatments[†] with any volume of self-reported exercise	46 (19.3)
All guideline-consistent treatments with ≥55 min/wk exercise threshold	39 (16.3)
All guideline-consistent treatments with ≥150 min/wk exercise threshold	31 (13.0)
First-line treatments[‡]	48 (19.2)
Guideline-inconsistent treatments[‡]	105 (42.0)
Education[‡]	150 (60.0)
All self-reported exercise[§]	185 (74.0)
≥55 min/wk exercise threshold	158 (63.2)
≥150 min/wk exercise threshold	124 (49.6)
Weight management[¶]	89 (37.2)
Medications[†]	228 (91.2)
Used at least 1 guideline-consistent therapy	247 (98.8)

Note: values represent n(%) unless otherwise stated.

[†]= used education, exercise, weight management (if body mass index ≥ 25 kg/m²), and at least 1 recommended medication (oral or topical anti-inflammatory, acetaminophen, or corticosteroid injection) unless gastrointestinal or cardiovascular contraindications are reported

[‡]= education, exercise, and weight management (if body mass index ≥ 25 kg/m²)

[§]= joint protection, opioid use, and injections (hyaluronic acid, platelet rich plasma, and stem cell therapy)

[¶]= reported that a registered health professional (orthopaedic surgeon, family doctor, physiotherapist, chiropractor, massage therapist, naturopath, or other registered health professional) provided formal instruction about OA and self-management techniques

[§]= participants self-reported use of any amount of any exercise requiring muscular contraction for the purpose of health benefits or managing knee OA symptoms

[¶]= attempted weight management by people with body mass index ≥25 kg/m². All people <25 kg/m² were defined as receiving guideline-consistent weight management if they did or did not report attempting weight management

[†]= used any dose of oral or topical anti-inflammatory, acetaminophen, or corticosteroid injection

Table 4. Relationship between participant characteristics and use of nonsurgical treatments.

	Use of Recommended Nonsurgical Treatments[†] Adjusted RR (95% CI) n=237
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Age, per yr increase	0.97 (0.94 – 0.99)*
Low back pain	0.59 (0.31–1.11)
Did not attend post-secondary education (attended post-secondary reference)	0.58 (0.33 –1.04)
Female sex (male reference)	1.50 (0.81–2.77)
3 or more co-morbidities	0.78 (0.39–1.59)
Not married (married reference)	1.37 (0.83–2.28)
Obese (non-obese reference)	0.85 (0.45–1.59)
Depression	1.29 (0.67–2.42)
Working (not working reference)	1.05 (0.77–1.44)
Had surgery later (did not have surgery reference)	1.48 (0.74–2.06)

Log likelihood = -112.50, AIC = 1.04, BIC = -1102.77

†= used education, exercise, weight management (if body mass index ≥ 25 kg/m²), and at least 1 recommended medication (oral or topical anti-inflammatory, acetaminophen, or corticosteroid injection) unless gastrointestinal or cardiovascular contraindications are reported

*= p-value < 0.05

RR=Risk Ratio, the risk of a health event in one group divided by the risk of a health event in another group¹⁴⁸; adjusted for age, low back pain, post-secondary education, sex, three or more comorbidities, marital status, obesity, depression, work status and proceeded to surgery after a subsequent orthopaedic consultation.

First-line treatments were used by 19% of participants after their initial orthopaedic consultation (Table 3). People were 3% less likely to use first-line treatments for each additional year of age (RR 0.97, 95% CI 0.94 to 0.99) and 45% less likely to use first-line treatments if they did not attend post-secondary education (RR 0.54, 95% CI 0.30 to 0.96) (Table 5).

Table 5. Relationship between participant characteristics and use of first-line treatments.

	Use of Recommended First-Line Treatments† Adjusted RR (95% CI) n=237
Age, per year increase	0.97 (0.94–0.99)*
Did not attend post-secondary education (attended post-secondary reference)	0.54 (0.30–0.96)*
Low back	0.60 (0.32–1.11)

3 or more co-morbidities	0.72 (0.36–1.44)
Female sex (male reference)	1.44 (0.80–2.60)
Working (not working reference)	1.14 (0.89–1.47)
Depression	1.23 (0.65–2.33)
Obese (non-obese reference)	0.87 (0.48–1.57)
Not married (married reference)	1.27 (.78–2.07)

Log likelihood = -115.65, AIC = 1.06, BIC = -1105.95

[†]= education, exercise, and weight management (if body mass index ≥ 25 kg/m²)

*= p-value < 0.05

RR=Risk Ratio, the risk of a health event in one group divided by the risk of a health event in another group¹⁴⁸; adjusted for age, post-secondary education, low back pain, three or more comorbidities, sex, work status, depression, obesity, and marital status.

Guideline-inconsistent treatments were used by 42% of participants after their initial orthopaedic consultation (Table 3). Participants reported using joint protection (33%), opioid use (10%), hyaluronic acid (9%), platelet rich plasma (1.2%), and stem cell therapy (0.8%) over the study period. People were 3% less likely to use guideline-inconsistent treatments for each additional year of age (RR 0.97, 95% CI 0.96 to 0.99) and 39% less likely to use guideline-inconsistent treatments if they were female (RR 0.62, 95% CI 0.47 to 0.81) (Table 6).

Table 6. Relationship between participant characteristics and use of guideline-inconsistent treatments.

	Use of Recommended Guideline-Inconsistent[†] Treatments Adjusted RR (95% CI) n=237
Age, per year increase	0.97 (0.96–0.99)*
Female sex (male reference)	0.62 (0.47–0.81)*
Working (not working reference)	0.97 (0.81–1.17)
Did not attend post-secondary education (attended post-secondary reference)	0.86 (0.64–1.14)
Had surgery later (did not have surgery reference)	0.88 (0.65–1.20)

Log likelihood = -181.99, AIC = 1.59, BIC = -1105.14

[†]= joint protection, opioid use, and injections (hyaluronic acid, platelet rich plasma, and stem cell therapy)

*= p-value < 0.05

RR=Risk Ratio, the risk of a health event in one group divided by the risk of a health event in another group¹⁴⁸; adjusted for age, sex, work status, post-secondary education, and proceeded to surgery after a subsequent orthopaedic consultation.

3.5 DISCUSSION

Only one in five people reported using all guideline-consistent nonsurgical treatments and first-line treatments after an orthopaedic surgeon recommended nonsurgical treatment. However, two in five people who were not recommended for a TJR by an orthopaedic surgeon reported using treatments which do not align with current clinical guidelines. Surgeon recommendation during initial orthopaedic consultation appeared to have minimal impact on use of guideline-consistent nonsurgical treatments. Older participants were 3% less likely to report using guideline-consistent, first-line and guideline-inconsistent treatments per year of age which is equivalent to 26% less likely over a 10-year age span. Meanwhile, people who did not attend post-secondary education were 45% less likely to use guideline-consistent treatments and females were 38% less likely to use guideline-inconsistent treatments. We assume these results are best interpreted as gender differences, rather than sex, because sociocultural factors (i.e., family, caregiving, or care-receiving roles) are more likely to impact use of treatments than biology. Our results suggest there is a wide gap between what guidelines recommend and what treatments people use to manage their knee OA before surgery is indicated.

We found that first-line treatments are underused in Alberta, like many other jurisdictions. Our results showed that 80% of participants have not used all the guideline-consistent treatments

after an orthopaedic surgeon recommended these proven interventions. These findings are lower than two systematic reviews^{91,138} which both found that 60% of eligible participants recruited in the community have not received appropriate first-line OA care based on a cumulative quality indicator in studies from the USA, UK, Norway, Canada, and Australia^{91,138}. Our results may have been different because our aggregate measure was more specific than the quality indicators used to combine results in the Hagen et al.⁹¹ and Basedow et al.¹³⁸ systematic reviews, and we included a much more selective sample than the systematic reviews' broad inclusion of participants from numerous community-based settings. Our results were also lower than King et al.³⁸ who observed that 40% of people with knee OA who proceed to TJR have not attempted first-line treatments before consultation with an orthopaedic surgeon at centralized intake clinics in Alberta, Canada. The participant characteristics in our population were comparable to the population in King et al., but their place in the continuum of care differed substantially – people who were not recommended TJR in our study vs people who were recommended and consented to have TJR in the King et al. study. It is possible that treatment preferences differed in these two populations based on their location in the continuum of care. However, the combination of our results and King et al. suggests that people referred to centralized intake clinics in Alberta, Canada may not be using optimal nonsurgical care to manage their OA before or after an orthopaedic consultation. Our results can be generalized to people with symptomatic knee OA who are not currently eligible for TJR, but our sample was younger, had higher income and was more highly educated than a population-level cohort in Ontario, Canada¹⁵⁰. Low uptake of first-line treatments aligns with global trends showing these safe, effective, and appropriate treatments continue to be

underused in routine clinical practice^{19,20,91,137,138}. Barriers to optimize use of first-line treatments include the availability of services, time, cost, referral patterns, and beliefs held by patients and healthcare professionals which may not align with current evidence^{48,151}. We observed that there might also be some important age, education, and gender-related differences associated with barriers and access to care. In a forthcoming publication, we report on our qualitative study which explored barriers to access in a subset of participants from this study.

We found a significant gap between “usual care” and clinical guidelines. Almost every participant used at least one guideline-consistent therapy, so people may have found a combination of treatments that managed their symptoms and fit their preferences, but using all treatments could provide significant health benefits^{122,152}. We were unable to separate exercise prescribed for osteoarthritis management from exercise performed for other reasons. However, 32% of participants reported seeing a physiotherapist so we can assume that only a small subset of our active participants were actually prescribed specific exercises to manage their OA. Half of our sample did not meet the Canadian Physical Activity Guidelines and 35% were not physically active enough to maintain their mobility. This level of sedentarism was surprising given that exercise improves pain, function, and health-related quality of life for people living with knee OA¹⁵³. Optimizing physical activity in the OA population presents an opportunity to improve OA-related health outcomes as well as prevent 35 chronic conditions^{154,155}. Enhancing physical activity could also produce multi-system health benefits because 87% of our sample had at least one co-morbidity where exercise was recommended as

standard treatment¹⁵⁴. Almost 90% of our sample was overweight or obese, but only 37% of participants reported that they attempted interventions to either manage or reduce their weight. Reducing body weight by even 5-10% has been shown to improve OA-related clinical health outcomes^{122,152,156}, but people may not believe weight management will have a meaningful impact on their OA symptoms and disease progression¹⁵⁷. Enhancing the use of weight management programs is critical because the combination of diet and exercise produces better clinical improvements than exercise or diet alone^{122,152}. Almost every participant used guideline-consistent pain medications which is similar to previous findings¹⁹, suggesting people's primary method of managing knee OA is with pharmaceuticals instead of lifestyle interventions.

First-line treatments are safe¹⁵, appropriate¹⁵, effective¹⁵³, and efficient¹⁵⁸, but these proven treatments continue to be underused. Increasing use of first-line treatments could improve health outcomes for people living with OA and lead to better healthcare system performance. A randomized controlled trial evaluating knee replacement observed that 68% of surgical candidates randomized to an education and exercise program had not proceeded to surgery two years after the intervention¹²⁸. The studied program would pay for itself if 8% of people avoided TJR¹²⁹. Efficient insurance systems typically invest in low-cost services before committing to high-cost care. Integrating structured education, exercise, and weight management programs into standardized clinical pathways could ensure first-line treatments are exhausted before surgical referral is made for patients with knee OA. Requiring, instead of encouraging, an appropriate trial of first-line treatments may also be considered as a policy

approach to maximize the judicious use of surgical resources. Customizing interventions to fit sociocultural factors related to age, education, and gender may help improve use of proven therapies in these subpopulations. Future research should focus on implementing referral pathways and structured first-line therapy programs in healthcare systems and health insurance plans. Developing implementation guidelines, health professional training programs, resources, models of care, and frameworks for quality monitoring have been identified as global priorities⁹.

Our study has limitations. We estimated a priori that 40% of our sample would use guideline-consistent nonsurgical treatments, but only 20% of our sample met the case definition. Fewer participants meeting the case definition meant our regression analyses were underpowered and limited our ability to evaluate associations between participant characteristics and use of nonsurgical treatments. Self-reported data can also be over or under-reported, potentially leading to systematic bias^{61,159}. However, alternative data sources such as administrative data could not be used because most education programs, exercise therapy, physiotherapy, and dietician consultations are paid privately in the Canadian healthcare system. Second wave data collection, which was used in our study, is known to produce lower response rates than the initial data collection¹⁶⁰. Our response rate (52%) could bias results, but similar respondent and nonrespondent characteristics would suggest that non-response bias is less likely in our study. The long duration between initial orthopaedic consultation and telephone interview could lead to recall bias, although the time period of three to six years post orthopaedic consultation allowed us to capture treatments for multiple years as this population manages their

permanent chronic disease. Lastly, our analysis was unable to separate the influence of sex (i.e., biological factors) and gender (i.e., sociocultural factors).

3.5.1 Conclusions

Only one in five participants used all guideline-consistent nonsurgical treatments to manage their knee OA within six years of orthopaedic surgeon consultation, while two in five people used treatments not consistent with clinical guidelines over the same time period. Increasing use of education, exercise, and weight management could improve health outcomes for people living with OA, reduce wait times for joint replacement, and increase value for money in the healthcare system. Findings may help inform decision-makers planning future OA service delivery to optimize nonsurgical care.

4 REAL-WORLD COST-EFFECTIVENESS OF A STANDARDIZED EDUCATION AND EXERCISE THERAPY PROGRAM HIP AND KNEE OSTEOARTHRITIS COMPARED TO USUAL CARE

This chapter has been submitted to the journal of *Osteoarthritis & Cartilage* as:

Mazzei DR, Faris P, Whittaker JL, Wasylak T, Marshall DA. *Real-world cost-effectiveness of a standardized education and exercise therapy program for hip and knee osteoarthritis compared to usual care*. Under review at Osteoarthritis & Cartilage.

Results from our systematic review were not transferable to the Canadian context. We considered using data from the literature to build a decision model but could not find costs and outcomes for community-based usual care. We undertook a prospective matched cohort study to collect cost and outcomes for a cost-utility analysis that would produce local evidence to support the policy-making process in Alberta. This manuscript was submitted to an OA journal so we used the broader term cost-effectiveness in the title and abstract because the OA audience might be unaware that cost-utility analysis is a specific method under the umbrella of cost-effectiveness research.

4.1 ABSTRACT

Objective: Estimate the real-world cost-effectiveness of a standardized education and exercise therapy program (GLA:D®) compared to usual care (UC) for people managing hip and/or knee osteoarthritis (HKOA).

Methods: We used a prospective matched cohort design to recruit people (age>45 years) diagnosed with HKOA who used GLA:D® or UC (not on a surgical waitlist) throughout Alberta, Canada. Demographics, pain, function, quality of life, and an HKOA-related cost-questionnaire were administered over 12-months. The primary Ministry of Health (MOH) perspective used administrative data to estimate all public healthcare costs. The secondary healthcare perspective included MOH, private insurance, and out-of-pocket costs. We calculated our cost-effectiveness measure, incremental net monetary benefit (INMB), over 12-months with a \$30,000/QALY willingness to pay threshold and adjusted for between-group differences. A Markov model was used to extend INMB over a lifetime time horizon (3% discounting). Model uncertainty was explored by probabilistic sensitivity analyses.

Results: 254 participants (GLA:D® n=127, UC n=127; 72% female), were a mean age of 64.3 years (95%CI:63.1-65.5), diagnosed with knee OA (63%), hip OA (24%) or both (13%) for a mean of 5.5 years (95%CI:4.8-6.3). The adjusted INMB of GLA:D® compared to UC was \$6,065 (95%CI:\$3,648-\$8,482) and \$499 (95%CI:-\$2,913-\$3,912) from a MOH and healthcare perspective over 12-months and \$6,574 and \$1,775 over a lifetime with 54% and 51% probability of being cost-effective.

Conclusions: GLA:D® had a positive INMB compared to UC from the MOH perspective over 12-months. The INMB remained positive but was less certain over a lifetime or when out-of-pocket and private insurance costs were considered.

4.2 INTRODUCTION

Osteoarthritis (OA) is highly prevalent, placing significant burden on people and health systems^{90,161}. Clinical guidelines recommend education and exercise therapy as first-line treatments for everyone with hip and knee OA¹⁵. Attempting first-line treatments is also an eligibility criteria for appropriate total joint replacement (TJR)¹⁷, but 40% of Canadians with knee OA have not attempted first-line treatments before having surgery³⁸. These findings are not unique, first-line treatments are underused globally¹³⁵. Barriers for first-line treatment include knowledge gaps, expectations, referral patterns, availability, and costs^{48,151}. Increasing uptake by reducing barriers is a global priority⁹.

Integrating standardized education and exercise therapy programs into funded or insured clinical pathways can increase access to first-line treatments. Most economic evaluations alongside randomized controlled trials (RCTs) show standardized education and exercise therapy programs are cost-effective in different health systems¹⁵⁸. Previous economic evaluations used RCTs to collect cost and effects, but RCTs may have limited generalizability for making resource decisions because they use controlled environments with targeted populations to evaluate efficacy. The comparator and sample population also impact cost-effectiveness results¹⁵⁸. Danish RCTs showed a 12-week individualized non-surgical knee OA

intervention including exercise, education, insoles, dietary advice, and/or pain medication was cost-effective compared to written advice in people not eligible for TJR¹⁶² but was not cost-effective compared to TJR in an eligible sample¹²⁸. Danish researchers then created an eight-week standardized group program called Good Life with osteoArthritis in Denmark (GLA:D®) to implement high quality hip and knee OA care in the Danish healthcare system²⁷. GLA:D® consists of two education sessions and twelve supervised neuromuscular exercise sessions delivered twice per week²⁷. GLA:D® has spread to ten countries and 85,000 people have taken the program³³. GLA:D® implementation presented an opportunity to evaluate the cost-effectiveness of a standardized education and exercise therapy program in the real-world. We evaluated the incremental net monetary benefit (INMB) of GLA:D® in comparison to usual care (UC) for managing hip and/or knee OA in the community.

4.3 METHODS

We followed the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) for transparently reporting health economic evaluations¹⁶³ (Appendix F).

4.3.1 Study Design

We compared real-world data from a cohort of GLA:D® participants with hip and/or knee OA to a cohort of people managing hip and/or knee OA with UC in Alberta, Canada. Usual care was defined as any community-based service people used to manage their OA symptoms before a TJR. Annually, 170,000 people see a family physician for hip and/or knee OA in Alberta, Canada

while 500 people participate in GLA:D® (0.3% of the eligible population)¹⁶⁴. During the study, GLA:D® was offered in-person or virtually at 68 clinics in Alberta, Canada⁴³.

4.3.2 Participants

Participants were eligible for the study if they were ≥45 years of age, diagnosed with hip and/or knee OA by a health professional, a natural joint was their primary complaint, not waiting for a TJR (waiting defined as eligible and waiting for TJR date), and were able to read/comprehend English.

4.3.3 Recruitment

Recruitment happened between January 4, 2021 – January 4, 2022. Participants were recruited with posters and in-person by clinicians or the lead author (DRM) at primary care, rehabilitation, and orthopaedic surgeon clinics. GLA:D® recruitment posters were only at GLA:D® sites. Usual Care posters were at clinics, community pharmacies, recreation centers, and posted on the internet. The Alberta government restricted access to group-based programs during the COVID-19 pandemic which coincided with the recruitment window.

4.3.4 Data collection

Characteristics including date of birth, sex, height, weight, education, employment status, private insurance, comorbidities, physical activity, fear of joint damage, and previous knee surgeries were collected at baseline. This study does not evaluate gender because the GLA:D® Canada database only collects information about sex. A cost-questionnaire was developed to

collect patient-reported healthcare use and out-of-pocket costs for physician, allied health, diagnostic imaging, injection, medications, and medical devices (Appendix G). The cost-questionnaire, European Quality of Life 5-Dimension five-level version (EQ-5D-5L), 12-item Hip Injury and Osteoarthritis Outcome Score (HOOS-12), and 12-item Knee Injury and Osteoarthritis Outcome Score (KOOS -12) were collected at baseline, 3-, 6-, 9-, and 12-months.

All surveys were completed electronically. We extracted data from the GLA:D® Canada national database to prevent duplicate collection¹⁶⁵. GLA:D® Canada uses DADOS to collect demographics and outcome measures prior to beginning the program then at 3- and 12-months after the pre-program survey date for all GLA:D® participants. In addition, GLA:D® participants used REDCap to complete cost-questionnaires at all timepoints as well as outcomes at 6- and 9-months. UC participants used REDCap to report all demographics, outcomes, and cost-questionnaires. DADOS is hosted on servers at the University Health Network¹⁶⁶. REDCap is hosted on servers at the University of Calgary Clinical Research Unit¹⁴².

All participants provided consent to link self-reported data to administrative data using personal health numbers. Administrative data linkage is used to collect all publicly funded healthcare resource use to estimate public payer healthcare costs. We used four administrative databases: Alberta Healthcare Insurance Plan (AHCIP) Population Registry, Ambulatory Care Classification / National Ambulatory Care Reporting System (NACRS), Discharge Abstract Database (DAD), and Practitioner Claims (PC). The AHCIP Population Registry contains individual level demographic information including personal health number, age, sex, and death for all

patients covered by the insurance plan. NACRS includes provider information, dates, diagnosis, and procedure codes for all ambulatory services and day surgeries in publicly insured facilities. DAD includes dates, provider information, diagnosis, examination, procedures, and discharge information for all inpatient hospital stays. PC includes all fee-for-service and shadow-billed data submitted for public reimbursement by physicians.

4.3.5 Health Outcomes

Quality-adjusted life years (QALY) were calculated as the primary health outcome measure. Participants used the EQ-5D-5L to select from five possible responses on five health domains which produces 3125 possible health states⁷⁴. Each health state was applied a health utility weight from the general Canadian population^{76,167}. Health utility was then used in an area under the curve calculation to estimate QALYs gained.

Clinical effectiveness was evaluated by calculating the change in pain, function, quality of life (QOL), and a summary score over 12-months using the HOOS-12 and KOOS-12. Question responses were summed then divided by the optimal score to produce a score from 0 (worst) to 100 (best)¹⁶⁸.

4.3.6 Costs

Costs were calculated from the Ministry of Health (MOH) and healthcare perspectives. The MOH perspective includes all publicly funded healthcare costs. The healthcare perspective includes costs incurred by the MOH, private insurers, and participants.

Ministry of Health was the primary perspective because it is the reference case in Canada⁵⁹.

Osteoarthritis services are funded by a variety of public and private providers in Alberta, Canada (population 4.4 million). The Alberta Healthcare Insurance Plan (AHCIP) provides 100% publicly funded coverage for medically necessary care to all residents except Indigenous peoples, members of military, and people who opt out of coverage. Osteoarthritis services covered by the AHCIP include physician consultations, diagnostic imaging, hospital stays, surgeries, inpatient medication, and inpatient rehabilitation. People over age 65 receive 70% publicly insured coverage for prescription medications on the formulary. Some rural hospitals and suburban Primary Care Networks provide limited access to publicly funded outpatient rehabilitation.

Ministry of Health costs were estimated from de-identified patient-level OA-related healthcare use collected by administrative data. Records were defined as an OA-related visit when the first three digits of the diagnostic code included 715 or M15 to M19 from the ninth and tenth revisions of the Internal Classification of Diseases (ICD)³⁴. Physician claims were costed using the Alberta Health Insurance Plan: Schedule of Medical Benefits¹⁶⁹. Resource use identified in NACRS and DAD was costed by the case mix grouper method¹⁷⁰. When participants reported allied health visits with \$0 out-of-pocket cost we assumed the visit was publicly funded and estimated the visit cost using the average hourly salary of an allied health professional in the public healthcare system (i.e. average physiotherapy wage is \$43.48/hour plus 20% for benefits). based on current salary bands¹⁷¹. Costs were calculated in 2022 Canadian dollars.

Out-of-pocket and private insurance costs were estimated from the cost-questionnaire.

Participants reported the number of visits and out-of-pocket cost per visit for all OA-related services used. Participants' out-of-pocket cost per visit was divided by their co-pay to calculate the total visit cost paid by the participant and insurance provider. Number of visits were multiplied by the visit cost to estimate total cost for allied health professional services, including GLA:D®, per quarter. Participants reported the 1-month supply cost for over-the-counter, prescription, gastric protection, and sleep/mood medications. Prescription medication costs were divided by the co-pay to estimate the total cost of prescription medications paid by the participant and insurance provider. The cost for a 1-month supply of all medications was added together then multiplied by three to estimate 3-month medication costs.

4.3.7 Sample Size

The sample size required to power economic evaluations to detect a statistically significant difference in the primary cost-effectiveness measure is not feasible, so economic evaluations are typically powered to detect a statistical difference in the effect size for the clinical effectiveness measure then use estimation techniques to evaluate cost-effectiveness¹⁷² A sample of 24 pairs were required to detect a 10-point difference (with a standard deviation of 14) on the HOOS-12/KOOS-12 using a paired two-sample test of means powered at 80% with a statistical significance of $\alpha = 0.05$ and assuming a correlation of 0.30. We increased the minimum sample by 20% to account for drop out then rounded up to get 30 pairs in four matched categories (female with knee OA, males with knee OA, females with hip OA and males

with OA). We needed a minimum of 120 participants in each cohort but kept recruitment open for 12-months to recruit additional male participants who were underrepresented in our sample.

4.3.8 Statistical Analysis

Data cleaning and analysis were performed in R version 4.2.2 (2022-10-31 ucrt). The study was approved by the Conjoint Health Research Ethics Board at the University of Calgary (REB 20-0613).

4.3.9 Missing Data and Outliers

We visually inspected patterns in missing and complete data (Appendix H). Missingness did not appear different between cohorts, so data were assumed to be missing at random. Missing data were imputed at 3-month intervals using multiple imputation. Convergence was assessed by checking summaries of imputed values across iterations. We generated five imputed data sets, and pooled estimates are reported. Total MOH and healthcare costs greater than 3.5 absolute deviations from the median were removed. Absolute deviation from the median allowed us to retain sample size because it is a more robust measure of dispersion than standard deviations from the mean¹⁷³.

4.3.10 Cost-Utility Analysis over 12-months

Incremental net monetary benefit (INMB), which calculates the difference in monetary value of two interventions, was calculated as the primary cost-effectiveness measure (Figure 5).

Incremental net monetary benefit converts the cost-effectiveness ratio into a linear expression which enables use of regression methods, adjustment for between-group differences, and subgroup analysis⁵². The INMB is also easier to interpret because dollar values above \$0 mean the intervention is more efficient than the comparator⁵². We used \$30,000/QALY as the decision-maker's willingness to pay (WTP) threshold^{174,175}, the maximum amount a decision-maker will pay for additional health benefits⁵². Linear regression was used to explore how baseline health utility, affected joint (hip, knee, or hip and knee), and sex (male or female) impacted cost-effectiveness results. Assumptions for linear regression were achieved (Appendix I). Four scenario analyses were completed in from the MOH and healthcare perspectives: 1) all participants with imputed data except those who proceeded to TJR, 2) all participants with imputed data including those who proceeded to TJR, 3) participants with complete data except those who proceeded to TJR, and 4) participants with complete data including those who proceeded to TJR. Discounting was not applied over 12-months.

Figure 5. Incremental net monetary benefit formula.

$$INMB = (QALYS_{GLA:D^{\circledast}} - QALYS_{UC}) * WTP - (COST_{GLA:D^{\circledast}} - COST_{UC})$$

Where:

INMB = Incremental net monetary benefit

QALYS = Quality-adjusted life years

WTP = Willingness to pay

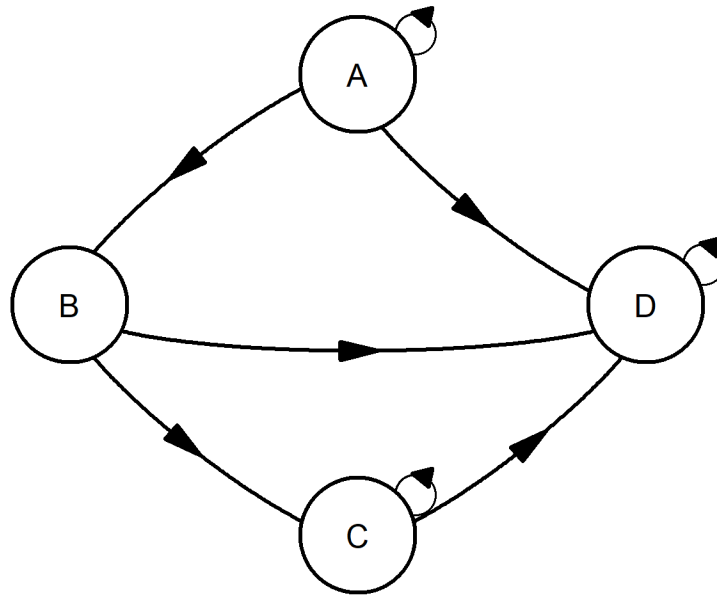
Cost = Total cost based on the Ministry of Health or healthcare perspective

4.3.11 Cost-Utility Analysis over Lifetime

Due to the chronic nature of OA, it is recommended to extend empirical findings past the observation period to estimate how the intervention impacts health and costs to end of life⁶⁰. A Markov model was built using the heemod package in R to extend cost and health outcomes to the lifetime time horizon¹⁷⁶. People with OA are a heterogeneous population who exhibit high variability in disease progression, severity, time since diagnosis, and response to treatment¹¹. We reduced model uncertainty by modelling the health services people use to manage OA instead of modelling disease progression⁵². The model consists of four health states: 1) community management, 2) TJR tunnel, 3) prosthetic joint, and 4) dead (Figure 6). All participants enter the model once managing OA in the community then some progress to a 12-month TJR tunnel followed by living the rest of their life with a prosthetic joint. An annual cost, health utility, and transition probability was applied to each health state. Model parameters and transition probabilities are shown in Table 7. Community management cost and health utilities were estimated from the adjusted costs and adjusted QALYs gained over 12-months in all participants with imputed data except those who proceeded to TJR. Health utility for the TJR tunnel and prosthetic joint health states were estimated from the literature^{177,178}. A universal publicly insured health authority who delivers approximately 20,000 TJRs annually provided TJR acute care cost estimates (\$10,116) from Alberta, Canada. Our TJR tunnel cost estimate added 39% to the acute care costs to account for post-operative care received within 12-months of surgery in the community⁴¹. We assumed the risk of death was the same in all health states. Revisions, infections, and TJR for a different joint were not included in the model because we assumed these clinical events were equal between cohorts. We also assumed the prosthetic

joint state had \$1,000 costs annually to account for these clinical events. We assumed GLA:D[®] reduced the risk of TJR because 11% of GLA:D[®] participants in Canada report being willing to have TJR before the program and unwilling to have TJR after the program¹⁷⁹. The same question is asked in Denmark and Australia where 7.8% (n=15,620) and 15% (n = 10,424) of GLA:D[®] participants change their mind about TJR before and after the program^{33,180}. Results from these three countries allowed us to produce a distribution surrounding the risk of TJR^{33,179,180}. Cycle lengths were 12-months. The model was run for 20 cycles (average life expectancy at age 65 in Canada¹⁸¹). Cost and outcomes were discounted at 3% annually to account for the time-preference for money and health⁵⁹.

Figure 6. Depiction of the Markov model used to evaluate lifetime horizon.



Where:

State A = Community management
 State B = Total joint replacement tunnel
 State C = Prosthetic joint
 State D = Dead

Table 7. Markov model parameters and transition probabilities (Ministry of Health perspective, All cases, No surgery).

Parameter	Value	Source
UC cost for community management (SD)	\$ 644 (\$ 419)	12-month results
GLA:D® cost for community management (SD)	\$ 554 (\$ 327)	12-month results
TJR tunnel cost ¹	\$ 16,584	AHS ¹⁸² and Marshall et al., 2012 ⁴¹
Prosthetic joint cost ²	\$ 1,000	Estimated
Dead cost	\$ 0	N/A
UC health utility for community management (SD)	0.69 (0.14)	12-month results
GLA:D® health utility for community management (SD)	0.71 (0.12)	12-month results

TJR tunnel health utility³ (SD)	0.72 (0.19)	Conner-Spady et al. ¹⁷⁷
Prosthetic joint health utility⁴ (SD)	0.77 (0.73)	Schilling et al., 2017 ¹⁷⁸
Dead health utility	0.00	N/A
Risk reduction (RR) of progressing to TJR tunnel for GLA:D® participants (SD)	0.11 (0.28)	Zywił et al. ¹⁷⁹
Transition probability of UC staying in community management	0.9113	Burn et al. ⁷
Transition probability from UC to TJR tunnel	0.0163	Burn et al. ⁷
Transition probability of GLA:D® staying in community management	0.9131	Calculated with RR
Transition probability from GLA:D® to TJR tunnel	0.0145	Calculated with RR
Transition probability from TJR tunnel to prosthetic joint	0.9276	N/A
Transition probability from UC, GLA:D®, TJR, or prosthetic joint to dead	0.0724	Government of Alberta ¹⁸³

¹ = sensitivity analysis #1 changed the TJR tunnel cost to \$10,116.

² = sensitivity analysis #2 changed the prosthetic joint cost to \$0.

³ = sensitivity analysis #3 changed the TJR tunnel health utility to 0.825.

⁴ = sensitivity analysis #4 changed the prosthetic joint health utility to 0.825.

Probabilistic sensitivity analysis was used to characterize uncertainty in parameter estimates for costs, utility, and risk reduction of progressing to the TJR tunnel. A randomly selected value was chosen from the distribution surrounding each parameter that has standard deviation in Table 7. Results stabilized after 2,000 iterations, but we conducted 10,000 iterations to align with best practice⁵⁹ (Appendix J). Sensitivity analyses assessed whether different cost and health utility estimates in the TJR tunnel and prosthetic joint health states impacted results (Table 7).

4.4 RESULTS

4.4.1 Participants

A total of 254 participants were included (Figure 7). Baseline characteristics were similar between cohorts except there were more females, and worse function in the GLA:D® cohort (Table 8). Most participants (96%) had private health insurance, but 29% of plans did not cover allied healthcare or medical devices.

Figure 7. Participant flow diagram.

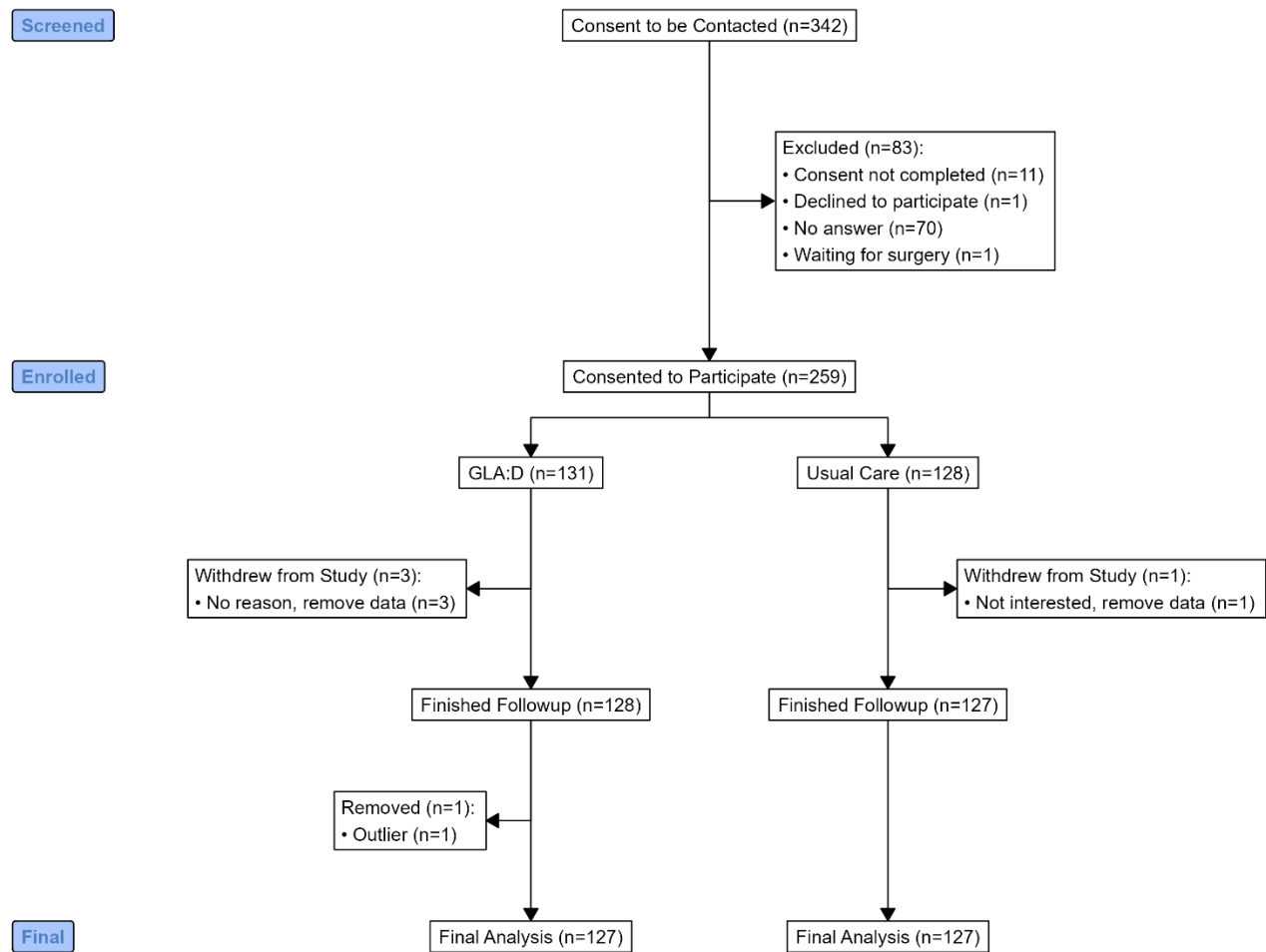


Table 8. Participant demographics.

Variable	GLA:D®, n = 127 ¹	Usual Care, n = 127 ¹	p-value ²
Joint			0.2
Knee	73 (57.5%)	87 (68.5%)	
Hip	34 (26.8%)	26 (20.5%)	
Knee and Hip	20 (15.7%)	14 (11.0%)	
Female sex	101 (79.5%)	82 (64.6%)	0.012
Age (years)	65.11 (7.09)	63.54 (11.94)	0.6
Body Mass Index (kg/m2)	30.42 (6.55)	29.39 (6.42)	0.2
Post-Secondary Education	61 (50.4%)	69 (54.8%)	0.2
Married	89 (73.6%)	87 (69.0%)	0.3
Symptom duration (years)	5.23 (5.79)	5.82 (5.66)	0.13
Want TJR?	52 (44.1%)	59 (47.6%)	0.6
Number of Co-morbidities			>0.9
0	28 (25.5%)	29 (24.8%)	
1	29 (26.4%)	28 (23.9%)	
2	25 (22.7%)	30 (25.6%)	
3+	28 (25.5%)	30 (25.6%)	
[Missing]	17	10	
Retired	74 (61.2%)	68 (54.4%)	0.3
Annual Household > \$60,000	72 (66.1%)	86 (69.4%)	
Baseline Health Utility (EQ-5D-5L)³	0.67 (0.19)	0.69 (0.21)	0.13
HOOS-12 / KOOS-12⁴			
Pain	48.24 (16.81)	49.58 (17.65)	0.3
Function	54.44 (19.58)	60.01 (20.92)	0.024
Quality of Life	36.15 (16.97)	39.79 (18.81)	0.072
Summary	46.29 (15.49)	49.86 (17.40)	0.054

¹n (%); Mean (SD)

²Pearson's Chi-squared test; Fisher's exact test; Wilcoxon rank sum test

³EQ-5D-5L is used to calculate baseline health utility ranging from -0.148 (worst) to 0.949 (best) quality of life.

⁴Scores in the HOOS-12 and KOOS-12 range from 0 (worst) to 100 (best).

4.4.2 Health Outcomes

GLA:D® and UC participants gained 0.71 (0.12) and 0.68 (0.12) adjusted QALYs over 12-months (Table 9). GLA:D® participants gained 7.76 (18.80), 4.50 (18.90), 11.66 (18.20), and 8.19 (16.61)

on the adjusted pain, function, QOL, and summary scores from baseline to 12-months.

Meanwhile, UC participants gained 1.12 (18.80), -2.84 (18.90), 4.68 (18.20), and 1.10 (16.61) on the adjusted pain, function, QOL, and summary scores. Differences in adjusted QALYs, pain, function, QOL, and summary scores were statistically significant between the GLA:D® and UC participants.

Table 9. Health outcomes over 12-months for participants with complete data.

	GLA:D®			Usual Care				
Variable	n ¹	Unadjusted Mean (SD)	Adjusted Mean (SD)	n ¹	Unadjusted Mean (SD)	Adjusted Mean (SD)	Unadjusted p-value	Adjusted p-value
QALYS gained								
Complete cases	68	0.699 (0.18)	0.712 (0.12)	91	0.684 (0.18)	0.682 (0.12)	0.60	0.04
Complete cases, no surgery	61	0.714 (0.18)	0.711 (0.12)	82	0.689 (0.18)	0.676 (0.12)	0.42	0.025
HOOS-12/KOOS-12¹								
Pain	83	7.76 (19.90)	7.76 (18.80)	99	0.25 (17.65)	1.12 (18.80)	<0.01	0.024
Function	79	4.98 (21.26)	4.50 (18.90)	99	-2.84 (16.40)	-2.84 (18.90)	<0.01	0.013
Quality of Life	84	8.93 (19.26)	11.66 (18.20)	101	1.79 (17.24)	4.68 (18.20)	<0.01	0.012
Summary	76	7.18 (18.28)	8.19 (16.61)	93	-0.31 (14.84)	1.10 (16.61)	<0.01	<0.01

¹Participants with complete data.

4.4.3 Costs

The mean 12-month cost to manage OA was \$1,604, and \$5,035 for the GLA:D® cohort compared to \$1,683, and \$3,913 for the UC cohort from a MOH and healthcare perspective (Table 10).

Table 10. Unadjusted costs for the GLA:D® and usual care cohorts by service type over 12-months.

	Ministry Perspective				Health Care Perspective			
	GLA:D®		UC		GLA:D®		UC	
	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)
Allied Health	\$121 (\$428)	\$0 (\$52)	\$59 (\$184)	\$0 (\$0)	\$1,933 (\$3,692)	\$672 (\$1,776)	\$985 (\$1,506)	\$380 (\$1,200)
Procedures	\$1,128 (\$3,594)	\$0 (\$198)	\$1,160 (\$3,579)	\$99 (\$297)	\$1,687 (\$5,102)	\$0 (\$297)	\$1,541 (\$4,438)	\$99 (\$396)
Medications	\$71 (\$310)	\$0 (\$0)	\$187 (\$1,324)	\$0 (\$0)	\$1,075 (\$1,785)	\$450 (\$765)	\$1,063 (\$2,707)	\$372 (\$710)
Doctors	\$293 (\$431)	\$108 (\$402)	\$291 (\$335)	\$188 (\$368)	\$293 (\$431)	\$108 (\$402)	\$291 (\$335)	\$188 (\$368)
Devices	\$0 (\$0)	\$0 (\$0)	\$0 (\$0)	\$0 (\$0)	\$199 (\$536)	\$0 (\$85)	\$154 (\$502)	\$0 (\$92)
Total	\$1,604 (\$3,789)	\$265 (\$967)	\$1,683 (\$3,890)	\$380 (\$877)	\$5,035 (\$7,778)	\$1,985 (\$5,273)	\$3,913 (\$5,483)	\$1,881 (\$3,808)

MOH = Ministry of Health, SD = Standard deviation, IQR = Interquartile range

4.4.4 Cost-Utility over 12-Months

We found that GLA:D® was associated with an adjusted INMB of \$6,065 (95% CI: \$3,648 to \$8,482) and \$499 (95% CI: -\$2,913 to \$3,912 compared to UC over 12-months from a MOH and healthcare perspective in the primary scenario analysis where all cases without surgery were included (Table 11). GLA:D® was associated with higher INMB in all scenarios in the MOH perspective but not all scenarios in the healthcare perspective. GLA:D® produced positive adjusted INMB for WTP thresholds ranging from \$7,000 - \$30,000 (Figure 8).

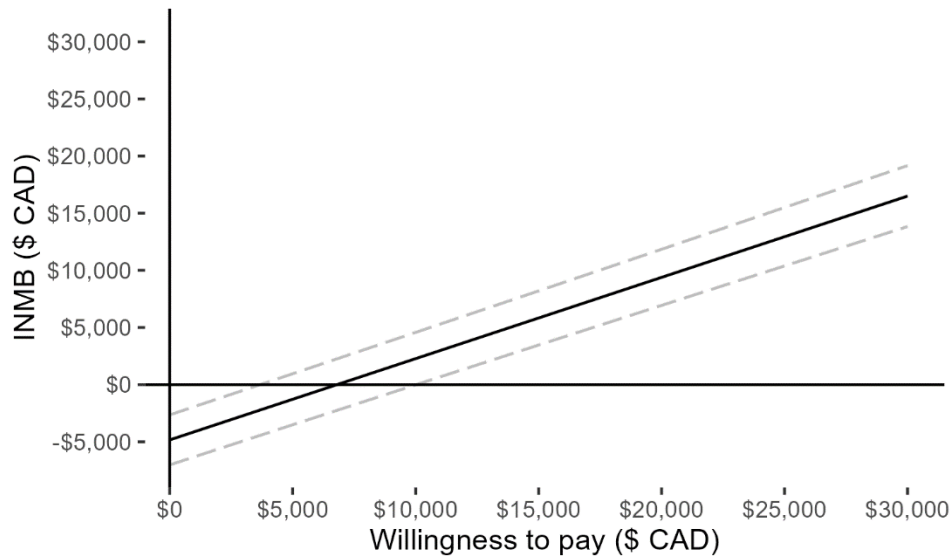
Table 11. Summary of incremental net monetary benefit over 12-months from the Ministry of Health and healthcare perspective.

	Scenario	n	INMB	95% Confidence Interval	Standard Deviation
MOH Perspective	All cases, no surgery*	231	\$6,065	(\$3,648, \$8,482)	\$1,223
	All cases	254	\$3,414	(\$341, \$6,487)	\$1,556
	Complete cases, no surgery	139	\$6,360	(\$3,549, \$9,171)	\$1,421
	Complete cases	154	\$4,657	(\$1,217, \$8,096)	\$1,740
Healthcare Perspective	All cases, no surgery	231	\$499	(-\$2,913, \$3,912)	\$1,731
	All cases	255	-\$1,581	(-\$5,906, \$2,774)	\$2,195
	Complete cases, no surgery	139	\$2,068	(-\$1,913, \$6,049)	\$2,195
	Complete cases	154	\$1,264	(-\$4,183, \$6,711)	\$2,756

Note: Ministry of Health (MOH) is the primary perspective.

*= primary scenario analysis, INMB = Incremental net monetary benefit

Figure 8. Incremental net monetary benefit at a range of willingness to pay thresholds (Ministry of Health perspective, Complete cases).



INMB = Incremental net-monetary benefit, CAD = Canadian Dollar

4.4.5 Cost-Utility over Lifetime

In the deterministic analysis, GLA:D® was associated with an adjusted INMB of \$6,298 and \$960 compared to UC over a lifetime time horizon from the MOH and healthcare perspectives in the primary scenario analysis where all cases without surgery were included. In the probabilistic analysis, GLA:D® was associated with an INMB of \$6,574 and \$1,775 compared to UC over a lifetime time horizon from the MOH and healthcare perspectives (Table 12).

Table 12. Probabilistic sensitivity analysis over lifetime from the Ministry of Health and healthcare perspective.

	Scenario	INMB	% CE at WTP	Cost Difference	Effect Difference	ICER
MOH Perspe	All cases, no surgery*	\$6,574	53.6%	-\$985	0.1863	-\$5,291
	All cases	\$5,108	51.8%	-\$892	0.1405	-\$6,352

Healthcare Perspective	Complete cases, no surgery	\$7,500	56.1%	-\$762	0.2246	-\$3,393
	Complete cases	\$8,394	58.0%	-\$2,749	0.1882	-\$14,610
	All cases, no surgery	\$1,775	50.9%	\$4,338	0.2038	\$21,288
	All cases	-\$5,607	48.1%	\$8,541	0.0978	\$87,320
	Complete cases, no surgery	\$4,043	53.5%	\$3,008	0.2351	\$12,798
	Complete cases	\$292	49.9%	\$5,200	0.1831	\$28,400

Note: Ministry of Health (MOH) is the primary perspective.

*= primary scenario analysis, INMB = Incremental net monetary benefit, CE = Cost-effective, WTP = Willingness to pay, ICER = Incremental cost-effectiveness ratio

Figure 9 shows the incremental difference in cost and outcomes between GLA:D® and UC over a lifetime time horizon from the MOH perspective in the probabilistic analysis (10,000 iterations). The likelihood of GLA:D® being cost-effective at a WTP threshold of \$30,000/QALY was 53.6% and 50.9% from a MOH and healthcare perspective (Figure 10). All sensitivity analyses moved the deterministic and probabilistic INMB results in favor of GLA:D® by less than 10% and the probability of being cost-effective by 0.1% or less.

Figure 9. Probabilistic incremental cost-effectiveness ratio of GLA:D® compared to UC over lifetime time horizon (Ministry of Health, All cases, No surgery).

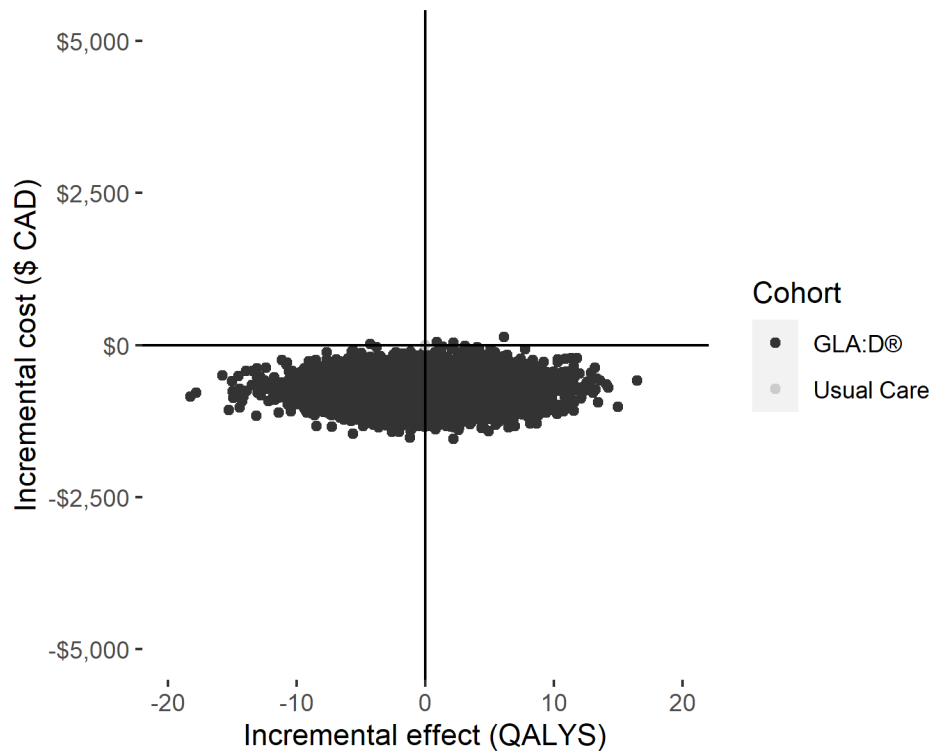
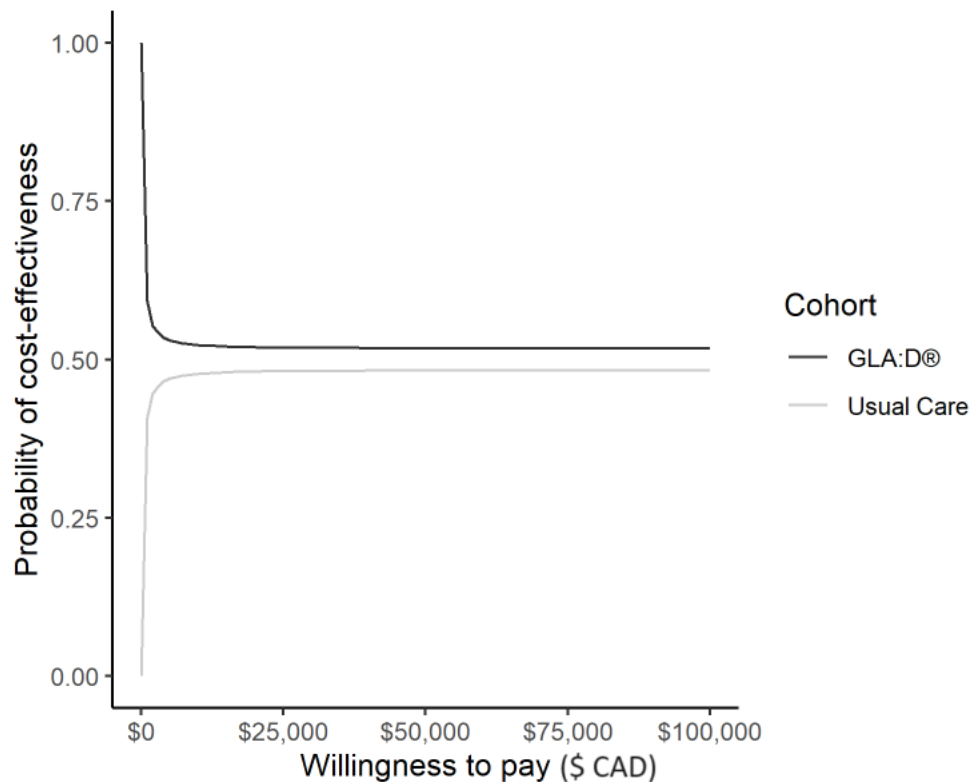


Figure 10. Cost-effectiveness acceptability curve comparing GLA:D® to UC at willingness to pay thresholds ranging from \$0-\$100,000 (Ministry of Health, All cases, No surgery).



4.5 DISCUSSION

Over 12-months, GLA:D® was associated with higher INMB than UC in the MOH perspective, but INMB was highly uncertain from the healthcare perspective. Similar results were observed over a lifetime time horizon but with a high degree of uncertainty. Our results suggest that healthcare systems can generate more value for money by funding first-line OA treatments, but monetary benefits may decline over time or when privately funded costs are considered. Our results can be generalized to people managing symptomatic hip and/or knee OA in the

community. Our sample was slightly younger, more educated, and had higher incomes than a population-level cohort in Ontario, Canada¹⁵⁰ but had similar demographics to GLA:D® participants in Alberta¹⁷⁹. Modest INMBs were generated from the combination of small health improvements in GLA:D® and small cost differences compared to UC. GLA:D® showed statistically significant improvements in unadjusted and adjusted pain, function, QOL, and summary scores compared to UC over 12-months. However, clinical outcomes did not meet the minimally important change, the smallest change that a patient perceives as clinically important (14.9 points¹⁸⁴). Interestingly, there was no differences in the unadjusted QALYs gained over 12-months by cohorts but statistically significant differences in adjusted QALYs. We further explored the unadjusted health outcome results by calculating the difference in health utility from baseline to 12-months instead of an area under the curve calculation and still did not find statistical differences between cohorts. This suggests the small unadjusted clinical effects observed with the disease-specific QOL measure (KOOS-12 /HOOS-12) and no unadjusted effects observed with the generic QOL (EQ-5D-5L) measure were related to the measure's sensitivity in our sample instead of the methods used to score each measure (slope versus area under the curve calculation). Controlling for baseline differences produced statistically significant differences in the adjusted QALYS gained and adjusted INMB from the MOH perspective over 12-months. This shows why controlling for baseline differences in non-randomized studies is crucial. Different results were also seen when a broader range of costs were considered in the healthcare perspective. Participants used many healthcare services from the private marketplace to manage their hip and/or knee OA symptoms which produced large out-of-pocket and private insurance costs. The average participant went to 3 massage, 2

chiropractor, and 1 acupuncture appointment during the study. We took a person-centered approach by including these costs in the healthcare perspective although many of these services are not recommended by clinical guidelines. Clinical guidelines focus on risks and benefits, but people living with OA may access services for a variety of reasons including symptom modification, treatment plan adherence, and psychosocial support. Value for money was reduced by including participants' and private insurance costs, but this finding is probably irrelevant to decision-makers who do not bear these costs. Meanwhile, participants must find value in using adjunct therapies because they showed preferences for these therapies by paying out-of-pocket for them even when our results from the healthcare perspective were negligible.

Our real-world results align with previous trial-based economic evaluations that showed exercise interventions were cost-effective at conventional WTP thresholds compared to UC¹⁵⁸. We found similar results to an economic evaluation conducted alongside a RCT by Skou et al.¹⁶² although our intervention was shorter (8-weeks versus 12-weeks), and our sample population was from the real-world. Standardized education and exercise therapy programs like GLA:D® may produce even greater INMB if these programs help participants avoid surgery. A recent Markov model suggests that first-line OA treatments could be cost-saving if surgery is avoided for two to five years¹⁸⁵. We cautiously estimated that GLA:D® reduced surgical risk by 11% then tested our assumption by dropping the estimate to 0% in an unreported secondary analysis which produced similar cost-effectiveness results to what was reported. Our assumption regarding surgical risk reduction is likely underestimated because RCTs have shown 68% of total

knee replacement candidates¹²⁸ and 44% of total hip replacement candidates¹⁸⁶ randomized to an exercise intervention did not proceed to surgery after long-term follow-up.

4.5.1 Policy Implication

Our results show important policy considerations in the Canadian healthcare system. Canada's universal publicly insured healthcare system provides 100% coverage for a narrow basket of services delivered in-hospital or by doctors but almost all community-based OA services delivered by allied health professionals are funded privately. Estimates suggest 70% of all healthcare costs in Canada are publicly funded¹⁸⁷, but our results showed the MOH funded only 10% of the total healthcare costs for managing hip and knee OA in the community. Participants paid 59% of healthcare costs out-of-pocket, which means access to first-line OA treatments in Canada are based on the ability to pay instead of need. Lack of access to first-line OA treatments will likely impact people with low socioeconomic status, who also have higher OA prevalence⁶. Including first-line OA treatments in Canada's basket of publicly insured services would be efficient and may also reduce inequitable access to proven treatments.

4.5.2 Strengths and Limitations

This is the first economic evaluation comparing a standardized education and exercise therapy program to UC in the real-world. Real-world data maximizes generalizability and provides the most relevant evidence to inform resource decisions. However, real-world data has several limitations. Regression techniques allowed us to control for baseline differences between cohorts, but unobserved confounding or effect modification is possible. Two data collection

portals were necessary to reduce respondent burden but could increase missing data. We did not see different missing and non-missing data patterns between cohorts, so assume data collection portals were not a primary cause of missing data. Missing data is also common in the GLA:D® Canada database because email notifications are auto-generated. We added phone call reminders which reduced missing data by 54%. We collected data every three-months to limit recall bias⁶¹. Lastly, a small sample means our results could be produced by randomness, but the probabilistic analysis found comparable results (albeit with increased uncertainty) when we re-sampled our observed cost and outcome distributions 10,000 times.

4.5.3 Recommendations for Future Research

Future research should evaluate the sensitivity of generic QOL measures in people with OA who are not eligible for TJR. Evaluating exercise therapy with weight management in a real-world setting could potentially deliver higher value for money because most people living with hip and knee OA also have excess body weight¹³⁵. Runhar et al. showed a diet and exercise intervention may not prevent OA in high-risk middle-aged women¹⁸⁸, but ample research shows first-line OA treatments are effective and cost-effective prior to TJR. Optimal timing of first-line OA treatments is poorly understood but could be important for maximizing clinical effects and healthcare system resources. Lastly, assessing whether implementing first-line OA treatment programs reduces surgical risk in the real-world has important implications as healthcare systems grapple with the growing burden of OA and surgical demand.

4.5.4 Conclusion

Publicly funding structured education and exercise therapy programs like GLA:D® would be an efficient use of healthcare system resources over 12-months based on the positive INMB compared to UC. The INMB of GLA:D® remained positive but was less certain when modelling was used to extend results to a lifetime time horizon. The INMB was positive in three out of four scenarios but had high uncertainty when all services paid by the MOH, private insurance, and out-of-pocket were considered.

5 ESTIMATING THE BUDGET IMPACT OF IMPLEMENTING A STANDARDIZED EDUCATION AND EXERCISE THERAPY PROGRAM FOR HIP AND KNEE OSTEOARTHRITIS IN A PUBLICLY INSURED HEALTHCARE SYSTEM

This chapter has been submitted to the journal of *Osteoarthritis & Cartilage* as:

Mazzei DR, Whittaker JL, Faris P, Wasylak T, Marshall DA. *Estimating the budget impact of implementing a standardized education and exercise therapy program for hip and knee osteoarthritis in a publicly insured healthcare system.* Under review at Osteoarthritis & Cartilage.

The Covid-19 pandemic happened while collecting data for our economic evaluation. Elective TJRs were reduced during the pandemic to maintain hospital bed capacity, causing wait times for TJR surgery to increase substantially. Decision-makers were committing resources to reduce surgical wait times as healthcare systems tried to recover from the challenges faced during the Covid-19 pandemic. Operational leaders encouraged our research team to consider options that could help optimize care for the population of people waiting for TJR consultation.

5.1 ABSTRACT

Objective: Estimate the budget impact of funding a standardized education and exercise therapy program (GLA:D®) for people with hip and knee OA waiting for total joint replacement (TJR) consultation in a universal publicly insured healthcare system.

Methods: We built a budget impact analysis (BIA) model to estimate the annual cost of treating people waiting for TJR consultation then forecasted a three-year budget cycle. The base case assumes 40% attend GLA:D®, 11% avoid surgery, care delivery is uniform, training costs are incurred separately, and the healthcare system has enough trained staff to meet demand. The population of people with hip and knee OA waiting for TJR consultation was estimated with government statistics, peer-reviewed evidence and routinely collected data from five orthopaedic centralized intake clinics (serving 80% of people seeking TJR). Patient-level costs were collected prospectively. International published evidence informed estimates of TJR avoidance. One-way sensitivity analysis of key parameters evaluated model robustness. Four scenarios were analyzed: public-funding for everyone (base case), low-income, rural, or uninsured persons.

Results: Offering GLA:D® to everyone waiting for TJR consultation would cost \$4.3 million, serve 12,500 people, and save approximately \$8.5 million by avoiding 1,300 TJRs in the first year. The number of TJR's performed annually produced the most uncertainty in budget impact (-\$15.3, -\$1.8 million). The most cautious parameter estimates still produce cost-savings.

Conclusions: Publicly funding a standardized education and exercise therapy program for everyone waiting for TJR consultation would avoid surgeries, improve equitable access to evidence-based treatments and save more than the program costs.

5.2 INTRODUCTION

Osteoarthritis (OA) is one of the most common chronic conditions globally¹³⁶. Healthcare system resources are strained by an aging population, obesity, and high OA prevalence¹⁸⁹. In Canada, \$1.26 billion is spent annually performing over 100,000 TJRs¹⁹⁰ and demand is expected to increase¹⁸⁹. Many publicly funded healthcare systems struggle with long wait times for TJR. Wait times have also worsened because surgery volumes were reduced during the Covid-19 pandemic to maintain hospital bed capacity¹⁹¹. National targets in Canada recommend the 90th percentile of people who are eligible for TJR should have surgery within 26 weeks after the orthopaedic surgeon and patient agree surgery is necessary. However, in 2022, the 90th percentile are being seen within 89.6 weeks for consultation and undergoing TJR surgery within 91.6 weeks¹⁹². Decision-makers have increased surgical capacity¹⁹³, but long wait times persist. Alternative solutions are necessary to address the wait time crisis for TJR.

Total joint replacements are appropriate and effective for end-stage OA after exhausting all other treatment options¹⁷. International clinical guidelines recommend everyone with hip and knee OA receive education, exercise therapy, and weight management as first-line treatment with adjunctive pharmacological pain management as needed^{15,194–196}. These guidelines have existed for 25 years¹⁸, but first-line treatments are consistently underused while medication and surgery are overused^{19,20,91,135,137,138}. Almost 40% of people with knee OA have not attempted first-line treatments before having a TJR³⁸. Standardized programs like Good Life with osteoArthritis in Denmark (GLA:D®) were developed to implement high quality hip and knee OA treatments into routine care^{27,28}. GLA:D® includes two education sessions and twelve

supervised neuromuscular exercise sessions delivered twice per week²⁷. 85,000 people in ten countries have taken GLA:D^{®33}, with most paying out-of-pocket because many healthcare systems and reimbursement plans do not include standardized education and exercise therapy programs⁹². A randomized controlled trial (RCT) evaluating knee replacement reported that 68% of surgical candidates randomized to an education and exercise program avoided surgery two years after the intervention¹²⁸. Optimizing nonsurgical care before surgery may help alleviate long wait times but resource implications are an important consideration for decision-makers. We conducted a budget impact analysis (BIA) to assess the affordability of publicly funding a standardized education and exercise therapy program like GLA:D[®] before TJR.

We used the publicly insured healthcare system in Alberta, Canada as an example in our BIA because the public healthcare provider, Alberta Health Services (AHS), has supported GLA:D[®] implementation since 2017. In Canada, the federal government provides co-funding for each province to deliver 100% publicly insured coverage for medically necessary doctor and hospital-based services. The Ministry of Health in each province provides additional co-funding and decides how to deliver healthcare for the population. The province of Alberta spends \$24.5 billion annually¹⁹⁷ delivering health care to a population of 4.4 million people. Community-based services like GLA:D[®] are funded by a complex mixture of public and private insurance or out-of-pocket payment. Patient-level costs were also recently collected in Alberta for a cost-effectiveness analysis¹⁹⁸ comparing persons receiving GLA:D[®] or usual care (defined as any community-based service people used to manage their OA symptoms before a TJR). Collecting

patient level costs for a standardized OA program and usual care presents an opportunity to estimate the budget impact and assess affordability of these programs from the healthcare system's perspective.

5.3 METHODS

We followed the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Budget Impact Analysis guidelines to transparently report the parameters and methods used when estimating the budget impact of adopting a new intervention in a healthcare system⁸⁰.

5.3.1 Model Design

Following standard practice, we programmed a cost calculator in Microsoft Excel[®] (Microsoft, USA) to estimate the public healthcare system's (Alberta, Canada) annual budget spent delivering care to people waiting for TJR consultation (Figure 11). Cost calculators produce annual budget estimates and are not time dependent, meaning clinical nuances like when an individual person is referred to TJR consultation are outside the scope of the research question and do not impact results. Our model takes the Ministry of Health (MOH) perspective because it includes all publicly funded healthcare costs and is considered the reference case in Canada⁵⁹. Costs were extrapolated over a three-year time horizon to be consistent with MOH budget forecasts and calculated in 2022 Canadian dollars. We assumed: 1) a proportion of people waiting for TJR consultation will participate in GLA:D[®] regardless of prior treatment, 2) the cost of training clinicians in GLA:D[®] delivery will be funded by employers' professional development budget, 3) GLA:D[®] delivery is uniform across all locations, 4) each GLA:D[®] class has six

participants, and 5) the healthcare system has reached a steady state by training enough staff to meet demand for the program. Infections, revisions, bilateral TJRs, and TJR for a different joint were excluded from our BIA model because we assumed GLA:D® participation would not change the costs related to these clinical characteristics.

Figure 11. Budget impact analysis formula.

$$\text{Annual Budget} = ((A - B + C) * D) + (E * F) - (C * G) + (B * G)$$

Where:

A = Number of people waiting for TJR consultation annually

B = Number of TJRs annually

C = Number of TJRs avoided annually

D = Cost of community management annually

E = Number of people waiting for TJR consultation who participate in GLA:D® annually

F = Cost of GLA:D® (per person)

G = Cost of TJR (per person)

5.3.2 Data Sources

Model inputs were estimated from peer-reviewed research, grey literature, local administrative data, and expert clinical opinion as described below (Table 13).

Table 13. Parameters used in the budget impact analysis model.

Parameter (Alberta specific)	Value	Source
Total population	4.44M	Government of Alberta ³⁵
Annual population growth rate	1.5%	Government of Alberta ³⁵

All-cause mortality rate	0.6%	Government of Alberta ¹⁸³
OA prevalence	8.0%	Marshall et al. ³⁴
OA incidence (annual)	0.9%	Marshall et al. ³⁴
OA population waiting for TJR consultation	31,227	Alberta Bone and Joint Health Institute ¹⁹⁹
Forecasted number of TJRs annually (2021/22- 2024/25)	13,071 – 14,267	Alberta Bone and Joint Health Institute ³⁷
Per person cost of GLA:D® at private clinics	\$400	GLA:D® Clinics
Per person cost of GLA:D® at public clinics	\$304	Expert opinion
Annual cost per person to manage OA with UC	\$653	Mazzei et al. ¹⁹⁸
Average cost per TJR	\$10,116	AHS ¹⁸²
Implementation costs	\$211,920	AHS ²⁰⁰
Percent avoiding TJR	11%	GLA:D® Canada ²⁰¹
GLA:D® participation rate from population waiting for a TJR	40%	Expert opinion

Note: Estimates in 2022 Canadian dollars. M = million

5.3.3 Population Estimate

Population waiting for TJR consultation: The population waiting for TJR consultation was estimated from routinely collected data at five orthopaedic centralized intake clinics who provide access to approximately 80% of TJRs throughout Alberta. We assumed the population of people waiting for TJR consultation would increase at the same rate as the population of people with OA in Alberta. The population of people with OA was estimated by multiplying population growth, mortality rates, and OA prevalence in Alberta^{34,35,183}.

GLA:D® participation rates: We extracted participation rates from peer-reviewed research evaluating exercise therapy in people with hip and knee OA then asked experts their opinion. Eighty percent of patients eligible for TJR consented to participate in RCTs of exercise therapy²²,

but clinical experts thought participation may be lower in real-world. We conservatively estimated that participation rates would be half of what was observed in peer-reviewed research (40%) when people were invited to participate in GLA:D® if it was publicly funded while they wait for TJR consultation.

Population avoiding TJR: Randomized controlled trials have observed that 44%¹⁸⁶ to 68%¹²⁸ of people with hip and knee OA avoided TJR after being randomized to exercise therapy, however, there might be selection bias in these samples. Only 9% (n = 127 / 1475) of those screened were eligible to participate in the Skou et al. study and 79% (n = 100 / 127) of eligible patients were willing to be randomized. We used real-world data from the GLA:D® Canada database to estimate that 11% of participants would avoid TJR. GLA:D® participants were asked, “are you so troubled by your knee/hip problems that you want surgery?” with “yes” or “no” as possible answers. Participants who responded “yes” before the GLA:D® program then “no” at 12-months were used to estimate the percent of the population who would avoid TJR for the three-year budget cycle¹⁷⁹.

5.3.4 Cost Estimate

Community management: The cost of managing OA in the community was estimated from administrative data in a cohort of participants receiving usual care in Alberta, Canada¹⁹⁸. The average cost was applied to each person in the population of people waiting for TJR.

GLA:D®: The price to attend GLA:D® ranges from \$375 to \$450 at private clinics in Alberta. We assumed the average price was \$400 because only one out of 68 clinics charged \$450 when the study was conducted. Public facility costs were estimated by taking an average physiotherapist salary (\$43.48 hourly plus 20% for benefits) multiplied by 2.5 hours per class (30-minute preparation, 60-minute class, 30-minute take down and 30-minute charting) for 14 classes producing an estimated cost of \$1,826 per class¹⁷¹. Assuming 6 participants per class produced a per person cost of \$304. Public facility cost estimates do not include facility costs such as electricity and maintenance because these costs are incurred in a separate part of the budget whether GLA:D® is delivered or not. We assumed clinics already had the necessary equipment because GLA:D® was designed to use minimal equipment and resistance bands would often be purchased by the patient for a nominal fee.

TJR Surgery: In 2022, AHS estimated that the average TJR costs \$10,116¹⁸². Surgical costs include physician compensation, materials, staff time, and bed days in hospital. This estimate does not include rehabilitation because these costs are pre-dominantly incurred out-of-pocket⁴¹.

Implementation: Implementation costs were estimated from AHS Bone and Joint Strategic Clinical Network™ (BJH SCN™) which began piloting GLA:D® in 2017. Strategic Clinical Networks are the innovation arm of Alberta's publicly funded healthcare system. Strategic Clinical Networks bring together clinical experts, operational leaders, patients, and researchers to produce transformative solutions to improve health care delivery. The BJH SCN™ supported

GLA:D® implementation by taking on administrative duties as well as offering annual clinician training classes, hosting regular community of practice meetings for clinicians to learn from one another, and fidelity checks during the pilot-phase. GLA:D® was implemented at 45 privately funded community rehabilitation clinics, 5 out of 40 primary care networks, and 18 out of 106 AHS facilities⁴³. The BJH SCN™ hired one additional staff member to support GLA:D® implementation and other team members contributed a portion of their time. Implementation costs include staff time, research grants, travel, training sessions, and event-related costs.

5.3.5 Sensitivity Analysis

Parameter uncertainty was evaluated using one-way sensitivity analysis with estimates from Table 14. Each parameter was varied with a high and low estimate to evaluate how variability surrounding each parameter would change the budget impact results. One standard deviation was used for parameters with distributions. The highest and lowest reported price to attend GLA:D® at a private facility in Alberta was used to show how price will change the budget impact. GLA:D® Denmark and GLA:D® Australia ask the same question about wanting surgery before participating in GLA:D® and at 12-months so we used real-world data from these databases as high and low estimates for the percent of people who would avoid TJR^{33,180}. All other parameters were varied by 5-50% based on the research team's confidence with each parameter. Results were visualized in a tornado diagram where parameters were ordered from most to least impact on the primary results⁵².

Table 14. Estimates used in the sensitivity analysis to examine parameter uncertainty.

Variable (Alberta specific)	Estimate	Low	High
Total population	+/- 5%	4.22M	4.65M
Annual growth rate	+/- 20%	1.22%	1.82%
All-cause mortality rate	+/- 10%	0.52%	0.64%
OA prevalence	+/- 20%	6.42%	9.64%
OA incidence (annual)	+/- 20%	0.69%	1.03%
OA population waiting for TJR consultation	+/- 5%	29,665	32,788
Per person cost of GLA:D® at private clinics	-	\$375	\$450
Per person cost of GLA:D® at public clinics	+/- 15%	\$259	\$350
Annual cost per person to manage OA with UC	+/- 1 SD	\$580	\$726
Number of TJRs (annual)	+/- 5%	13,174	15,779
Average cost per TJR*	+/- 10%	\$9,104	\$11,128
Average percent avoiding TJR	Observed	7.8% ³³	15.5% ¹⁸⁰
GLA:D® participation rate from population waiting for a TJR	+/- 50%	20%	60%

M = million, OA = osteoarthritis, GLA:D® = Good Life with osteoarthritis Denmark, SD = standard deviation, UC = usual care, TJR = total joint replacement

5.3.6 Scenario Analysis

Decision-makers may choose to publicly fund GLA:D® for various subpopulations based on costs, expected benefits, clinical characteristics, or equity considerations. Operational leaders within the BJH SCN™ helped us select four different funding scenarios to assess how publicly funding GLA:D® for different subpopulations would impact affordability: 1) low-income people to reduce economic inequities, 2) people in rural communities to reduce geographic inequities, 3) high risk subpopulations where TJR surgical risks outweigh the potential benefits (e.g., contraindications to general anesthetic), and 4) people who do not have private health insurance that covers allied health professional (e.g., rehabilitation) visits (Table 15).

Table 15. Scenario analysis population estimates.

Scenario	Percent of Population	Source
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Low income	8.2%	Statistics Canada ²⁰²
High surgical risk*	14%	Mazzei et al. ¹³⁵
Rural population	20%	Government of Alberta ³⁵
Uninsured	30%	Mazzei et al. ¹⁹⁸

* = defined as subpopulations where the TJR surgical risks outweigh the benefits.

5.4 RESULTS

5.4.1 Base Case Analysis

We estimate that the MOH will spend \$155.4 million in the first year delivering OA care to people waiting for TJR consultation and publicly funding GLA:D® would reduce the annual budget to \$146.7 million (Figure 12). In the first year, it would cost \$4.3 million to publicly fund GLA:D® and 1,374 people would avoid surgery, producing net savings of approximately \$8.5 million by reducing demand for TJR. Over three years, the population waiting for TJR consultation is expected to grow from 31,227 to 32,817 people. The number of people participating in GLA:D® and avoiding TJR would also grow. The total budget impact is -\$8.5, -\$8.8, and -\$8.7 million in year 1, 2, and 3 respectively (Table 16).

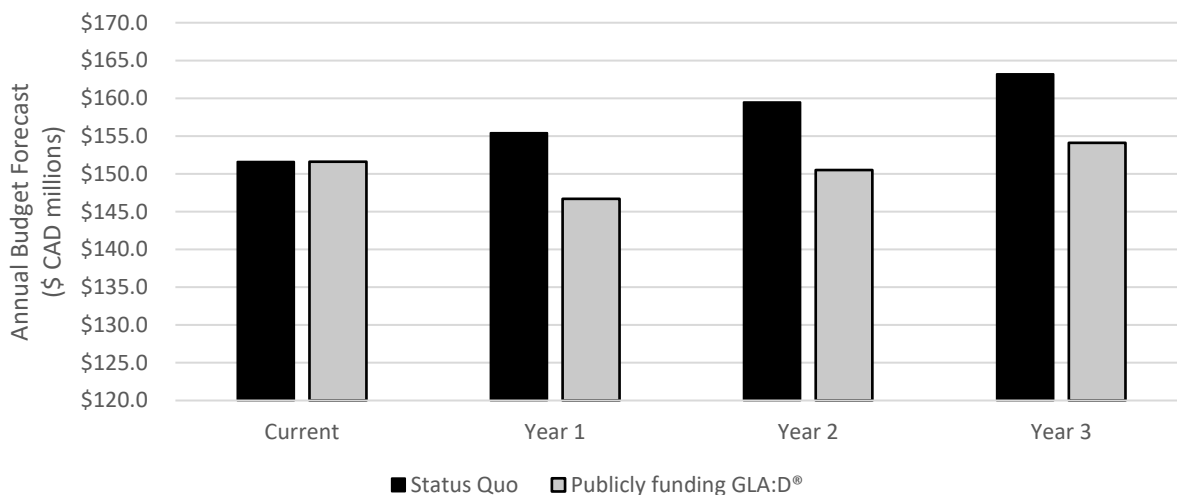
Table 16. Budget impact for publicly funding GLA:D®.

	Current	Year 1	Year 2	Year 3
OA population waiting for TJR consultation	31,227	31,227	31,521	32,817
Status Quo				
Total annual budget for managing OA population waiting for TJR consultation with status quo	\$151.6	\$155.4	\$159.5	\$163.0
Publicly funding GLA:D®				
Population who attends GLA:D® in publicly funded scenario	739	12,491	12,608	12,727
Avoided TJR	0	1,374	1,387	1,400
Cost of publicly funding GLA:D®	\$0	\$4.3	\$4.3	\$4.4

Cost of avoided total joint replacements	\$0	-\$13.9	-\$14.0	-\$14.2
Implementation costs	-	\$0.2	\$0.2	\$0.2
Total annual budget for managing OA population waiting for TJR consultation with publicly funding GLA:D®	\$151.6	\$146.7	\$150.5	\$154.1
Budget Impact	-	-\$8.5	-\$8.8	-\$8.7
Budget Impact (percent of status quo annual budget)	-	-5.5%	-5.5%	-5.3%

Note: Dollar figures are in millions (2022 Canadian dollars) and rounded to the nearest decimal so rows may not add.

Figure 12. Annual budget forecast of publicly funding GLA:D® compared to status quo.



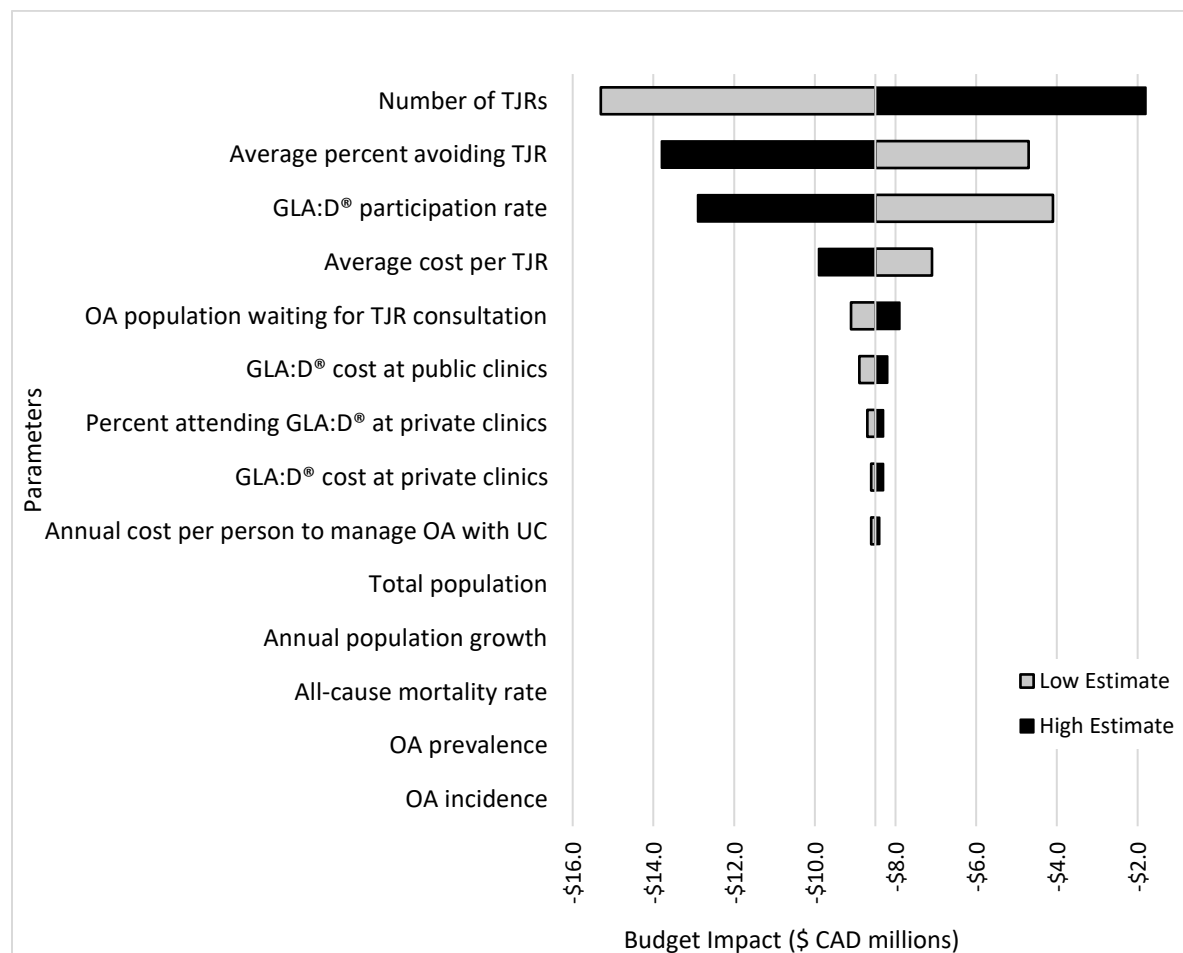
Note: Budget impact is the difference in annual budget forecast between status quo and publicly funding GLA:D® in each year.

5.4.2 Sensitivity Analysis

Parameter uncertainty is shown in Figure 13. All estimates produced cost-savings shown by negative budget impacts. The annual number of TJRs produces the most uncertainty, causing the budget impact in year 1 to range from -\$15.3 million if there are 5% less TJR's than what was forecasted to -\$1.8 million if there are 5% more TJR's than what was forecasted in the base

case. The budget impact ranges from -\$13.8 to -\$4.7 million if the percentage of people avoiding surgery changes from 15.5% to 7.8%. The budget impact will be -\$12.9 million if the participation rate is 60% or -\$4.7 million with participation rates of 20%. No estimates pass the breakeven point (budget impact of \$0) where cost-savings are greater than the budget to deliver GLA:D®.

Figure 13. Change in budget impact estimates based on parameter uncertainty.



Note: Figure is centered around the Year 1 estimate (-\$8.5 million) from the base case analysis.

5.4.3 Scenario Analysis

All scenarios would save more than the budget needed to publicly fund GLA:D® for the identified subpopulations. Publicly funding GLA:D® for low-income, high surgical risk, rural, and uninsured subpopulations would cost \$0.4, \$0.6, \$0.9, and \$1.3 million while saving \$0.5, \$1.0, \$1.5, and \$2.4 million respectively (Table 17). Publicly funding GLA:D® for more people will save more.

Table 17. Scenario analysis for publicly funding GLA:D® in select subpopulations.

Scenario*	Percent of Population	Number of annual GLA:D® participants	Cost to deliver GLA:D®	Budget Impact
All (base case)	40%	12,491	\$4.3	-\$8.5
Low-income	8%	1,024	\$0.4	-\$0.5
High surgical risk	14%	1,749	\$0.6	-\$1.0
Rural	20%	2,498	\$0.9	-\$1.5
Uninsured	30%	3,747	\$1.3	-\$2.4

Note: Dollar figures are in millions (2022 Canadian dollars) and rounded to the nearest decimal.

*= Subpopulations waiting for TJR consultation.

5.5 DISCUSSION

Investing \$4.3 million will allow 12,491 people awaiting hip and knee TJR consultation to participate in GLA:D® free-of-charge and save the MOH approximately \$8.5 million in the first year by avoiding 1,374 TJRs. Over three years, cost-savings will grow to \$8.7 million annually as the population awaiting TJR consultation grows.

We estimated that 40% of people would participate if GLA:D[®] was offered free-of-charge and 11% of participants would avoid surgery. Parameter uncertainty changes the budget impact, but even pessimistic estimates for participation rates and the percentage of people who avoid surgery will still break even (shown by negative budget impacts). Based on our findings, publicly funding the GLA:D[®] program would pay for itself if as few as 3% of people who participated in GLA:D[®] or 1% of those waiting for TJR consultation avoid surgery. Our scenario analysis showed that funding GLA:D[®] for subpopulations instead of everyone would cost less but also lead to lower savings. A healthcare system will save more if more people participate in GLA:D[®]. Providing universal public funding to a structured education and exercise therapy program like GLA:D[®] ensures everyone has equitable access to evidence-based OA treatments, regardless of socioeconomic, geographic, or clinical characteristics.

Our results align with other budget impact models evaluating standardized education and exercise therapy programs. Ackerman et al. found that the Australian healthcare system could save \$300-690 million if standardized education and exercise therapy programs were implemented nationally¹²⁹. Their results showed more savings than ours because they assumed surgical avoidance and intervention costs from RCT data¹²⁸. Populating our model with real-world data from people accessing OA care in the community is more likely to be generalizable to the policy options that decision-makers face. Smith et al. showed an exercise and diet intervention for OA would be a similar cost to other health promotion programs from the perspective of commercial insurance or Medicare Advantage plans in the United States²⁰³. Our results add to the evidence-base by evaluating a standardized education and exercise therapy

program from the perspective of a publicly insured healthcare system delivering universal access.

Other healthcare systems can learn from the implementation experience in Alberta although some context is unique⁸⁵. The implementation costs in our model were quite small because only one full-time equivalent staff member was hired to support implementation and three other staff members reported working on GLAD implementation for 10-30% of their work hours. The SCNs act as supportive infrastructure within AHS by providing teams and resources to support innovation. Academics and non-profit organizations like Bone and Joint Canada also played an important role setting up and maintaining routine data collection. Healthcare systems may incur additional implementation costs if innovation teams are not already embedded within their organization and partners do not offer in-kind support for common goals. Administrative costs were also not included because the GLA:D® program and AHS do not have centralized referral pathways or patient navigation services for people with hip and knee OA. Our BIA model assumed a ramp up of training had already occurred and the healthcare system has reached a steady state with enough capacity in GLA:D® trained staff to deliver the program to 12,000 people annually in the first year of the program. This volume is feasible in a healthcare system like AHS who has supported implementation of GLA:D® for several years, but healthcare systems adopting a new program may have reduced volumes before reaching a steady state. Increasing capacity of trained allied health professionals is a primary barrier during the initial stages of implementation. Training multiple providers at each clinic is important to deliver the program sustainably. Publicly funding a program like GLA:D® may

incentivize clinicians to take the training course faster than what occurred in Alberta. A community of practice, pre-packaged materials, and the ability to perform the exercise program without specialized equipment facilitated program uptake⁸⁵. However, implementing GLA:D[®] took longer than expected, with most clinicians delivering their first class 3-4 months after training⁸⁵. Marketing the program is critical to increase patient uptake. Clinicians believed referral pathways would also remove barriers to the program. The GLA:D[®] program was originally delivered in-person but was adapted to a virtual delivery model during the Covid-19 pandemic. Virtual delivery is an important option in countries with large land mass like Canada, specifically for people in rural and remote communities. Our model shows that the difference in cost based on delivering GLA:D[®] at private or public clinics is marginal. When deciding the delivery location, healthcare systems should consider what is feasible to rapidly scale the program based on the local context of allied healthcare professionals.

Our budget impact results are complementary to the previously published economic evaluations showing standardized OA programs are cost-effective in many healthcare systems¹⁵⁸. Cost-effectiveness helps decision-makers understand whether a new intervention generates more value (i.e., health benefit) for money than an alternative intervention. However, it is possible for a new intervention to be cost-effective, but not affordable if the price is high and a large percentage of the population uses the new intervention. We estimated that a standardized education and exercise therapy program like GLA:D[®] is cost-effective and affordable because it may help people avoid TJRs which cost 25 times more than the GLA:D[®]

program per person. Combining cost-effectiveness and affordability provides a comprehensive economic picture of implementing GLA:D® into a publicly insured healthcare system.

5.5.1 Policy Implications

Publicly insured healthcare systems use waitlists to control demand for finite resources like TJRs. This means cost-savings in the real-world would be observed as reduced wait times instead of budget reductions because another person will have the TJR that was avoided. Using queuing theory, we estimate that the 90th percentile wait time for TJR would be reduced by 12.3 weeks if 11% of GLA:D® participants avoided surgery. This means a publicly insured healthcare system in Canada could reduce the 90th percentile wait time for TJR surgery from 91.6 weeks to 79.3 weeks. Healthcare systems could spend \$4 million offering GLA:D® to everyone waiting for TJR consultation or \$14 million increasing surgical volumes to achieve the same wait time reductions. However, increased surgical volumes also assume there is operating room capacity and trained staff (e.g., orthopaedic surgeons, anesthesiologists, and nurses) to meet the increased surgical demand. Publicly funding a structured education and exercise program like GLA:D® is an affordable solution that could help decision-makers reduce long wait times.

Our BIA model can help decision-makers in publicly insured healthcare systems understand the financial considerations of implementing standardized education and exercise therapy programs into funded clinical pathways or reimbursement plans. Chronically long wait times for TJR are a persistent issue in public-insured healthcare systems. Operating room and human

resource capacity often constrains the ability to rapidly increase surgical capacity. Optimizing nonsurgical care by funding standardized education and exercise therapy programs before surgery is an affordable solution that may help decision-makers address chronically long wait times in publicly insured healthcare systems.

5.5.2 Strengths, Limitations and Future Research

Our BIA model uses real-world costs and implementation experiences within a publicly insured healthcare system to showcase the financial considerations of implementing standardized education and exercise therapy programs into a large publicly insured healthcare system. However, healthcare system benefits are likely underestimated because our model only considers the benefits for OA and ignores the additional health benefits that can be gained from exercise for 35 other chronic diseases¹⁵⁴. Our model assessed funding a standardized education and exercise therapy program for people waiting for TJR consultation because long wait lists are the most relevant problem for decision-makers, however, clinical guidelines recommend education and exercise therapy right after diagnosis. Future research will need to evaluate optimal timing of education and exercise therapy to maximize clinical benefits and healthcare system resources. We also assumed surgeries were avoided for the entire budget cycle when some people may delay but still go on to having TJR. Skou et al. showed 26% of randomized patients randomized to structured education and exercise therapy program proceeded to surgery at one year and 9% after two years, suggesting a diminishing percentage of people delaying surgery^{22,128}. We expect delayed surgery would be an insignificant cost compared to the total annual cost of managing everyone waiting for hip and knee TJR

consultation. Assessing whether standardized education and exercise therapy programs actually help people avoid TJR in the real-world also has important implications. Lastly, implementation research can help healthcare systems reduce other barriers like knowledge gaps, expectations, and referral patterns to increase participation rates.

5.5.3 Conclusion

Our results suggest that providing GLA:D® to everyone waiting for a TJR consultation would avoid surgeries and save more than the program costs. Funding GLA:D® prior to TJR consultation would be an affordable solution to reduce wait times in publicly funded healthcare systems.

6 SUMMARY

6.1 Summary of Key Findings

Clinical guidelines for hip and knee osteoarthritis have recommended education and exercise therapy programs like GLA:D® for 25 years¹⁵, but these proven treatments remain underused globally^{15,194–196,204}. In Chapter Three, we observed that only 20% of participants who were recommended nonsurgical care by an orthopaedic surgeon used all guideline-consistent nonsurgical treatments to manage their knee OA within six years of consultation. Our results highlight a significant gap between usual care and best practice in Alberta. Addressing barriers will be critical to increase use of proven treatments. A feasibility evaluation of GLA:D® highlighted that out-of-pocket costs were a real and perceived barrier to accessing the programs in Alberta⁸⁵. Our cost-effectiveness analysis in Chapter Four showed that publicly funding GLA:D® would be an efficient use of health system resources over 12-months, and potentially a lifetime from the MOH perspective. Our BIA results in Chapter Five suggest that providing GLA:D® to everyone waiting for a TJR consultation would avoid surgeries and save more than the program costs. Together, our cost-effectiveness and budget impact results show that funding GLA:D® is associated with increased value for money and might be an affordable solution to reduce wait times in Alberta. Publicly funding GLA:D® could increase use of first-line treatments in Alberta by filling an important care gap, offer more equitable access to evidence-based care, reduce significant out-of-pocket expenses for people living with OA, and improve healthcare system performance.

6.2 Strengths and Limitations

Our research has several limitations. First, observational research is more vulnerable to bias than randomized controlled-trials. Self-reported data can be impacted by recall, non-response, or the Hawthorne effect which potentially leads to systematic bias. Our budget impact model also estimated a reduction in surgical risk that has not yet been observed in the real world. We attempted to reduce these limitations where possible and interpreted results cautiously.

However, collecting observational data in Alberta allowed us to produce evidence that can inform resource decisions in Alberta, which was the primary goal of this thesis. Collecting patient-level cost and outcomes allowed for a more robust comparison than building a decision-analytic model with parameter inputs from other healthcare systems. Previous estimates using administrative data estimated that community-based management of OA had minimal costs. However, in Chapter 4 we observed that the MOH only covers 10% of costs people incur while managing their hip and knee OA prior to TJR. Our economic evaluation is the first to show that Albertans with hip and knee OA incur significant costs managing their OA using services delivered by the private marketplace. These results have significant equity considerations because low-income and uninsured people also have higher OA prevalence⁶.

6.3 Policy Implications

Publicly insured healthcare systems can put health economics theory into practice by reallocating budgets to optimize the opportunity cost of finite resources. This thesis suggests that Alberta Health (AH) could increase value for money by shifting budgets from low-value to

high-value services. Alberta Health publicly funds a variety of nonsurgical OA treatments that are not supported by current evidence. Alberta Health Services offers OA self-management education classes through the Alberta Healthy Living Program. However, our systematic review showed education alone was not cost-effective for managing hip and knee OA¹⁵⁸. Alberta Health also spends approximately \$3 million dollars annually providing publicly funded knee braces for people with knee OA through the Alberta Aids to Daily Living program²⁰⁵. Meanwhile, knee braces were removed from the most recent international clinical guidelines because they have poor quality evidence and lack efficacy¹⁵. Evidence suggests that education classes and knee braces provide little or no value for money. Alberta Health could stop funding low-value services like education classes and knee braces then use these resources to publicly fund structured OA management programs like GLA:D®. Shifting budget from low-value services to evidence-based programs like GLA:D® is a practical policy solution that will help AH achieve their goal of delivering a sustainable, high-performing healthcare system.

This doctoral thesis project is a timely contribution to the policy-making process in Alberta. The covid-19 pandemic exacerbated chronically long wait times for TJR surgery. Alberta's government has also committed to reducing TJR surgery wait times. Historically, governments have reduced wait times by funding more surgeries. The MOH has already increased funding for surgeries and started to contract private facilities to deliver more publicly funded surgeries. However, increasing surgical supply will always be limited by operating room capacity and availability of trained staff with surgical expertise (e.g., orthopaedic surgeons, anesthesiologists, and nurses). This thesis work shows that government could also reduce wait times by funding

structure OA management programs like GLA:D® to reduce surgical demand. There are currently 134 allied health professionals trained to deliver GLA:D® in Alberta. Expanding public funding of GLA:D® could optimize this under used workforce. Exhausting nonsurgical treatments prior to surgery is an alternative and affordable solution that may help the government reach its goals.

6.4 Implementation

The remaining policy questions in Alberta center around implementation. Implementation must consider workforce demands, who should receive public funding to attend GLA:D®, how to deliver public funding, and where the program should be delivered to address geographic and cost-related inequitable access to first-line OA treatments in Alberta.

A workforce already exists to support the spread and scale for GLA:D®, but more staff will need to be trained to meet projected demand for the program. Budget impact analyses are regularly conducted in a steady state and our results forecast demand for 12,500 participants annually. However, only about 750 people currently participate in GLA:D® each year in Alberta. The AHS BJH SCN™ would need to support a ramp up phase to meet demand for GLA:D® if the program received public funding. There are currently 134 trained clinicians in Alberta who could be called upon to deliver more classes. Every clinician could reasonably deliver GLA:D® twice per quarter to an average of 6 participants, serving a total of 48 participants annually. The current number of GLA:D®-trained clinicians could provide immediate capacity for 6,432 participants annually. Adding 126 more clinicians would meet projected demand for the program.

Historically, one weekend clinician training course has been offered each year for 50 clinicians, but additional weekend course could be organized. There are over 3,000 physiotherapists practicing in Alberta so doubling the number of trained clinicians appears reasonable²⁰⁶. Increasing the number of GLA:D® classes offered by each trained clinician and training more clinicians could meet forecasted demand for GLA:D® in approximately two years.

The scenario analysis in our BIA suggests that offering publicly funded GLA:D® classes to everyone with hip and knee OA is likely the most equitable funding solution to reduce cost-related barriers for accessing first-line treatments. The more people who attend GLA:D® will produce greater wait time reductions for TJR. However, some decision-makers might want to leverage private health insurance as well because approximately 70% of Albertans in our sample had private health insurance coverage for allied healthcare professional visits. A public funding model similar to the community rehabilitation program (CRP) for physiotherapist access in Alberta could be implemented. The CRP program allocates an annual budget per clinic and sets the price per publicly funded visit to see a physiotherapist. Rehabilitation clinics typically spread those publicly funded visits equally throughout the year. People who need to see a physiotherapist can wait for a publicly-funded visit or use private health insurance to pay for the next available visit. This two-tier funding arrangement uses a waitlist to manage access to publicly funded visits like all other publicly funded healthcare services in Canada. It also provides patients with an option for using private insurance if they would like to. Alberta Health would likely spend less than forecasted using a two-tier funding model because some patients will choose to access GLA:D® with funding from their private health insurance provider.

The final implementation challenge must address where publicly funded GLA:D® classes are located. Our sensitivity analysis in Chapter Five estimated that the cost savings would be \$8.9 million, \$8.5, or \$8.3 million if GLA:D® classes were delivered at public facilities only, at the current mixture of private and public facilities or private facilities only. Where publicly funded GLA:D® classes are delivered produces a 7% difference in cost-savings, however, the ability to ramp up capacity in only private or public facilities would be slower than continuing the current mixture of private and public facilities. Harnessing trained staff at both private and public facilities is likely the best solution to rapidly increase capacity while still leading to cost-savings which will be observed as wait time reductions. The geographic distribution of public and private facilities is also a consideration. Many rural communities would only be able to access GLA:D® as outpatient rehabilitation visits at publicly funded hospitals while most urban communities would only have access to GLA:D® at private rehabilitation clinics. Publicly funding GLA:D® that is delivered at public and private facilities ensures equitable access regardless of geographic location in the province. Delivering GLA:D® virtually is another tool that can be leveraged to provide GLA:D® in rural and remote communities that do not currently have GLA:D®-trained clinicians. Delivering first-line OA treatments virtually can produce similar reductions in pain and improvements in function as in-person services²⁰⁷. Publicly funding GLA:D® that is delivered in-person at public and private facilities as well as offering virtual care options provides Albertans with choice that will also reduce geographic inequitable access to first-line treatments.

6.5 Contributions to the Research Field

This body of work can help decision-makers in Alberta identify a funding model that provides equitable access to GLA:D®, but also contributes notable additions to the research field of economic evaluations for first-line OA treatments as well. Our systematic review found that education alone is not cost-effective, primarily driven by the fact that education did not change health outcomes over short or long-term follow-up. However, structured OA management programs that delivered evidence-based care were cost-effective in many different countries. These results suggest that healthcare systems should implement referral pathways and structured OA management programs to generate value from first-line OA treatments instead of relying on education alone. However, healthcare systems may be hesitant to implement structure OA management programs because the RCTs included in our systematic review may have limited generalizability to the policy questions that decision-makers face. Our CEA in Chapter Four aimed to address the generalizability limitation by using real-world data to assess value for money. The clinical effect we observed may have been lower than RCT designs, but cost-effectiveness remained positive suggesting that implementing structured OA management programs in the real-world may improve value for money compared to UC. Our BIA findings also provide unique insights into how a structured OA management program may save healthcare system resources, which in the real-world will be experienced by reduced wait times in publicly insured healthcare systems. This provides valuable results for decision-makers who may consider publicly funding and implementing structured OA management programs in the real-world.

6.6 Knowledge Translation

During a CIHR-funded Health System Impact Fellowship, I used preliminary findings from this body of work to develop a draft business case for publicly funding the GLA:D® program in Alberta while I was embedded within the AHS BJH SCN™. The business case summarizes the effectiveness, safety, appropriateness, return on investment, value for money, budget impact, and implementation plan for scaling GLA:D® across Alberta. I will update the business case with results from the manuscripts in Chapter Four and Five after they are published. Our healthcare system partners will be able to use the business case to inform funding decisions in Alberta.

By engaging our healthcare system partners throughout the research process we have made our results more useful to the end-user. The AHS BJH SCN™ is currently developing a grant proposal for operational funding to scale GLA:D® across Alberta. AHS uses the Innovation Pipeline as a framework for making decisions based on real-world evidence in Alberta to achieve the quadruple aim: better outcomes, better experiences, better quality, and better value for money²⁰⁸. The Innovation Pipeline is a mechanism designed for generating standardized evidence and evaluating innovations during the pilot, implementation, and sustainment phases²⁰⁸. Cost-effectiveness and budget impact estimates are required for the final phase of evidence generation to apply for Health Innovation, Implementation and Spread (HIIS) funding grant. The AHS BJH SCN™ will use results from Chapter Four and Five in this doctoral thesis in their HIIS funding proposal.

6.7 Future Research

Future research should focus on implementing referral pathways and structured first-line treatment programs into healthcare systems and health insurance plans. Our economic estimates assume programs like GLA:D® would help people delay TJR. Publicly funding GLA:D® in Alberta would create an opportunity to evaluate this assumption in the real world. Funding could increase participation rates but other barriers like knowledge gaps, expectations, and referral patterns could be addressed with further research. Developing implementation guidelines, health professional training programs, resources, models of care, and frameworks for quality monitoring have been identified as global priorities⁹. Future research could evaluate optimal timing of first-line treatments to maximize clinical benefits and health system resources. The EQ-5D was expanded from a three-level to a five-level questionnaire to address ceiling effects in people with hip and knee OA undergoing TJR^{75,131}. However, our cost-effectiveness analysis in Chapter Four showed interesting discrepancy between the generic and disease-specific QOL measures in a sample receiving community-based services. There is an opportunity to evaluate potential ceiling effects of generic QOL measures in a nonsurgical OA population.

Appendix A. Comparison of Structured Osteoarthritis Management Programs Implemented in Healthcare Systems.

Table 1. Comparison of structured osteoarthritis management programs implemented into healthcare systems.

Program	Countries Where Program is Implemented	Education for Clinicians	Education for Participants	Exercise for Participants	Data Collection Time Points	Duration	Group Size	Reference
GLA:D®	Denmark, Ireland, Canada, China, Australia, New Zealand, Switzerland, Austria, Norway, Netherlands, United States, Germany	2-day course	2 90-minute sessions	12 60-minute group exercise sessions (twice per week)	Baseline 3-months 12-months	8 weeks	6-10 people	Skou et al. ²⁷ , Roos et al. ²⁸ , GLA:D® Annual Report ³³
BOA	Sweden	1 or 2-day course	2 90-minute sessions	1 60-minute individual session then 12 optional 60-minute group exercise sessions (twice per week) or home exercise program	Baseline 3-months 12-months	7-8 weeks	7-12 people	Jönson et al. ²⁶
ESCAPE-pain	United Kingdom	1.5-day course	12 sessions (twice per week) consisting of 20-minute education and 40-minute group exercise circuit		Baseline 6-weeks	6 weeks	6-10 people	ESCAPE-pain ²⁵ Hurley et al. ²⁰⁹

Appendix B. PRISMA Checklist.

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	4
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	6
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	7
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7

Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	8
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	8
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	8

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	8
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	8
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	9
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	9
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	13
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	13
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	N/A
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	13
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	13
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	14-21
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	19

Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	20-21
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	21

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: www.prisma-statement.org.

Appendix C. Systematic Review Search Criteria.

Medline

1. Economics/
2. Cost/
3. Economics, Nursing/
4. Economics, Medical/
5. Economics, Pharmaceutical/
6. exp Economics, Hospital/
7. exp "Fees and Charges"/
8. exp Budgets/
9. budget*.ti,ab,kf.
10. (economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ti,kf.
11. (economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ab. /freq=2
12. (cost* adj2 (effective* or utilit* or benefit* or minimi* or analy* or outcome or outcomes)).ab,kf.
13. (value adj2 (money or monetary)).ti,ab,kf.
14. or/1-13
15. Hip Osteoarthritis/ or Knee Osteoarthritis/
16. (osteoarthriti* or osteoarthros* or arthrit* or arthros* or degenerative or joint disorder* or joint disease* or knee oa or hip oa) adj3 (knee* or hip*).ti,ab,kf
17. 15 or 16
18. Exercise Therapy/ or Exercise/
19. (physiother* or exercis* or therap* or program* or structured or targeted or semi structured or supervised or self management).ti,ab,kf.
20. (strength* or train* or exercis* or muscle train* or muscle strengthening or functional exercise* or flexibility train* or perturbation train* or proprioceptiv* or motor control or sensorimotor control or functional stability or dynamic stability or quality of movement or agility).ti,ab,kf.

21. exp Patient Education/ or exp Education/ or exp Health Education/ or education.tw,kf.
22. educat*.ti,ab,kf.
23. exp Diet/ or Weight Loss/ or Diet Therapy/
24. (diet or diet therapy or weight or weight management or weight loss or calor* or calor* restriction or body mass).ti,ab,kf.
25. 18 or 19 or 20 or 21 or 22 or 23 or 24
26. 14 and 17 and 25

Embase

1. Economics/
2. Cost/
3. Exp Health Economics/
4. Budget/
5. budget*.ti,ab,kw.
6. (economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ti,kw.
7. (economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ab. /freq=2
8. (cost* adj2 (effective* or utilit* or benefit* or minimi* or analy* or outcome or outcomes)).ab,kw.
9. (value adj2 (money or monetary)).ti,ab,kw.
10. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9
11. Hip Osteoarthritis/ or Knee Osteoarthritis/
12. (osteoarthriti* or osteoarthros* or arthrit* or arthros* or degenerative or joint disorder* or joint disease* or knee oa or hip oa) adj3 (knee* or hip*).ti,ab,kw
13. 11 or 12
14. Exercise Therapy/ or Exercise/
15. (physiother* or exercis* or therap* or program* or structured or targeted or semi structured or supervised or self management).ti,ab,kw.

16. (strength* or train* or exercis* or muscle train* or muscle strengthening or functional exercise* or flexibility train* or perturbation train* or proprioceptiv* or motor control or sensorimotor control or functional stability or dynamic stability or quality of movement or agility).ti,ab,kw.
17. exp Patient Education/ or exp Education/ or exp Health Education/ or education.tw,Kw.
18. educat*.ti,ab,kw.
19. Diet/ or Weight Loss/ or Diet Therapy/
20. (diet or diet therapy or weight or weight management or weight loss or calor* or calor* restriction or body mass).ti,ab,kw.
21. 14 or 15 or 16 or 17 or 18 or 19 or 20
22. 10 and 13 and 21

Cochrane Central Register of Controlled Trials (CENTRAL)

1. Exp Economics/
2. Economics, Pharmaceutical/ or Economics, Behavioral/ or Economics, Medical/ or Economics/ or Economics, Hospital/ or Economics, Nursing/
3. (Fees and Charges).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
4. Budgets/
5. budget*.ti,tw,kw.
6. (economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ti,ab,kw.
7. (cost* adj2 (effective* or utilit* or benefit* or minimi* or analy* or outcome or outcomes)).ti,ab,kw.
8. (value adj2 (money or monetary)).ti,ab,kw.
9. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
10. exp Osteoarthritis/ or exp Osteoarthritis,Hip/ or exp Osteoarthritis,Knee/
11. (osteoarthriti* or osteoarthros* or arthrit* or arthros* or degenerative or joint disorder* or joint disease* or knee oa or hip oa) adj3 (knee* or hip*).ti,ab,kw.
12. 10 or 11
13. Exercise Therapy/ or Exercise/

14. (physiother* or exercis* or therap* or program* or structured or targeted or semi structured or supervised or self management).ti,ab,kw.
15. (strength* or train* or exercis* or muscle train* or muscle strengthening or functional exercise* or flexibility train* or perturbation train* or proprioceptiv* or motor control or sensorimotor control or functional stability or dynamic stability or quality of movement or agility).ti,ab,kw.
16. Exp Patient Education as Topic/ or exp Education/ or exp Health Education/ or education.tw,kw.
17. educat*.ti,ab,kw.
18. Diet/ or Weight Loss/ or Diet Therapy/
19. (diet or diet therapy or weight or weight management or weight loss or calor* or calor* restriction or body mass).ti,ab,kw.
20. 13 or 14 or 15 or 16 or 17 or 18 or 19
21. 9 and 12 and 20

National Health Services Economic Evaluation Database

22. Economics, Pharmaceutical/ or Economics, Behavioral/ or Economics, Medical/ or Economics/ or Economics, Hospital/ or Economics, Nursing/
23. (Fees and Charges).mp. [mp=title,text, subject heading word]
24. Budgets/
25. budget*.ti,tw,sh.
26. (economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed) .ti,tw,sh.
27. (cost* adj2 (effective* or utilit* or benefit* or minimi* or analy* or outcome or outcomes)) .ti,tw,sh.
28. (value adj2 (money or monetary)) .ti,tw,sh.
29. 1 or 2 or 3 or 4 or 5 or 6 or 7
30. exp Osteoarthritis/ or exp Osteoarthritis,Hip/ or exp Osteoarthritis,Knee/
31. (osteoarthriti* or osteoarthros* or arthrit* or arthros* or degenerative or joint disorder* or joint disease* or knee oa or hip oa) adj3 (knee* or hip*)). .ti,tw,sh.
32. 9 or 10

33. Exercise Therapy/ or Exercise/
34. (physiother* or exercis* or therap* or program* or structured or targeted or semi structured or supervised or self management).ti,tw,sh.
35. (strength* or train* or exercis* or muscle train* or muscle strengthening or functional exercise* or flexibility train* or perturbation train* or proprioceptiv* or motor control or sensorimotor control or functional stability or dynamic stability or quality of movement or agility) .ti,tw,sh.
36. exp Education/ or exp Health Education/ or education.tw,sh.
37. educat* .ti,tw,sh.
38. Diet/ or Weight Loss/ or Diet Therapy/
39. (diet or diet therapy or weight or weight management or weight loss or calor* or calor* restriction or body mass).ti,tw,sh.
40. 12 or 13 or 14 or 15 or 16 or 17 or 18
41. 8 and 11 and 19

EconLit

#	Query	Limiters/Expanders	Last Run Via
S39	(S17 AND S23 AND S38)	Search modes - Find all my search terms	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - EconLit
S38	S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35 OR S36 OR S37	Search modes - Find all my search terms	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - EconLit

S37	AB (diet or diet therapy or weight or weight management or weight loss or calor* or calor* restriction or body mass)	Search modes - Find all my search terms	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - EconLit
S36	TI (diet or diet therapy or weight or weight management or weight loss or calor* or calor* restriction or body mass)	Search modes - Find all my search terms	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - EconLit
S35	MH Caloric Restriction	Search modes - Find all my search terms	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - EconLit
S34	MH (diet therapy or dietetic therapy or diet or nutrition interventions)	Search modes - Find all my search terms	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - EconLit
S33	MH (weight loss or weight reduction or lose weight or obesity or overweight or weight management)	Search modes - Find all my search terms	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - EconLit
S32	MH (diet or nutrition or food habit or eating habit or lifestyle)	Search modes - Find all my search terms	Interface - EBSCOhost Research Databases

			Search Screen - Advanced Search Database - EconLit
S31	AB (educat*)	Search modes - Find all my search terms	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - EconLit
S30	TI (educat*)	Search modes - Find all my search terms	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - EconLit
S29	MH (Patient Education or Education or Health Education)	Search modes - Find all my search terms	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - EconLit
S28	AB (strength* or train* or exercis* or muscle train* or muscle strengthening or functional exercise* or flexibility train* or perturbation train* or proprioceptiv* or motor control or sensorimotor control or functional stability or dynamic stability or quality of movement or agility)	Search modes - Find all my search terms	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - EconLit
S27	TI (strength* or train* or exercis* or muscle train* or muscle strengthening or functional exercise* or flexibility train* or perturbation train* or proprioceptiv* or motor	Search modes - Find all my search terms	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - EconLit

	control or sensorimotor control or functional stability or dynamic stability or quality of movement or agility)		
S26	AB (physiother* or exercis* or therap* or program* or structured or targeted or semi structured or supervised or self management)	Search modes - Find all my search terms	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - EconLit
S25	TI (physiother* or exercis* or therap* or program* or structured or targeted or semi structured or supervised or self management)	Search modes - Find all my search terms	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - EconLit
S24	MH (Exercise Therapy OR Exercise)	Search modes - Find all my search terms	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - EconLit
S23	S18 OR S19 OR S20 OR S21 OR S22	Search modes - Find all my search terms	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - EconLit
S22	AB (osteoarthriti* or osteoarthros* or arthrit* or arthros* or degenerative or joint disorder* or joint disease* or knee oa or hip oa)	Search modes - Find all my search terms	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - EconLit

S21	TI (osteoarthriti* or osteoarthros* or arthrit* or arthros* or degenerative or joint disorder* or joint disease* or knee oa or hip oa)	Search modes - Find all my search terms	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - EconLit
S20	MH (Osteoarthritis, Knee)	Search modes - Find all my search terms	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - EconLit
S19	MH (Osteoarthritis, Hip)	Search modes - Find all my search terms	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - EconLit
S18	MH (Osteoarthritis)	Search modes - Find all my search terms	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - EconLit
S17	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16	Search modes - Find all my search terms	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - EconLit
S16	AB (value money or value monetary)	Search modes - Find all my search terms	Interface - EBSCOhost Research Databases

			Search Screen - Advanced Search Database - EconLit
S15	TI (value money or value monetary)	Search modes - Find all my search terms	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - EconLit
S14	AB (cost* effective* or cost* utilit* or cost* benefit* or cost* minimi* or cost* analy* or cost* outcome or cost* outcomes)	Search modes - Find all my search terms	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - EconLit
S13	TI (cost* effective* or cost* utilit* or cost* benefit* or cost* minimi* or cost* analy* or cost* outcome or cost* outcomes)	Search modes - Find all my search terms	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - EconLit
S12	(economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ab. /freq=2	Search modes - SmartText Searching	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - EconLit
S11	TI (economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or	Search modes - Find all my search terms	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - EconLit

	expenses or financial or finance or finances or financed).ab. /freq=2		
S10	AB (economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed)	Search modes - Find all my search terms	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - EconLit
S9	TI (economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed)	Search modes - Find all my search terms	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - EconLit
S8	MH (Budgets)	Search modes - Find all my search terms	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - EconLit
S7	MH Fees and Charges	Search modes - Find all my search terms	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - EconLit
S6	MH Economics, Hospital	Search modes - Find all my search terms	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - EconLit

S5	MH Economics, Pharmaceutical	Search modes - Find all my search terms	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - EconLit
S4	MH Economics, Medical	Search modes - Find all my search terms	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - EconLit
S3	MH Economics, Nursing	Search modes - Find all my search terms	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - EconLit
S2	MH Costs and Cost Analysis	Search modes - Find all my search terms	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - EconLit
S1	MH economics	Search modes - Find all my search terms	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - EconLit

Appendix D. Economic Evaluations of Education, Exercise and Dietary Weight Management to Manage Hip and Knee

Osteoarthritis Summary Tables.

Table 1. Study characteristics for economic evaluations of education, exercise, and dietary weight management to manage hip and knee osteoarthritis.

Author, Year, Country	Population	Study Design, Sample Size, Analysis	Interventions	Control	Health Outcome, Preference Weights	Time Horizon	Discount Rate	Perspective
Abbott ¹¹² , 2019 ^A , New Zealand	Hip or knee OA, ACR criteria	RCT, N = 206, CUA	Individual exercise and adjunct manual therapy in isolation and combination	Physician - delivered Usual Care	SF-6D (SF-12), United Kingdom Tariffs	2 years	3.5%	Societal and Healthcare Payer
Abbott ¹⁰⁵ , 2019 ^A , New Zealand	Hip or knee OA, ACR criteria	RCT, N = 206, CUA	Individual exercise and adjunct manual therapy in isolation and combination	Physician - delivered Usual Care	SF-6D (SF-12), United Kingdom Tariffs	5 years (observed) and Lifetime (modelled)	3.5%	Societal and Healthcare Payer
Losina ¹¹³ , 2019, United States	Knee OA, K&L grade 2 or 3, pain on most days due to OA, overweight or obese	RCT, N = 399, CUA	Supervised intensive weight loss program and individual exercise program in	Physician - delivered Usual Care	WOMAC cross-walked to SF-6D (SF-12), N/R	Lifetime (modelled , from 18-months observed)	3%	Societal and Healthcare Payer

	(≥27 kg/m ² and <41 kg/m ²), age ≥55		isolation and combination					
Bove ⁶⁶ , 2018, United States	Knee OA, ACR criteria	RCT, N = 300, CUA	Individual exercise with booster sessions and and/or adjunct manual therapy	Exercise Only	EQ-5D-3L, United States Tariffs	2 years (observed) and 5 years (modelled)	3%	Societal
Kigozi ⁶⁸ , 2018, United Kingdom	Knee OA, clinical Dx meeting NICE criteria, age ≥45	RCT, N = 514, CUA	Individual and group exercise	Usual Rehab Care	EQ-5D-3L, United Kingdom Tariffs	18 months	N/R	Healthcare Payer
Kloek ⁶⁵ , 2018, Netherlands	Hip or Knee OA, ACR criteria age 40-80, not on a Sx waitlist, insufficiently active	RCT, N = 207, CUA	Individual exercise with e-exercise web-application	Usual Rehab Care	EQ-5D-3L, Netherlands Tariffs	1 year	N/A	Societal and Healthcare Payer
O'Brien ²¹⁰ , 2018, Australia	Knee OA, ≥18 yrs, overweight or obese (≥27 kg/m ² and ≤40 kg/m ²), ≥3/10 numerical rating scale, moderate level of interference ADL	Pragmatic RCT, N = 120, CUA	Weight management education and coaching phone calls	Physician - delivered Usual Care	SF-6D (SF-12), United Kingdom Tariffs	6 months	N/A	Societal and Healthcare Payer
Fernandes ⁶⁷ , 2017, Denmark	Scheduled for Hip or Knee OA due to symptomatic OA, age ≥ 18	RCT, N = 165, CUA	Combined group exercise and education	Pre-operative education package	EQ-5D-3L, Denmark Tariffs	1 year	N/A	Healthcare Payer

Bennell ¹¹⁵ , 2016, Australia	Knee OA, Age ≥ 50, ACR criteria, pain for ≥3 months, ≥40/100 on VAS, difficulty with ADLs	RCT, N = 222, CUA	Combined individual exercise and education	Exercise only and educatio n only	AQoL-6D, Australia Tariffs	1 year	N/A	Societal
Tan ⁶² , 2016 Netherlands	Hip OA, ACR criteria, age ≥45	RCT, N = 203, CUA	Individual exercise therapy	Physician - delivered Usual Care	EQ-5D-5L, Netherland Tariffs	1 year	N/A	Societal and Healthcare Payer
Pinto ¹¹⁶ , 2013 ^A , New Zealand	Hip or knee OA, ACR criteria	RCT, N = 206, CUA	Individual exercise and adjunct manual therapy in isolation and combination	Physician - delivered Usual Care	SF-6D (SF- 12), United Kingdom Tariffs	1 year	N/A	Societal and Healthcare Payer
Hurley ¹⁰⁸ , 2012 ^B , United Kingdom	Knee OA, clinical Dx, age ≥50, mild to severe knee pain ≥6 months	Pragmati c RCT, N = 418, CEA	Combined group exercise and education	Physician - delivered Usual Care	WOMAC, N/A	30 months	3.5%	Societal and Healthcare Payer
Jessep ¹¹⁷ , 2009, United Kingdom	Knee OA, age ≥50, have consulted with a GP for mild to severe knee pain lasting ≥6 months	Pragmati c RCT, N = 64, CUA	Combined group exercise and education	Physician - delivered Usual Care	EQ-5D-3L, N/R	1 year	N/A	N/R
Patel ¹¹⁸ , 2009, United Kingdom	Hip and/or knee OA, age ≥50, self- reported pain and/or disability	RCT, N = 812, CUA	Group education class	Educatio n Booklet	SF-6D (SF- 36), United Kingdom Tariffs	1 year	N/A	Societal and Health and Social Care

Sevick ¹⁰⁹ , 2009, United States	Knee OA, age ≥60, BMI ≥28 kg/m ²	RCT, N = 316, CEA	Exercise and diet in isolation and combination	Healthy Lifestyle Education	WOMAC, Weight, 6-Minute Walk, Stair Climb	18 months	5%	Healthcare Payer
Coupe ⁶⁴ , 2007, Netherlands	Hip or knee OA, ACR criteria	Cluster RCT, N = 200, CUA	Individual exercise with booster sessions	Usual Rehab Care	EQ-5D-3L, United Kingdom Tariffs	65 weeks	N/R	Societal
Hurley ¹⁰⁷ , 2007 ^B , United Kingdom	Knee OA, clinical Dx, age ≥50, mild to severe knee pain ≥6 months	Pragmatic RCT N = 418, CEA	Combined group exercise and education	Physician - delivered Usual Care	WOMAC	7.5 months	N/A	Societal and Healthcare Payer
Richardson ^{119,1} ²⁰ , 2006, United Kingdom	Knee OA, ACR criteria, referred to physiotherapy by GP	Pragmatic RCT, N = 214, CUA	Group exercise and individual home exercise program	Home- exercise program	EQ-5D-3L, United Kingdom Tariffs	1 year	N/A	Healthcare Payer
Cochrane ¹²¹ , 2005, United Kingdom	Hip or knee OA, age ≥ 60 , current pain and/or stiffness, X-ray confirmed OA by a physician	RCT, N = 106, CUA	Group water- based exercise	Physician - delivered Usual Care	EQ-5D-3L, United Kingdom Tariffs	1 year	N/A	Societal
Thomas ¹¹¹ , 2005, United Kingdom	Self-reported knee pain (localized pain and tenderness or pain on movement, or both), age ≥45	RCT, N = 759, CEA	Exercise therapy with or without telephone support	Telephone support only	WOMAC, N/A	2 years	5%	Healthcare Provider and Patient

Sevick ¹⁰⁹ , 2000, United States	Knee OA, age ≥ 60, pain in one or both days of the month, difficulty with ADLs, X-ray confirmed	RCT, N = 439, CEA	Group exercise (aerobic and weight training)	Group educatio n	Self- Reported Disability, 6- Minute Walk, Stair Climb, Lift and Carry Task, Car Task	18 months	N/R	Healthcare Payer
Lord ¹⁰⁶ , 1999, United Kingdom	Knee OA, clinical Dx, X-ray confirmed	Cluster RCT, N = 174, CMA	Group education	Physician - delivered Usual Care	WOMAC, N/A	1 year	N/A	Societal and Healthcare Payer
Mazzuca ⁷⁰ , 1999, United States	Knee OA, X-ray confirmed	Non- random clinical trial, N = 211, CMA	Individual education	Placebo Educatio n	QWB, United States Tariffs	1 year	N/A	N/R

^A = same clinical trial with different time horizons, ^B = same clinical trial with different time horizons, BMI = Body Mass Index, Dx = Diagnosis

RCT = Randomized Controlled Trial, CUA = Cost-Utility Analysis, CEA = Cost-Effectiveness Analysis, CMA – Cost-Minimization Analysis, N/A = Not Applicable, N/R = Not Reported, SF-6D = Short-Form Six-Dimension, SF-12 = 12-item Short Form Survey, SF-36 = 36-Item Short Form Survey, EQ-5D-3L = European Quality of Life 5-Dimension Three-Level Version, EQ-5D-5L = European Quality of Life 5-Dimension Five-Level Version, Rehab = Rehabilitation, QWB = Quality of Well Being, WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index

Table 2. Key results for economic evaluations of education, exercise, and dietary weight management to manage hip and knee osteoarthritis.

Author, Year (price year)	Intervention	QALY Diff.	Results [†]	Conclusion
Abbott ¹¹² , 2019 (2009 NZD)	1) Individual physiotherapist supervised exercise vs. physician-delivered usual care	0.15	R: \$8,237/QALY U: 95% @ 1 x GDP WTP Threshold	Physiotherapist-delivered exercise therapy and/or manual therapy in addition to usual care was cost-effective relative to usual care from both societal and health system perspective.
	2) Manual therapy vs. physician-delivered usual care	0.08	R: \$6,330/QALY U: 95% @ 1 x GDP WTP Threshold	
	3) Combined Individual physiotherapist supervised exercise and manual therapy vs. physician-delivered usual care	0.07	R: \$6,330/QALY U: 95% @ 1 x GDP WTP Threshold	
Abbott ¹⁰⁵ , 2019 (2013 NZD)	1) Individual physiotherapist supervised exercise vs. physician-delivered usual care	0.076	R: Exercise cost-saving @ 5 yr U: N/A, intervention dominated control	Individualized exercise therapy with or without manual therapy were cost-effective interventions compared to usual GP care over 5-year and lifetime from both societal and healthcare payer perspectives. Exercise therapy provided the most health benefit per dollar and was cost-saving compared to usual GP care in both perspectives.
		0.12	R: Exercise cost-saving @ 5 yr	

			U: N/A, intervention dominated control	
	2) Manual therapy vs. physician-delivered usual care	-0.004	R: \$2,921/QALY @ 5 yr U: N/R	
		0.04	R: Manual therapy cost-saving @ LT U: N/A, intervention dominated control	
	3) Combined Individual physiotherapist supervised exercise and manual therapy vs. physician-delivered usual care	0.009	R: Exercise and manual therapy cost-saving @ 5 yr U: N/A, intervention dominated control	
		0.03	R: Exercise and manual therapy cost-saving @ LT U: N/A, intervention dominated control	
Losina ¹¹³ , 2019 (2016 USD)	1) Supervised dietary caloric restriction and individual exercise program vs. physician-delivered usual care	0.054*	R: \$30,000/QALY U: 68% @ WTP of \$50,000/QALY	Supervised diet and exercise interventions compared to usual GP care are highly cost-effective from both societal and health system perspective.
Bove ⁶⁶ , 2018 (2011 USD)	1) Physiotherapist supervised exercise with booster sessions and manual therapy vs. exercise only	-0.10	R: Exercise with booster sessions and manual therapy produced higher QALYS and lower costs @ 2 yr U: Exercise with booster sessions and manual therapy favored 33% and 30% of the time @ WTP of \$50,000/QALY and \$100,000/QALY over 2 yr	Over a 2- or 5-year time horizon exercise therapy delivered by a physiotherapist with booster sessions dispersing treatment over 1 year provided the most cost-effective treatment compared to exercise therapy alone or exercise combined with manual therapy.

		0.062	R: \$5,059/QALY @ 5 yr U: N/R @ 5 yr	
	2) Physiotherapist supervised exercise only vs. physiotherapist supervised exercise with booster sessions	0.08	R: \$12,900/QALY @ 2 yr U: Exercise and booster session preferred at 60% and 63% of the time @ WTP of \$50,000/QALY and \$100,000/QALY over 2 yr	
		0.09	R: \$21, 548/QALY @ 5 yr U: N/R @ 5 yr	
	3) Physiotherapist supervised exercise with booster sessions vs. physiotherapist supervised exercise with manual therapy	-0.35	R: Exercise with booster sessions cost-saving @ 2 yr U: N/A, intervention dominated control	
		-0.81	R: Exercise with booster sessions cost-saving @ 5 yr U: N/A, intervention dominated control	
Kigozi ⁶⁸ , 2018 (2012-2013 GBP)	1) Individually tailored exercise vs. physiotherapist-delivered usual care	-0.015	R: intervention produced less QALYS and cost more U: <40% @ WTP of £20,000 per QALY	From a healthcare payer perspective individual tailored exercise and targeted exercise adherence were not cost-effective compared to usual care delivered by a physiotherapist.
	2) Targeted exercise adherence vs. physiotherapist-delivered usual care	-0.03	R: Intervention produced less QALYS and cost more U: <40% @ WTP of £20,000 per QALY	
Kloek ⁶⁵ , 2018 (2015 EUR)	Physiotherapy and e-exercise web-application vs. physiotherapist-delivered usual care	0.01	R: intervention produced slightly more QALYs and cost slightly less U: 68% @ WTP of €10,000 per QALY	Minimal difference in health outcomes with less cost related to the e-Exercise intervention although large variability in results suggest e-exercise is not cost-effective compared to physiotherapist-delivered usual care from either a healthcare or societal perspective.

				Adoption decision should be based on preferences of the patient and provider rather than costs.
O'Brien ¹¹⁴ , 2018 (2016 AUD)	Weight management education and 10 tailored coaching phone calls vs. physician-delivered usual care	0.00	R: \$581,828/QALY U: 63% @ WTP of \$0/QALY	From a societal perspective tailored coaching phone calls are not cost-effective compared to usual care
Fernandes ⁶⁷ , 2017 (2012 EUR)	Supervised group neuromuscular exercise and preoperative educational package vs preoperative educational package	0.05	R: Intervention produced more QALYs and cost slightly less U: ~60% @ WTP of €20,000*	From a societal perspective preoperative supervised neuromuscular exercise was cost-effective in patients scheduled for TJR surgery at common willingness to pay thresholds.
Bennell ¹¹⁵ , 2016 (AUD) (price year N/R)	1) Pain coping skills training + exercise vs. exercise only	0.03	R: Pain coping skills + exercise cost-saving U: 95% CI [-\$3,329 to \$1,795]	From a societal perspective cost-savings and a small improvement in QALYs was observed for combined treatment compared to either individual treatment, but this was a nonsignificant result.
	2) Pain coping skills training + exercise vs. pain coping skills training only	0.03	R: Pain coping skills + exercise cost-saving U: 95% CI [-\$3,325 to \$1,638]	
	3) Pain coping skills training only vs. exercise only	0.01	R: Not reported U: Not reported	
Tan ⁶² , 2016 (2011 EUR)	1) Exercise therapy vs. physician-delivered usual care	0.006	R: €97,195 saved per QALY lost U: 68% @ WTP of €20,000 per QALY and 76% probability of cost-saving	From a societal perspective exercise therapy is likely cost-saving compared to physician-delivered usual care
Pinto ¹¹⁶ , 2013 (2009 NZD)	1) Manual therapy only vs. physician-delivered usual care	0.005*	R: manual therapy was cost-saving U: 77% @ WTP of \$29,149/QALY	From New Zealand healthcare payer perspective and society manual therapy and exercise therapy interventions are cost-

	2) Individual physiotherapist supervised exercise vs. physician-delivered usual care	0.035*	R: \$163/QALY U: 99% @ WTP of \$29,149/QALY	effective compared to usual care at conventional willingness to pay thresholds.
	3) Combined Individual physiotherapist supervised exercise and manual therapy vs. physician-delivered usual care	0.008*	R: Combined exercise therapy and manual therapy were cost-saving U: 35% @ WTP of \$29,149/QALY	
Hurley ¹⁰⁸ , 2012 (2003-2004 GBP)	Group exercise and education vs. physician-delivered usual care	N/A	R: Exercise and education cost-saving U: 81% @ WTP of £0 for 1% gain in proportion of patients receiving clinically significant improvement on WOMAC	Interventions showed significant improvement in function and cost-savings from a societal and healthcare perspective.
Jessep ¹¹⁷ , 2009 (2005 GBP)	Group exercise and education vs. physiotherapist-delivered usual care	0.05*	R: Group exercise and education were cost-saving U: N/A, intervention dominated control	Intervention showed improved health outcomes and cost-savings, but results need to be confirmed in a larger study
Patel ¹¹⁸ , 2009 (2002-2003 GBP)	Arthritis self-management program (6 sessions) and education booklet vs. education booklet	-0.01	R: Less QALYs and cost less U: 20% @ WTP of £30,000 per QALY	From a societal perspective, the intervention is likely not cost-effective compared to standard care
Sevick ¹⁰⁹ , 2009 (2000 USD)	1) Exercise vs. healthy lifestyle control	N/A	R: \$10 per % improvement on distanced walked in 6-min walk test U: P < 0.05	Exercise was the most efficient intervention for improving functional measures, diet was the most efficient for reducing weight and combined exercise and diet intervention was most efficient for improving WOMAC scores. It remains difficult to make direct cost-
	2) Diet	N/A	R: \$35 per % of body weight lost U: P < 0.01	

	vs. healthy lifestyle control			effectiveness conclusions without a willingness to pay threshold; however, authors note healthcare utilization is driven by pain so combined exercise and diet interventions are likely the most efficient use of healthcare resources.
	3) Exercise and diet vs. healthy lifestyle control	N/A	R: \$56 per % improvement in WOMAC stiffness score U: P = 0.057	
Hurley ¹⁰⁷ , 2007 (2002-2003 GBP)	1) Combined individual and group exercise and education vs. physician-delivered usual care	N/A	R: Not reported U: >90% if WTP is £6,000	Moderate investment in rehabilitation was likely more cost-effective than usual care from a healthcare or societal perspective if decision-makers are willing to pay for improvements in function measured by WOMAC. Higher costs for rehabilitation than usual care.
	2) Individually administered exercise and education vs. group administered exercise and education	N/A	R: Not reported U: <38% @ WTP of £19,200	
Coupe ⁶⁴ , 2006 (2003 EUR)	Behavioral graded exercise and booster session vs. physiotherapist-delivered usual care	-0.02	R: Behavioral grade exercise and booster sessions produced less QALYS and cost less U: -£811 95% CI [-£2106 to £946]	From a societal perspective behavioral grade activity had lower costs but may be incidental due to large uncertainty surrounding the estimate
Richardson ^{119, 120} , 2006 (1999 – 2000 GBP)	8-Week group exercise and home-exercise program vs. home-exercise program	0.023*	R: More QALYs with lower costs U: 50% chance of being cost saving, 70% @ WTP of £30,000 per QALY	Healthcare systems should consider adding a supplemental class-based exercise and education because they are likely cost-effective for most reasonable willingness to pay thresholds.

Cochrane ¹²¹ , 2005 (2003 GBP)	Group water-based exercise classes vs. physician-delivered usual care	0.013	R: £5,007/QALY U: 50% probability of being cost-effective @ WTP threshold of £6857	From a societal perspective results showed incremental improvements in health with lower costs.
Thomas ¹¹¹ , 2005 (1996 GBP)	1) Exercise with and without telephone support vs. no exercise with and without telephone support	N/A	R: £2,570/patient with 50% improvement in WOMAC U: 80% @ £8,000 WTP	From a healthcare payer perspective exercise has an 80% probability of being cost-effective if the healthcare payer is willing to pay £8,000 per patient who experiences a clinically significant improvement in knee pain. No significant health differences were observed between telephone support and no telephone.
	2) Telephone support with and without exercise vs. no telephone support with and without exercise therapy	N/A	R: Not reported U: Not reported	
Sevick, 2000 (2000 USD)	1) Aerobic training vs. education	N/A	R: -\$114/point gained in self-reported disability U: Not reported	From a healthcare payer perspective exercise interventions may reduce utilization and produce cost-savings in the health system more than education services although this post hoc cost analysis should be interpreted with caution.
	2) Weight training vs. education	N/A	R: -\$117/point gained in self-reported disability U: Not reported	
Lord ¹⁰⁶ , 1999 (1996 - 1997 EUR)	Group education vs. physician-delivered usual care	N/A	R: Intervention increased healthcare, social and indirect costs by £225, £239, and £98 U: No statistically significant difference in costs between groups in any perspective.	Group education programs in primary care are not a cost-effective use of resources providing no evidence of clinical benefit and greater costs than usual care.
Mazucca ⁷⁰ , 1999, (1996 USD)	Individualized self-care instruction	N/A	R: Net savings of \$76 per participant receiving education	Investing in self-management education programs produced fewer clinic visits.

	vs. attention control placebo		U: Statistically significant between group difference (p = 0.015)	
--	-------------------------------	--	---	--

*= calculated by review authors, ‡ = societal results are reported if authors documented both healthcare payer and societal perspective,

vs. = Versus, R= Results, U = Uncertainty, LT = Lifetime horizon, N/R = Not reported, N/A = Not applicable, GDP = Gross Domestic Product,

WTP = Willingness To Pay, QALY = Quality Adjusted Life Year, QALY Diff = Difference between intervention QALY and control QALY, WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index

NZD = New Zealand Dollar, AUD = Australian Dollar, USD = United States Dollar, EUR = Euro, GBP = Pound Stirling,

“intervention dominated by control” = a sensitivity analysis does is not calculated in a scenario where the intervention produced more QALYS with less cost, “cost-saving” = an intervention produced more QALYs and cost less than the control,

Note: study designs, intervention, controls, and health system characteristics limit comparability so we chose to report natural prices instead of converting to common units

Appendix E. Telephone Questionnaire Used in Chapter Three.



Telephone
Questionnaire Final.px

Appendix F. CHEERS Checklist.

Topic	No.	Item	Location where item is reported
Title			
	1	Identify the study as an economic evaluation and specify the interventions being compared.	Pg. 1
Abstract			
	2	Provide a structured summary that highlights context, key methods, results, and alternative analyses.	Pg. 2
Introduction			
Background and objectives	3	Give the context for the study, the study question, and its practical relevance for decision making in policy or practice.	Pg. 5-6
Methods			
Health economic analysis plan	4	Indicate whether a health economic analysis plan was developed and where available.	-
Study population	5	Describe characteristics of the study population (such as age range, demographics, socioeconomic, or clinical characteristics).	Pg. 6
Setting and location	6	Provide relevant contextual information that may influence findings.	Pg. 6/9-10
Comparators	7	Describe the interventions or strategies being compared and why chosen.	Pg. 6
Perspective	8	State the perspective(s) adopted by the study and why chosen.	Pg. 9-10

Topic	No.	Item	Location where item is reported
Time horizon	9	State the time horizon for the study and why appropriate.	Pg. 12-13
Discount rate	10	Report the discount rate(s) and reason chosen.	Pg. 13
Selection of outcomes	11	Describe what outcomes were used as the measure(s) of benefit(s) and harm(s).	Pg. 9
Measurement of outcomes	12	Describe how outcomes used to capture benefit(s) and harm(s) were measured.	Pg. 7-9
Valuation of outcomes	13	Describe the population and methods used to measure and value outcomes.	Pg. 9
Measurement and valuation of resources and costs	14	Describe how costs were valued.	Pg. 9-10
Currency, price date, and conversion	15	Report the dates of the estimated resource quantities and unit costs, plus the currency and year of conversion.	Pg. 10
Rationale and description of model	16	If modelling is used, describe in detail and why used. Report if the model is publicly available and where it can be accessed.	Pg. 12-14
Analytics and assumptions	17	Describe any methods for analysing or statistically transforming data, any extrapolation methods, and approaches for validating any model used.	Pg. 11
Characterising heterogeneity	18	Describe any methods used for estimating how the results of the study vary for subgroups.	Pg. 12-14
Characterising distributional effects	19	Describe how impacts are distributed across different individuals or adjustments made to reflect priority populations.	Pg. 14

Topic	No.	Item	Location where item is reported
Characterising uncertainty	20	Describe methods to characterise any sources of uncertainty in the analysis.	Pg. 14
Approach to engagement with patients and others affected by the study	21	Describe any approaches to engage patients or service recipients, the general public, communities, or stakeholders (such as clinicians or payers) in the design of the study.	-
Results			
Study parameters	22	Report all analytic inputs (such as values, ranges, references) including uncertainty or distributional assumptions.	Pg. 14-16
Summary of main results	23	Report the mean values for the main categories of costs and outcomes of interest and summarise them in the most appropriate overall measure.	Pg. 18-19
Effect of uncertainty	24	Describe how uncertainty about analytic judgments, inputs, or projections affect findings. Report the effect of choice of discount rate and time horizon, if applicable.	Pg. 22-24
Effect of engagement with patients and others affected by the study	25	Report on any difference patient/service recipient, general public, community, or stakeholder involvement made to the approach or findings of the study	-
Discussion			
Study findings, limitations, generalisability, and current knowledge	26	Report key findings, limitations, ethical or equity considerations not captured, and how these could affect patients, policy, or practice.	16-19

Topic	No.	Item	Location where item is reported
Other relevant information			
Source of funding	27	Describe how the study was funded and any role of the funder in the identification, design, conduct, and reporting of the analysis	Pg. 24-28
Conflicts of interest	28	Report authors conflicts of interest according to journal or International Committee of Medical Journal Editors requirements.	Pg. 29

From: Husereau D, Drummond M, Augustovski F, et al. Consolidated Health Economic Evaluation Reporting Standards 2022 (CHEERS 2022) Explanation and Elaboration: A Report of the ISPOR CHEERS II Good Practices Task Force. Value Health 2022;25.
[doi:10.1016/j.jval.2021.10.008](https://doi.org/10.1016/j.jval.2021.10.008)

Appendix G. Cost-Questionnaire Used in Chapter Four.

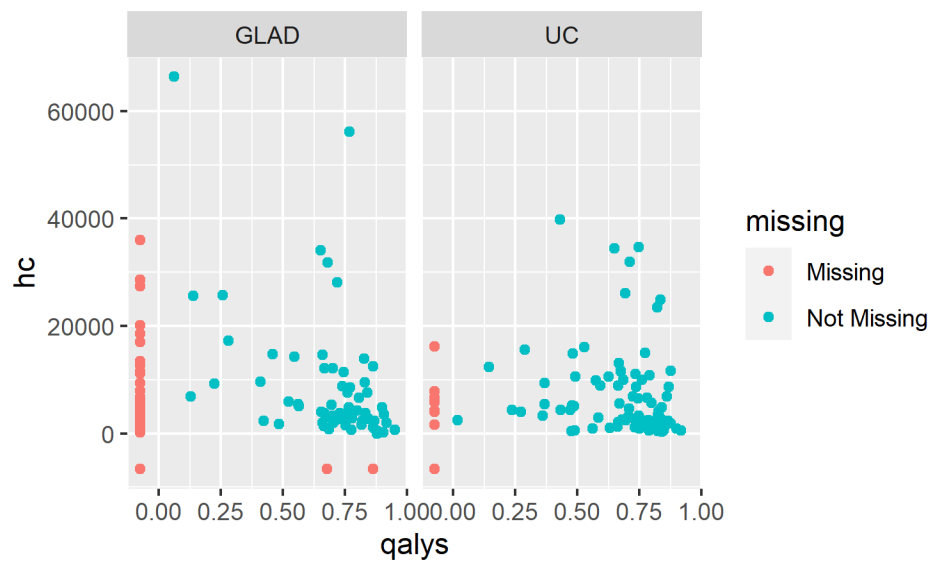


Mazzei et
al_Cost-Questionnaire

Appendix H. Missing Data Analysis and Multiple Imputation Performance from Cost-Effectiveness in Chapter Four.

MISSING DATA

Figure 1. Cost and Outcomes over Twelve Months with Missing Data (jitter = 0)



Note: Missing data is shown below 0

Figure 2. QALYS in each cohort with and without missing data (Ministry perspective).

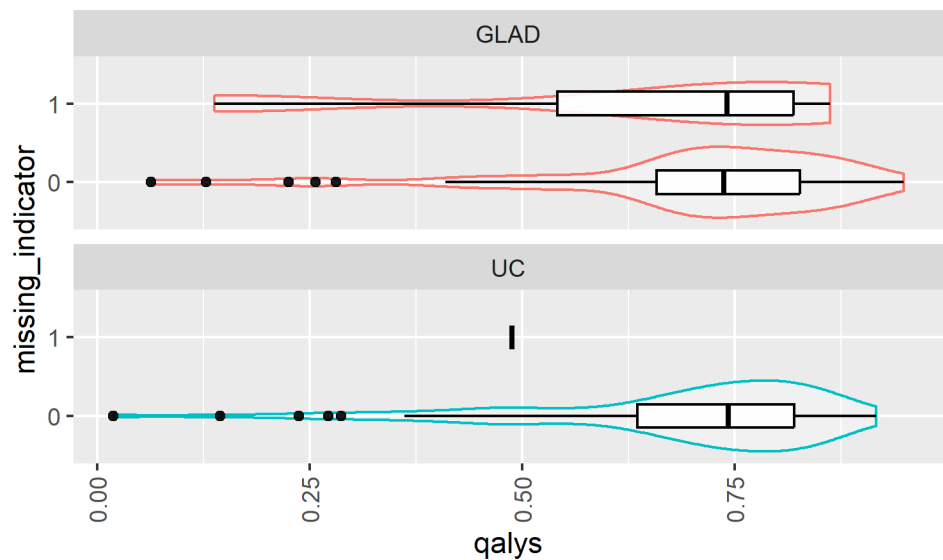


Figure 3. Costs in each cohort with and without missing data (Healthcare Perspective).

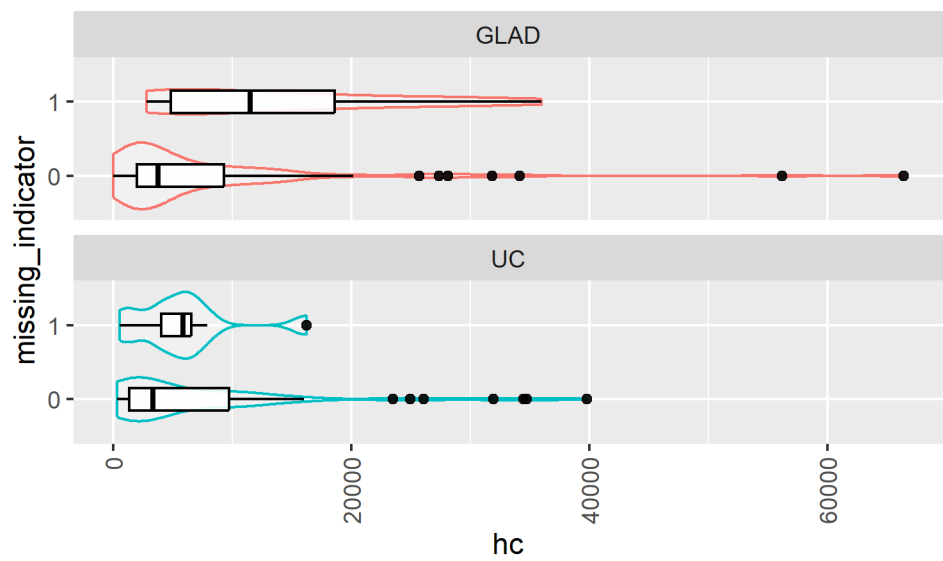


Figure 4. Percent of Missing Data in Each Variable.

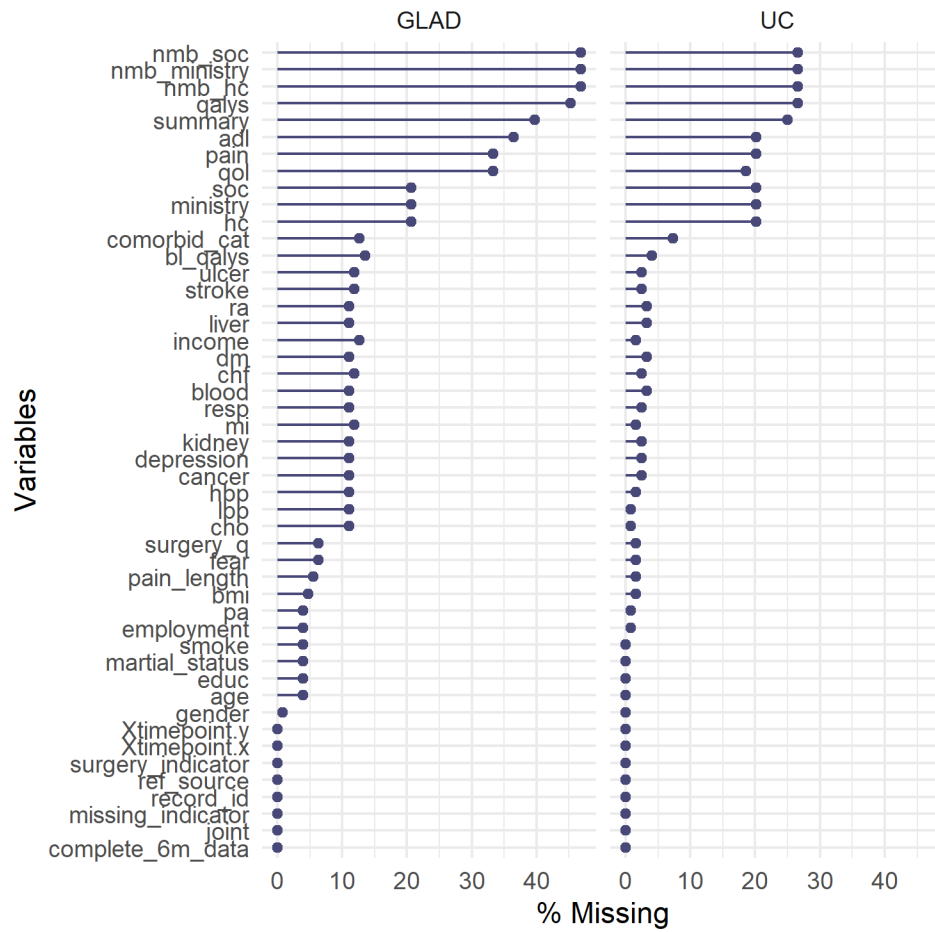
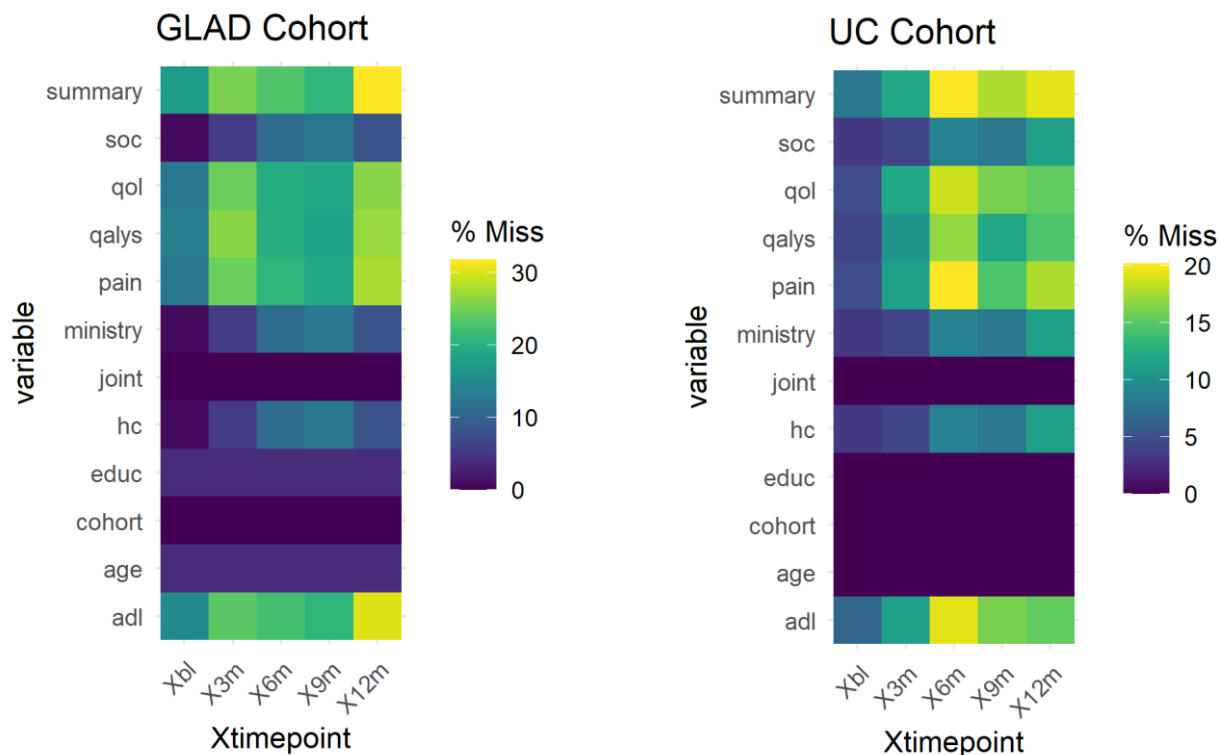


Figure 5. Percent of Missing Data in Each Variable (GLAD and UC Cohort).



ASSUMPTIONS

Multiple imputation makes the following assumptions about the data:

1. **Variables are Missing at Random (MAR)** – Assume MAR because we do not see significant differences in missingness based on where the data was collected (DADOS vs REDcap).
1. **Normality** - Each variable should be approximately normally distributed. This was observed in the RMarkdown cleaning file.
2. **Missing values can occur at any of the variables** - Participants are just as likely to not answer any question, and just as likely to not complete the questionnaire at any time point. However, the cohort variable was completed by the researcher at study intake and administrative data will not be missing.

MULTIPLE IMPUTATION PERFORMANCE (Ministry perspective)

Figure 7. Comparison of INMB values calculated using observed and imputed data (observed = blue, imputed = red).

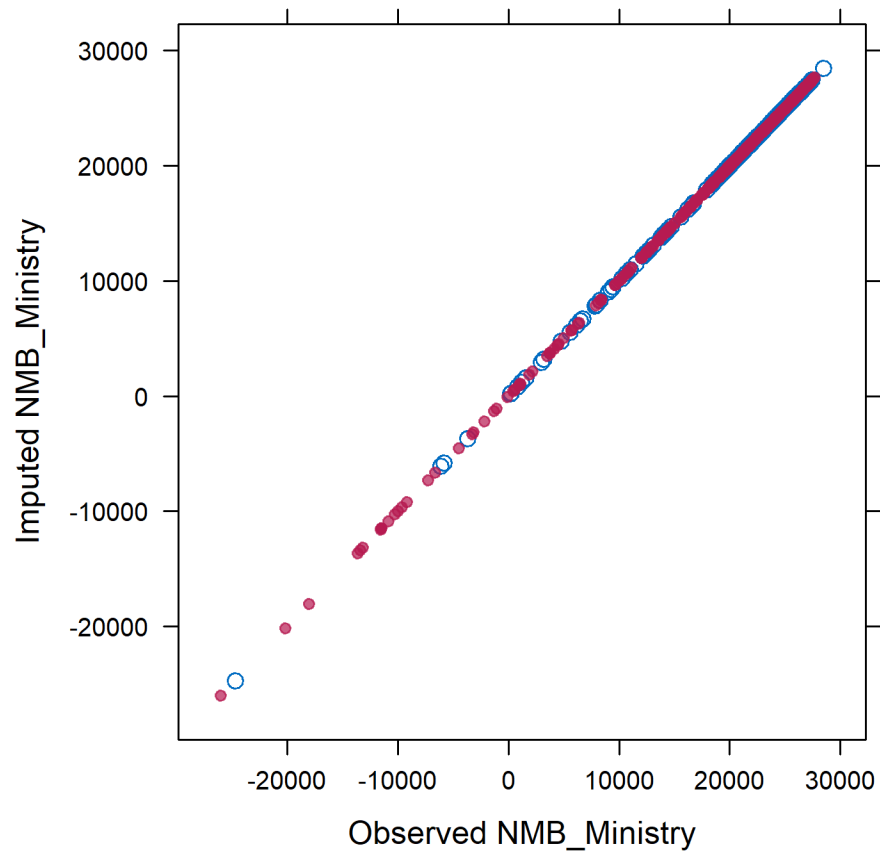


Figure 8. Comparison of INMB values calculated using observed and imputed data by quarter (ministry perspective) (observed = blue, imputed = red).

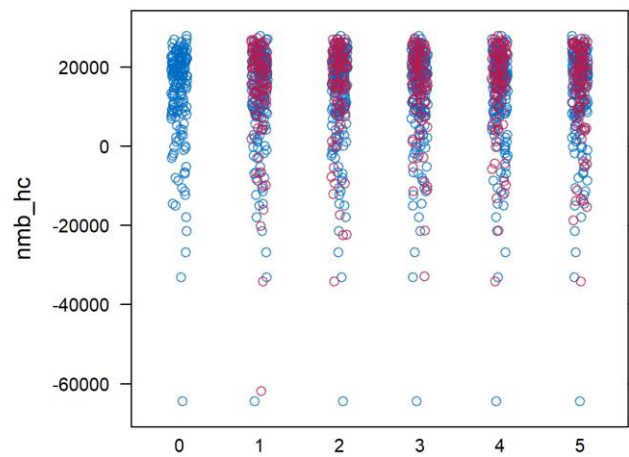


Figure 9. Comparison of INMB values calculated using observed and imputed data by quarter (ministry perspective) (observed = blue, imputed = red).

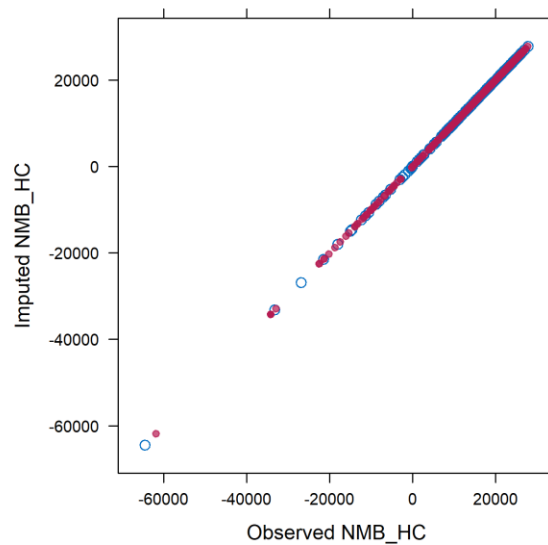


Figure 10. Frequency of observed and imputed baseline QALYS in the sample data set (observed = blue, imputed = red).

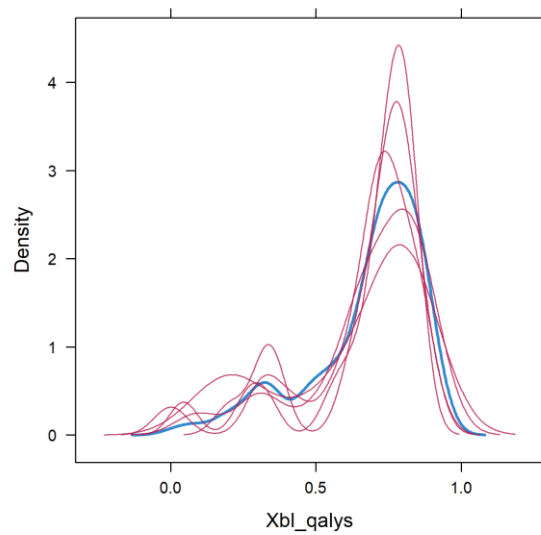


Figure 11. Frequency of observed and imputed QALYS gained over 12-months in the sample data set (observed = blue, imputed = red).

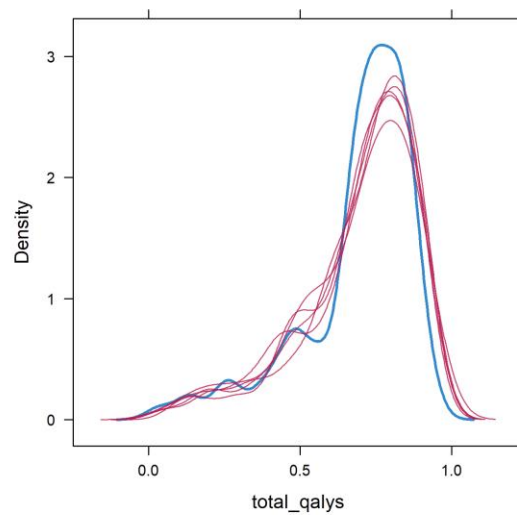


Figure 12. Frequency of observed and imputed healthcare costs from the ministry's perspective in the sample data set (observed = blue, imputed = red).

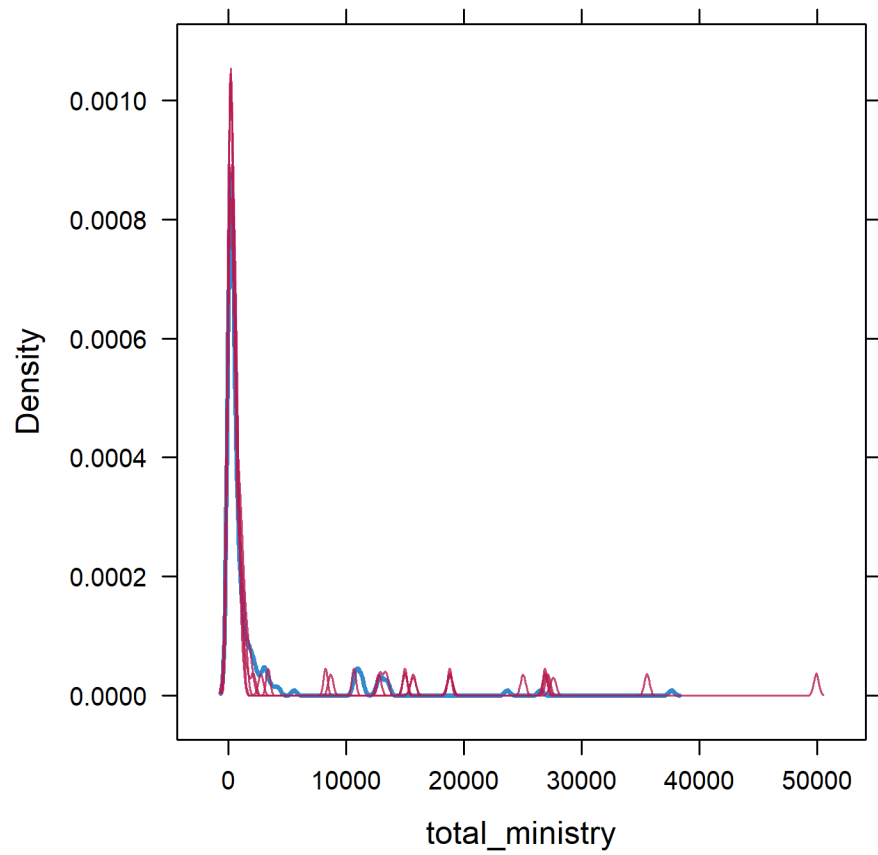


Figure 13. Frequency of observed and imputed NMB from the ministry perspective in the sample data set (observed = blue, imputed = red).

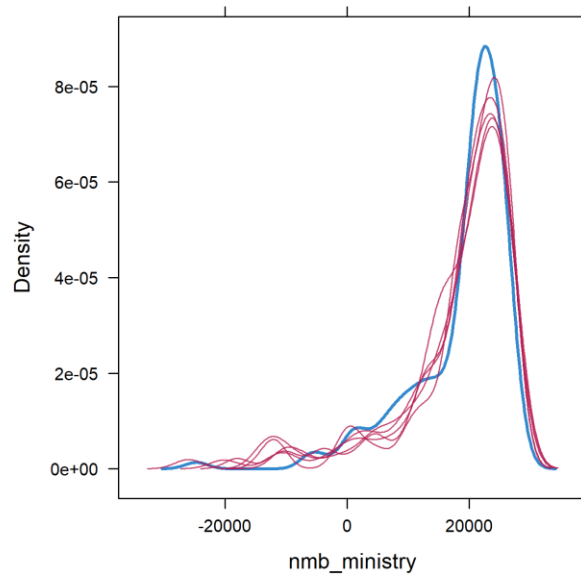


Figure 14. Frequency of observed and imputed NMB from the ministry perspective in the sample data set.

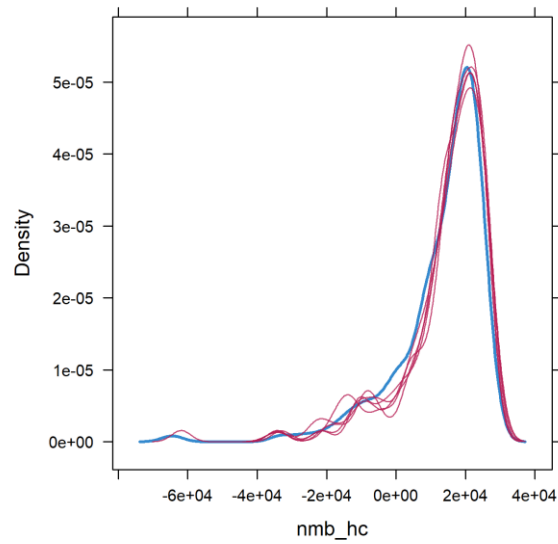


Figure 15. Trace lines for imputed data in the sample data set.

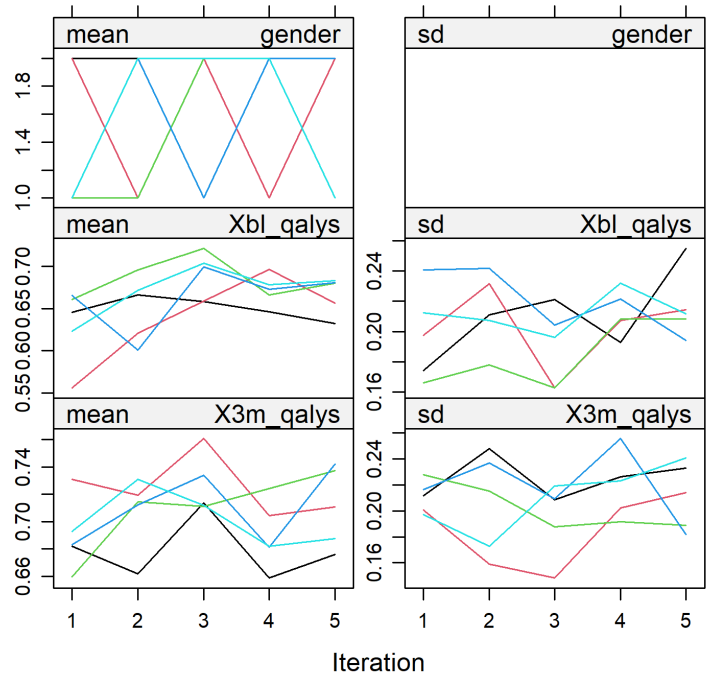


Figure 16. Trace lines for imputed data in the sample data set.

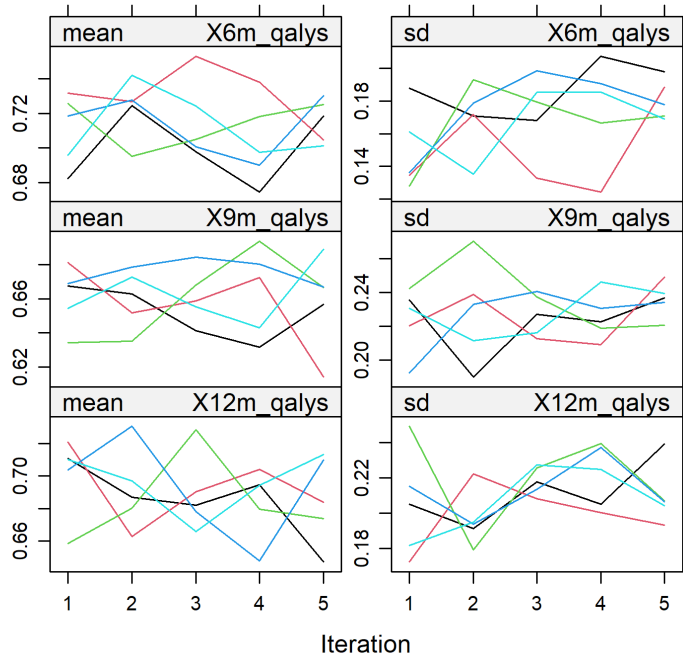


Figure 17. Trace lines for imputed data in the sample data set.

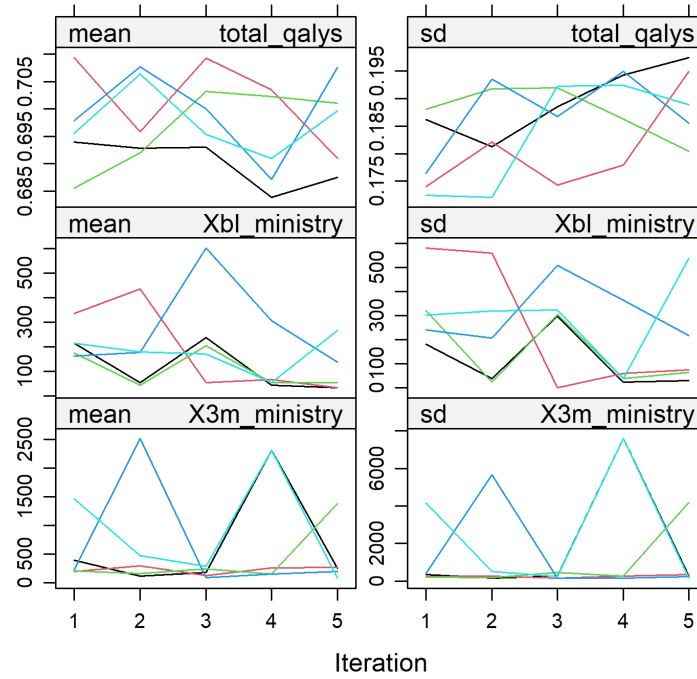
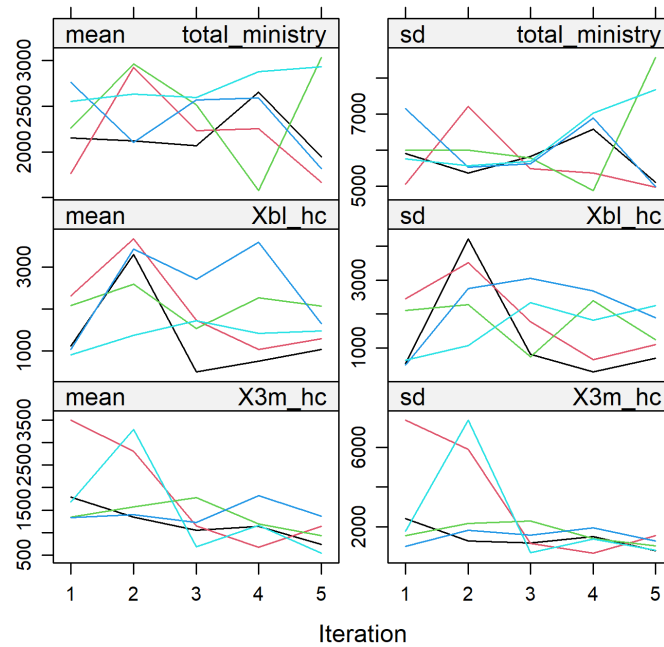


Figure 19. Trace lines for imputed data in the sample data set.



Appendix I. 12-Month Linear Regression Performance from Cost-Effectiveness Analysis in Chapter Four.

Figure 1. Net monetary benefit for the GLA:D® and UC Cohort over 12-months (Ministry of Health Perspective) at \$30,000/QALY.

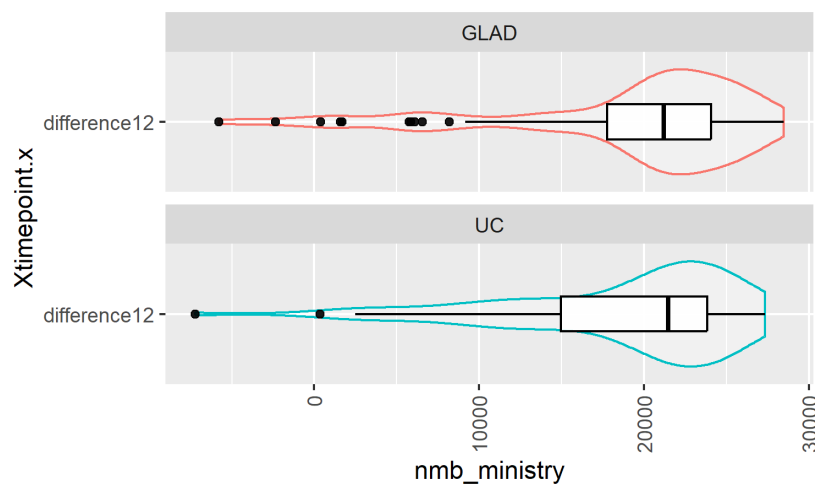


Figure 2. Cost and QALYs over 12-Months (Ministry of Health Perspective, complete cases).

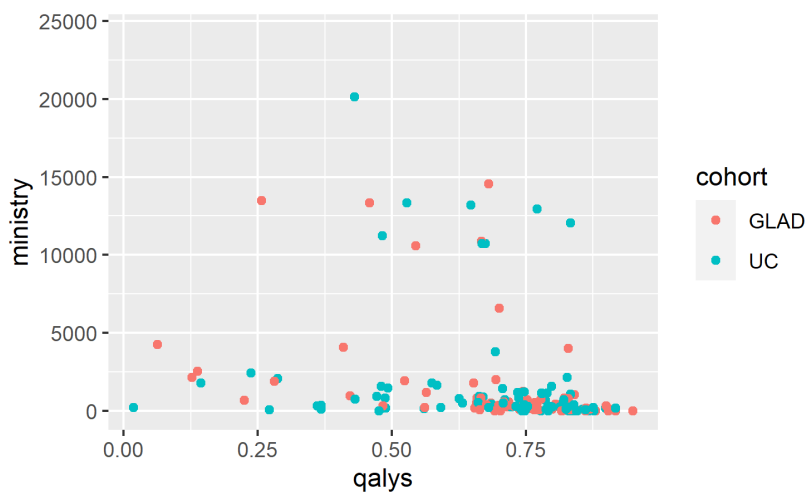
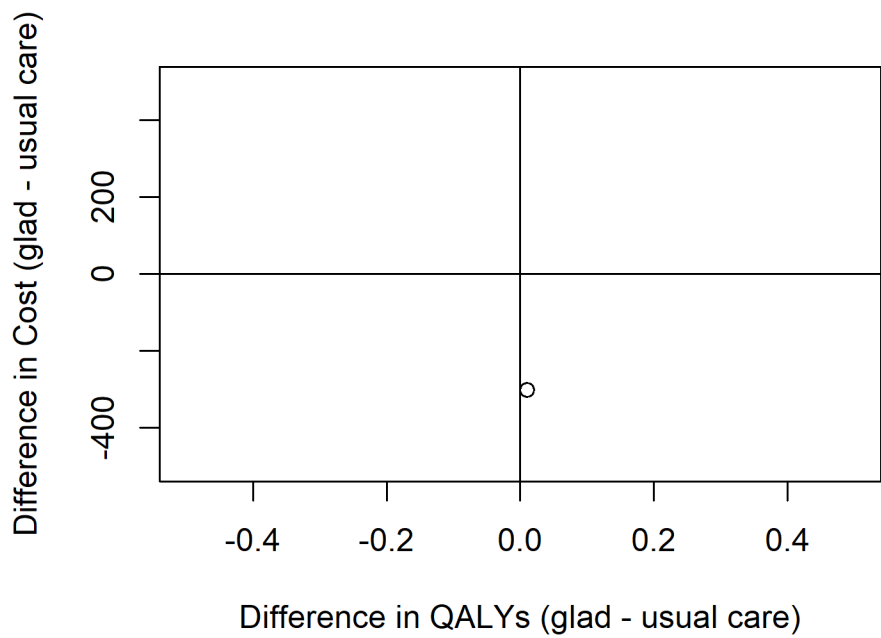


Figure 3. Deterministic incremental cost-effectiveness over 12-month time horizon.

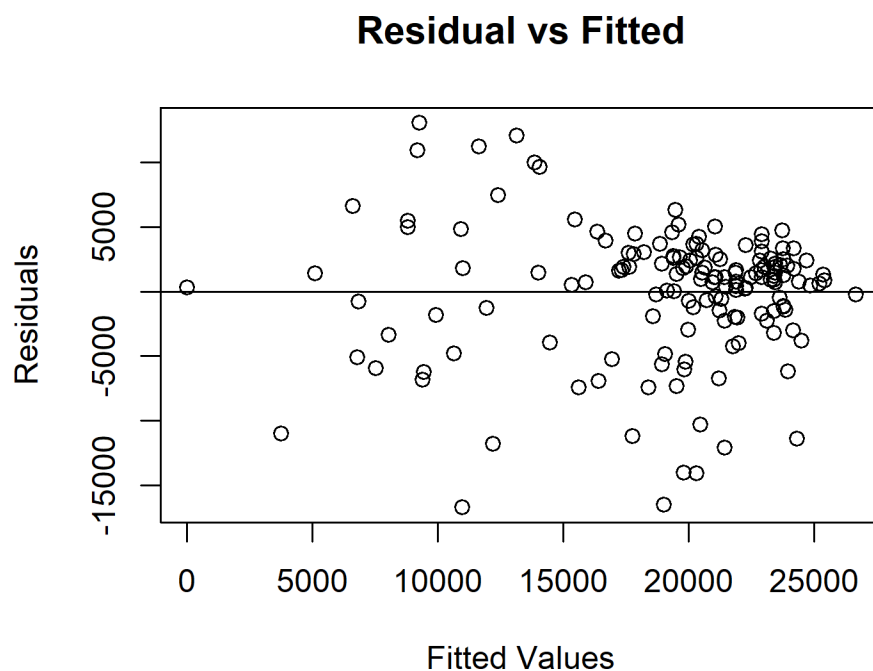


LINEAR REGRESSION ASSUMPTIONS

1. Linearity (of $E(Y/X)$) that is, the expected value of outcome conditional on variables.
2. Normality of errors (at each value of X) with mean 0
3. Constant variance of errors
4. Independence (outcome (between observations) and errors)

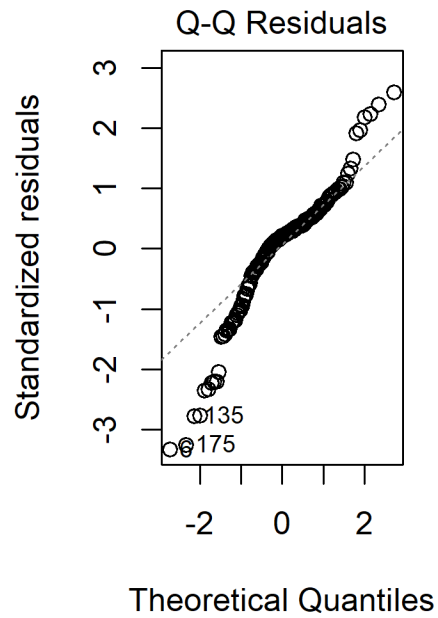
#1. Linearity

- Scatterplots before doing LR (remember the near 0 and local fits?)
- Plots of residuals vs fitted values (or variables)
- Now we look at the residuals:



#2. Normality of errors (at each value of X) with mean 0

QQplots of residuals



Normality test

```
##
```

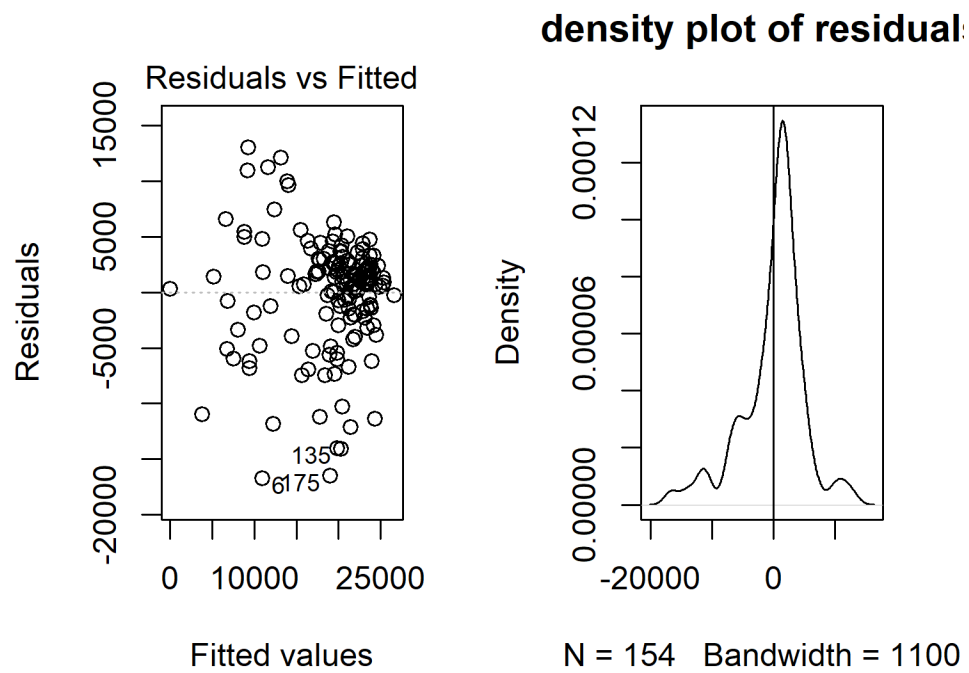
```
## Shapiro-Wilk normality test
```

```
##
```

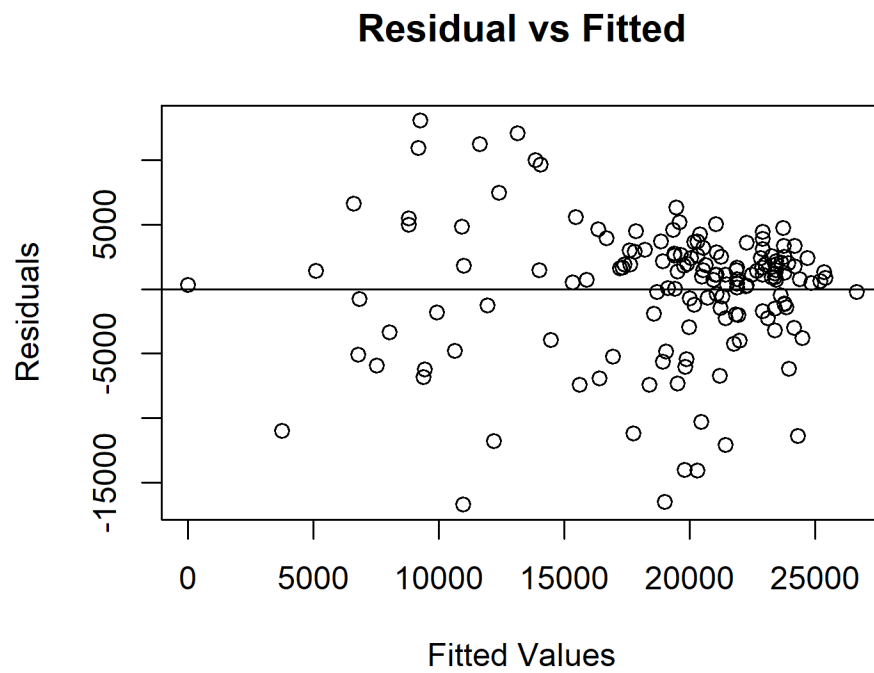
```
## data: residuals(lmNMB_ministry_complete)
```

```
## W = 0.92877, p-value = 6.105e-07
```

Mean around 0



#3. Constant variance



Heteroscedasticity test (Breusch-Pagan test)

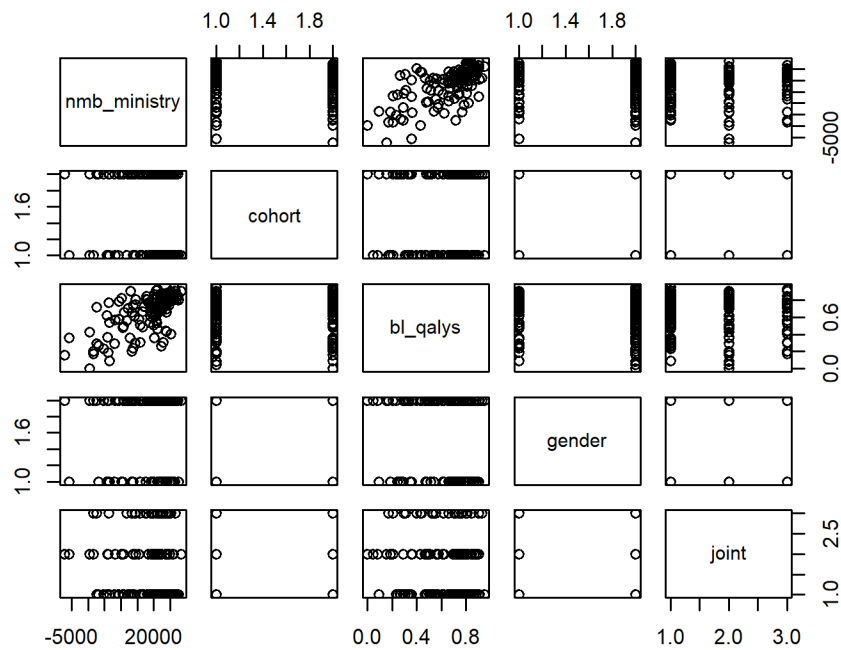
```
##
```

```
## Studentized Breusch-Pagan test
```

```
##
```

```
## data: lmNMB_ministry_complete
```

```
## BP = 18.808, df = 5, p-value = 0.002087
```



Multicollinearity

Variance inflation factor (VIF)

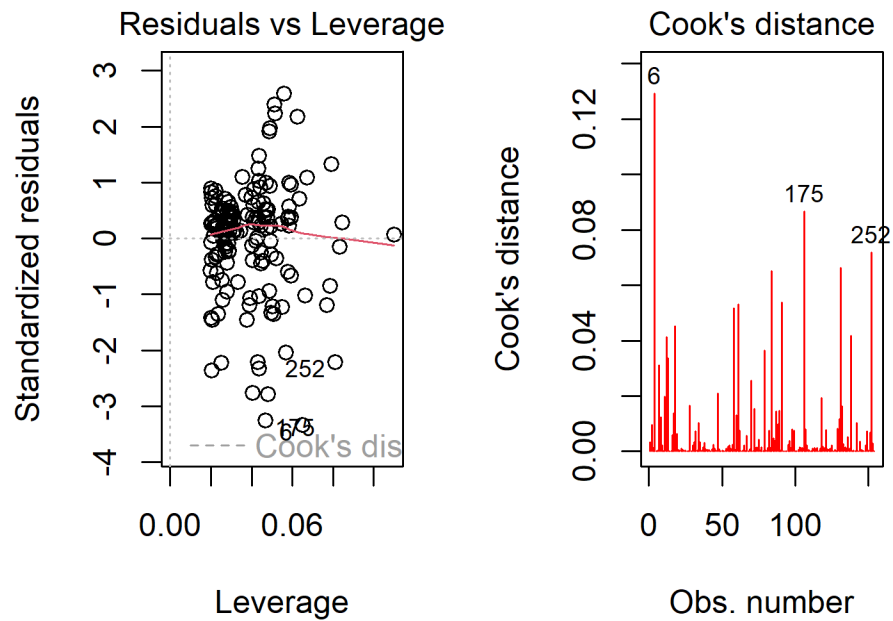
If VIF >5 flag

```
##          GVIF Df GVIF^(1/(2*Df))
## cohort  1.066444 1    1.032688
## bl_qalys 1.035572 1    1.017631
## gender  1.105675 1    1.051511
## joint   1.146279 2    1.034719
```

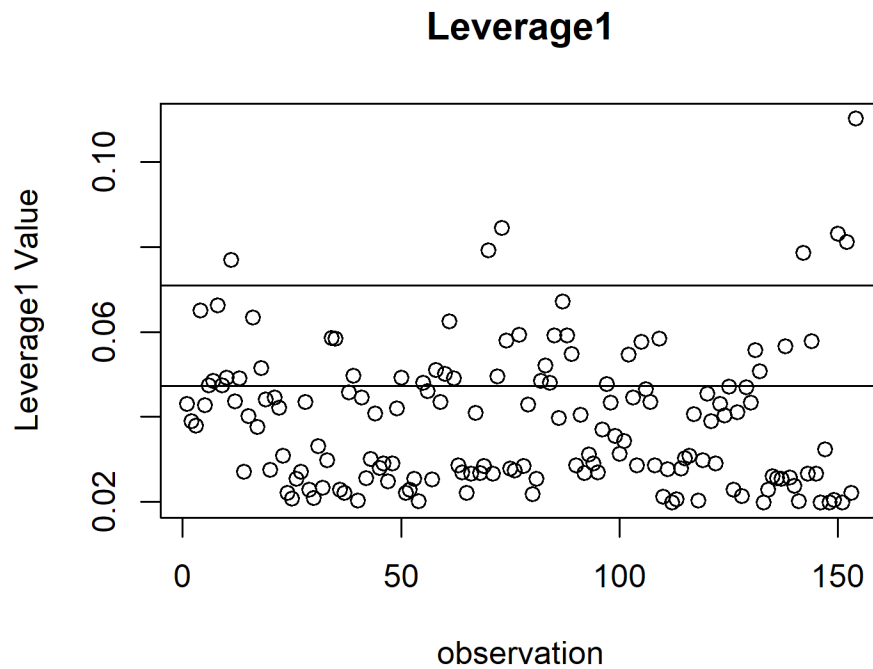
Influential points

Cook's distance (D_i)

If $D_i > 1$ (or If $D_i > 0.5$) flag



Leverage points (h_i) Points that fall far from the line are points of high leverage If $h_i > 2p/n$



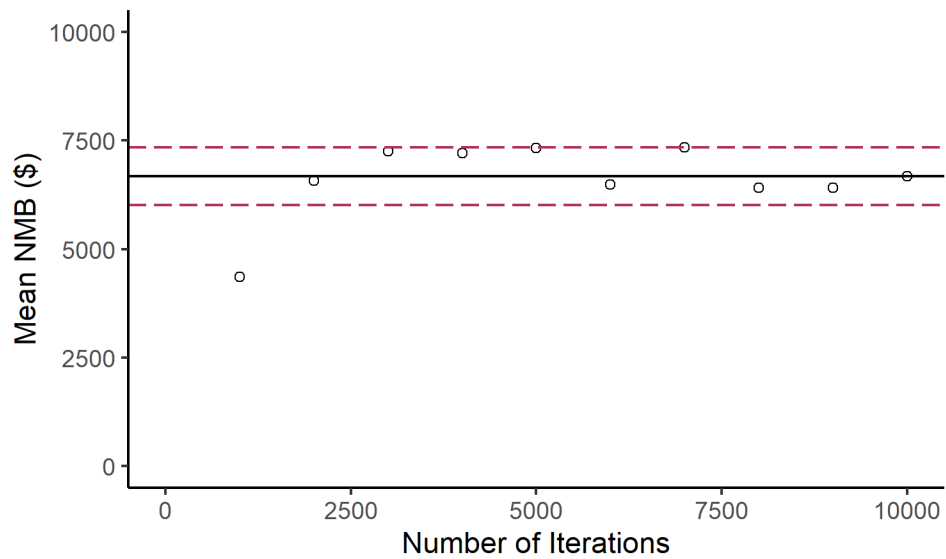
MAD TEST for Outliers (threshold 3.5 MAD)

14 outlier cases were identified where ministry costs are > 3.5 MAD. Visual inspection shows all had surgery, so costs are $> \$12,000$.

1 outlier case was identified where healthcare costs are > 3.5 MAD. Visual inspection shows reported extreme number of rehabilitation visits and private surgery. MAD outlier justifies dropping this case.

Appendix J. Lifetime Markov Model Convergence Testing from Cost-Effectiveness Analysis in Chapter Four.

Figure 1. Convergence Test Showing the Mean Incremental Net Monetary Benefit by Number of Iterations (Ministry perspective, complete cases).



Note: red-dashed line shows +/- 10% of mean at 10,000 iterations

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