# Advancing economic evaluation methods for better medical decision making through real-world, longitudinal data

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# Abstract

Health economic evaluation is a fundamental component in helping inform health care providers and policy makers in making decisions on priorities in health care. This is particularly relevant in today's tight budgetary climate and in response to continued calls for sustainable health care systems. Economic evaluation evidence has influenced and contributed to many areas of health policy making, at all levels of the health care system – from shaping guidelines that guide clinical care to informing decision for subsidy of pharmaceuticals and medical services. For these evaluations to be useful to decisions makers, they need to provide useful and reliable information and to achieve this, methodological guidelines should be followed, and robust evidence of effectiveness and cost is paramount. With recent advances in information technology, data and statistical methods and implementation of electronic health records, health decision makers are increasingly seeking real-world, generalisable evidences to complement and support policy and clinical decisions.

This thesis aims to demonstrate the usefulness and practicality of applying real-world longitudinal data in health economics research and applications. It features six individual health economics studies which explore longitudinal data and show their value and contribution towards advancing economic evaluation methodologies and better decision making. Each of the studies answer specific research questions and contribute to the research literature through methodological research to improve consistency in extrapolating costs, utility inputs and modelling long-term outcomes, generating robust evidence for resource allocation decisions, promoting a better understanding of real-world heterogeneity and approaches to optimise patient outcomes. Collectively, these studies highlight important variations in the cost and outcomes of health care delivery in real-world settings, provide useful insights into the implications of such variations and demonstration of translating research findings to implementation.

# Declaration

This is to certify that:

i. The thesis comprises only my original work towards the Doctor of Philosophy (PhD), except where indicated in the acknowledgements.

ii. Due acknowledgement has been made in the text to all other material used.

iii. The thesis is fewer than 100, 000 words in length, exclusive of tables, bibliographies and appendices.

Michelle Tew

# Preface

This thesis contains six original research studies – five published papers and one submitted paper currently under review – all of which were conducted during my PhD candidature. I was the primary author for each paper, leading the writing of the manuscripts, from initial drafting to the final revisions. I contributed to 90% of the statistical analyses and over 65% of the planning, study design and interpretation of results. I gratefully acknowledge the guidance and work of many others in the six studies contained in this thesis. My supervisors and co-authors, Associate Professor Kim Dalziel, Professor Philip Clarke, Professor Karin Thursky, Associate Professor Michelle Dowsey and Professor Peter Choong, provided guidance in conceiving the research question, development of the study design and contributed to reviewing of study results by providing valuable comments and edits.

## Publications arising from this thesis

1. **Tew M**, Clarke P, Thursky K, Dalziel K. Incorporating future medical costs: Impact on cost-effectiveness analysis in cancer patients. ***PharmacoEconomics***. 2019 Jul 1; 37(7):931-41.
2. **Tew M**, Forster D, Teh BW, Dalziel K. National cost savings from an ambulatory program for low-risk febrile neutropenia patients in Australia. ***Australian Health Review***. 2019 Oct 17; 43(5):549-55.
3. **Tew M**, Dowsey MM, Choong A, Choong PF, Clarke P. Co-morbidities and sex differences in long-term quality-of-life outcomes among patients with and without diabetes after total knee replacement: five-year data from registry study. ***Journal of Clinical Medicine***. 2020 Jan; 9(1):19.
4. **Tew M**, Dalziel K, Dowsey M, Choong PF, Clarke P. Exploring the impact of quality of life on survival: a case study in total knee replacement surgery. ***Medical Decision Making***. 2020 Apr; 40(3):302-13.
5. **Tew M**, Dalziel K, Clarke P, Smith A, Choong PF, Dowsey M. Patient-reported outcome measures (PROMs): can they be used to guide patient-centered care and optimize outcomes in total knee replacement? ***Quality of Life Research***. 2020 Jul; 10:1-1.

6. **Tew M**, Dalziel K, Thursky K, Krahn M, Abrahamyan L, Morris A, Clarke P. High excess cost of care associated with sepsis in first year of cancer diagnosis: Results from a population-based case-control matched cohort. *Submitted to PLOS One;* 2020 Nov.

## Other co-authored publications during the course of PhD

1. Si L, Willis MS, Asseburg C, Nilsson A, **Tew M**, Clarke PM, Lamotte M, Ramos M, Shao H, Shi L, Zhang P. Evaluating the ability of economic models of diabetes to simulate new cardiovascular outcomes trials: a report on the Ninth Mount Hood Diabetes Challenge. ***Value in Health***. 2020 Sep 1;23(9):1163-70.
2. Kent S, Becker F, Feenstra T, Tran-Duy A, Schlackow I, **Tew M**, Zhang P, Ye W, Lizheng S, Herman W, McEwan P. The challenge of transparency and validation in health economic decision modelling: a view from Mount Hood. ***Pharmacoeconomics***. 2019 Nov 1;37(11):1305-12.
3. Thursky K, Lingaratnam S, Jayarajan J, Haeusler GM, Teh B, **Tew M**, Venn G, Hiong A, Brown C, Leung V, Worth LJ. Implementation of a whole of hospital sepsis clinical pathway in a cancer hospital: impact on sepsis management, outcomes and costs. ***BMJ Open Quality***. 2018 Jul 1;7(3):e000355.
4. Palmer AJ, Si L, **Tew M**, Hua X, Willis MS, Asseburg C, McEwan P, Leal J, Gray A, Foos V, Lamotte M. Computer modeling of diabetes and its transparency: a report on the eighth Mount Hood Challenge. ***Value in Health***. 2018 Jun 1;21(6):724-31.
5. **Tew M**, Efron D, Hiscock H, Dalziel K. What medications are Australian children prescribed? Evidence from the Longitudinal Study of Australian Children. ***Journal of Paediatrics and Child Health***. 2018 Mar; 54(3):335-6.

## Conferences and speaking engagements

### *Conference presentations (Abstract accepted)*

1. High excess cost of care associated with sepsis in the first year of cancer diagnosis: Results from a population-based matched cohort. **University of Melbourne Faculty of Medicine, Dentistry and Health Sciences (MDHS) Graduate Research Conference. December 2020.**

2. Tew M, Dalziel K, Thursky K, Krahn M, Abrahamyan L, Morris A, Clarke P. 5-year health care costs of sepsis in cancer patients: results from a population-based case-control matched cohort. [Virtual poster presentation] **ISPOR Europe. November 2020.**
3. Tew M, Dalziel K, Thursky K, Krahn M, Abrahamyan L, Morris A, Clarke P. The 5-year health care costs of sepsis in cancer patients: results from a population-based case-control matched cohort. **42nd Annual Meeting of the Society for Medical Decision Making. October 2020. Finalist in Lee B. Lusted Student Prize Competition.**
4. Tew M, Dalziel K, Clarke P, Smith A, Choong PF, Dowsey M. Using quality-of-life trajectories to guide value-based care for total knee replacement patients. **Australian Health Economics Society (AHES) Annual Conference, Melbourne. September 2019.**
5. Tew M, Dalziel K, Clarke P, Smith A, Choong PF, Dowsey M .Using latent class growth analysis to identify quality of life trajectories in total knee replacement patients: Potential for assessing sub-groups and heterogeneity in cost-effectiveness analysis. **International Health Economics Association (iHEA) 2019 Congress, Basel Switzerland. July 2019.**
6. Tew M, Clarke P, Stiles J, Goh A, Tran AD. Quantifying the impact of Huntington's Disease on quality adjusted life years and overall survival. **International Health Economics Association (iHEA) 2019 Congress, Basel Switzerland. July 2019.**
7. Tew M, Dalziel K, Clarke P, Smith A, Choong PF, Dowsey M. Quality of life trajectories in total knee replacement patients: What can they tell us? **Summer Health Economics Study Group (HESG), University of East Anglia, UK. July 2019.**
8. Tew M, Dalziel K, Clarke P, Smith A, Choong PF, Dowsey M. Quality-of-life trajectories in total knee replacement patients: What can they tell us? [Poster presentation] **OPUS Forum, Melbourne. March 2019. Awarded Judges' Selection for Best Poster Presentation.**
9. Tew M, Dowsey MM, Choong A, Choong PF, Clarke P. Health-reported quality-of-life following total knee replacement by diabetes status. **Mount Hood Challenge 2018, Dusseldorf, Germany. October 2018.**

10. Tew M, Clarke P, Thursky K, Dalziel K. Incorporating future medical costs: Implications on the cost-effectiveness of sepsis management in cancer patients. **Australian Health Economics Society (AHES) conference, Hobart. September 2018.**
11. Tew M, Clarke P, Thursky K, Dalziel K. Incorporating future medical costs: Implications on the cost-effectiveness of sepsis management in cancer patients. **Australian Health Economics Society Doctoral Workshop (AHED), Hobart. September 2018.**
12. Tew M, Dalziel K, Dowsey M, Choong PF, Clarke P. Using Health-related Quality of Life as Predictors of Outcomes in Lower Limb Arthroplasty Patients. **Australian Health Economics Society (AHES) conference, Sydney. September 2017.**

***Invited presentations***

13. Applications of real-world, longitudinal data to support health policy in cancer and infections. **Department of Health and Human Services, Victoria. November 2020.**
14. Economic burden of sepsis in cancer: Health care cost estimates from a population-based study. **The Toronto Health Economics and Technology Assessment (THETA) Collaborative Rounds Lecture Series. October 2020.**
15. Health economic evaluation: Applications in cancer and infection research. **National Centre for Infections in Cancer (NCIC) Symposium. September 2019.**
16. Quality of life trajectories in total knee replacement patients: What can they tell us? **Health Economics Research Centre, University of Oxford. July 2019.**
17. Using latent class growth analysis to identify quality of life trajectories: Application in total knee replacement patients. Joint presentation with Professor Anne Smith (Curtin University). **OPUS Education Webinar Series. May 2019.**
18. Incorporating future medical costs: Implications on the cost-effectiveness of sepsis management in cancer patients. Joint presentation with Associate Professor Pieter van Baal (Erasmus University Rotterdam). **Health Economics Research Centre, University of Oxford. October 2018.**

19. Estimating survival: Does patient-reported quality-of-life matter? **Health Economics Research Centre, University of Oxford. October 2018.**
20. Incorporating future medical costs: Implications on the cost-effectiveness of sepsis management in cancer patients. **Institute of Health Management and Policy, Erasmus University Rotterdam. October 2018.**
21. Cost-effectiveness analysis of a hospital-wide sepsis pathway in cancer patients. **National Centre for Infections in Cancer, Victorian Comprehensive Cancer Centre (VCCC). May 2018.**

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22. Cost analysis: preliminary findings from a case-control matched cancer cohort. **Work-in-Progress seminar, Health Economics Unit, Melbourne School of Population and Global Health. July 2020.**
23. (Very) Brief overview of statistical methods for assessing cost data. **Work-in-Progress seminar, Health Economics Unit, Melbourne School of Population and Global Health. July 2020.**
24. Using Patient-Reported Outcomes to Guide Value-Based Care for Total Knee Replacement. **11th Annual Health Economics Workshop by University of Melbourne Health Economics Group (UMHEG). November 2019.**
25. Using latent class growth analysis to identify quality of life trajectories in total knee replacement patients. **Work-in-Progress seminar, Health Economics Unit, Melbourne School of Population and Global Health. February 2019.**
26. Incorporating future medical cost: Implications on cancer patients. **10th Annual Health Economics Workshop by University of Melbourne Health Economics Group (UMHEG). November 2018.**
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# Contents

Abstract ..... i

Declaration ..... ii

Preface ..... iii

Publications arising from this thesis ..... iii
Other co-authored publications during the course of PhD ..... iv
Conferences and speaking engagements ..... iv
Sources of funding ..... viii

Acknowledgements ..... ix

Contents ..... x

List of Tables ..... xiv

List of Figures ..... xvi

Chapter 1 : Introduction ..... 1

1.1. Health economics and medical decision making ..... 1
1.2. Limits and quality of economic evaluations ..... 3
1.3. Real-world, longitudinal data for health economics research and applications ..... 7
1.4. Overarching aim ..... 10
1.5. Chapter content ..... 12
1.6. Thesis structure ..... 16
1.7. References ..... 18

SECTION I : Extrapolation of Costs ..... 31

Chapter 2 : Incorporating future medical costs: Impact on cost-effectiveness analysis in cancer patients ..... 32

2.1. Abstract ..... 33
2.2. Key points for decision makers ..... 34
2.3. Introduction ..... 34

2.4. Methods ..... 37
2.5. Results ..... 40
2.6. Discussion ..... 41
2.7. Conclusion ..... 45
2.8. Tables and figures ..... 46
2.9. References ..... 53
2.10. Supplementary materials ..... 60

Chapter 3 : National cost savings from an ambulatory program for low-risk febrile neutropenia patients in Australia ..... 85

3.1. Abstract ..... 86
3.2. Key question summary ..... 87
3.3. Introduction ..... 87
3.4. Methods ..... 89
3.5. Results ..... 90
3.6. Discussion ..... 92
3.7. Conclusions ..... 94
3.8. Tables and figures ..... 96
3.9. References ..... 102

SECTION II : Modelling Long-Term Outcomes ..... 106

Chapter 4 : Patient-reported outcome measures (PROMs): Can they be used to guide patient-centered care and optimise outcomes in total knee replacement? ..... 107

4.1. Abstract ..... 108
4.2. Key points for decision makers ..... 109
4.3. Introduction ..... 109
4.4. Material and Methods ..... 110
4.5. Results ..... 113
4.6. Discussion ..... 115
4.7. Conclusion ..... 119
4.8. Tables and figures ..... 120
4.9. References ..... 127
4.10. Supplementary materials ..... 134

Chapter 5 : Co-morbidities and sex differences in long-term quality-of-life outcomes among patients with and without diabetes after total knee replacement: Five-year data from registry study ..... 142

5.1. Abstract ..... 143
5.2. Introduction ..... 143
5.3. Methods ..... 144
5.4. Results ..... 146
5.5. Discussion ..... 148
5.6. Conclusions ..... 151
5.7. Tables and figures ..... 152
5.8. References ..... 157
5.9. Supplementary materials ..... 163

Chapter 6 : Exploring the impact of quality-of-life on survival: A case study in total knee replacement surgery ..... 165

6.1. Abstract ..... 166
6.2. Introduction ..... 167
6.3. Methods ..... 170
6.4. Results ..... 173
6.5. Discussion ..... 176
6.6. Conclusion ..... 179
6.7. Tables and figures ..... 181
6.8. References ..... 186
6.9. Supplementary materials ..... 193

SECTION III : Generating Real-World Evidence ..... 207

Chapter 7 : Economic burden of sepsis in cancer patients ..... 208

7.1. Abstract ..... 209
7.2. Introduction ..... 210
7.3. Materials and methods ..... 211
7.4. Results ..... 213
7.5. Discussion ..... 215
7.6. Conclusion ..... 218

7.7. Tables and figures ..... 219
7.8. References ..... 223
7.9. Supplementary materials ..... 228

Chapter 8: Discussion & Conclusion ..... 252

8.1. Chapter summary ..... 252
8.2. Implications and translational value of findings ..... 258
8.3. Strengths, limitations and future research directions ..... 261
8.4. Conclusions ..... 266
8.5. References ..... 267

# List of Tables

Table 1.1: Studies presented in this thesis and their health economic applications ..... 12

Table 1.2: Summary of methods employed and key contributions from each of the studies presented in this thesis ..... 16

Table 2.1: Data input for lifetime model ..... 46

Table 2.2: Incremental cost-effectiveness results ..... 48

Table S2.1: Description of patient characteristics between cohorts ..... 67

Table S2.2: Estimated costs to implement SP protocol in PMCC ..... 70

Table S2.3: Data inputs for cancer sub-group analyses ..... 71

Table S2.4: Incremental cost-effectiveness results across cancer types ..... 78

Table 3.1: Characteristics of patients across the two cohorts ..... 96

Table 3.2: Components and associated costs of ambulatory program ..... 97

Table 3.3: Comparison of length of stay and total cost between cohorts ..... 98

Table 4.1: Baseline characteristics ..... 120

Table 4.2: Description of each QoL trajectories by phases and estimated QALYs over 5-years ..... 122

Table 4.3: Multivariable multinomial logistic regression showing relative risk (RRR) of belonging in each of the trajectory groups compared to Trajectory 5 (highest incremental QALYs/health gains) ..... 123

Table 4.4: Patient characteristics associated with each of the trajectories compared to Trajectory 5 (highest incremental QALYs/health gains). ..... 125

Table S4.1: Comparison of fit statistics for models containing 1 to 8 classes ..... 134

Table S4.2: Group membership probability diagnostics for models containing 1 to 8 classes ..... 135

Table S4.3: Patient profiles by QoL trajectories (Traj) ..... 136

Table S4.4: Univariable multinomial logistic regression showing relative risk (RRR) of belonging in each of the trajectory groups compared to Trajectory 5 (highest incremental QALYs) ..... 138

Table 5.1: Demographic and clinical characteristics according to diabetes status ..... 152

Table 5.2: Effect of patient characteristics on changes in QoL over time: coefficients estimated from multilevel regression model ..... 153

Table 6.1: Coefficients and hazard ratios from Gompertz proportional hazards survival model for all-cause mortality ..... 181

Table 6.2: Estimated life expectancies and QALYs of the cohort from each of the models ..... 182

Table S6.1: Patient characteristics ..... 196
Table S6.2: Measures of model fit for survival models ..... 198
Table S6.3: Coefficients, hazard ratios from Gompertz proportional hazards survival model for all-cause mortality (including patient socio-demographic and clinical characteristics) ..... 202
Table S6.4: Estimated life expectancies and QALYs of the cohort from each of the models (including patient socio-demographic and clinical characteristics) ..... 203
Table 7.1: Characteristics of cancer patients with sepsis by malignancy type ..... 219
Table 7.2: Cumulative cost of care ($CAD 2018, 95% CI) between sepsis cases and matched controls ..... 220
Table S7.1: List of datasets and costing methodology ..... 228
Table S7.2: ICD-10-CA codes used in the identification of sepsis ..... 230
Table S7.3: Cumulative cost of care ($CAD 2018) results from sensitivity analysis (i) ..... 233
Table S7.4: Cumulative cost of care ($CAD 2018) results from sensitivity analysis (ii) ..... 234
Table S7.5: Cumulative cost of care ($CAD 2018) results from sensitivity analysis (iii) ..... 235
Table S7.6: Characteristics of sepsis cases vs. matched controls for haematology patients ..... 238
Table S7.7: Characteristics of sepsis cases vs. matched controls for solid tumour patients ..... 239
Table S7.8: Characteristics of sepsis cases vs. unmatched cases for haematology patients ..... 241
Table S7.9: Characteristics of sepsis cases vs. unmatched cases for solid tumour patients ..... 242
Table S7.10: Cumulative cost of care ($CAD 2018) between sepsis cases and matched controls among females ..... 245
Table S7.11: Cumulative cost of care ($CAD 2018) between sepsis cases and matched controls among males ..... 246
Table S7.12: Cumulative cost of care ($CAD 2018) between haematology sepsis cases and matched controls by age categories ..... 247
Table S7.13: Cumulative cost of care ($CAD 2018) between solid tumour sepsis cases and matched controls by age categories ..... 249
Table 8.1: Real-world data sources used in this thesis ..... 252
Table 8.2: Overall summary ..... 256

# List of Figures

Figure 1.1: Annual number of publications involving use of longitudinal data published in selected health economics journals between 1984 and 2019 ..... 10

Figure 2.1: Cost-effectiveness acceptability curve for all cancers combined (base-case) reflecting the impact of costs included in analysis. ..... 49

Figure 2.2: Tornado diagram showing the impact of different variables and assumptions on cost per QALY from one-way sensitivity analysis (base-case). ..... 50

Figure 2.3: Breakdown of lifetime costs and QALYs across different cancer types. Base-case represents all cancers combined. ..... 51

Figure 2.4: Cost-effectiveness acceptability curves across various cancer types for all healthcare costs scenario (all future medical costs). ..... 52

Figure S2.1: TreeAge model for lifetime modelling ..... 71

Figure S2.2: Net monetary benefit (NMB) for different costing scenarios across cancer types. ..... 80

Figure S2.3: Correlations of cost-effectiveness (cancer costs only scenario) by cancer types, with (A) lifetime recurring medical costs and (B) 5-year relative survival. ..... 81

Figure S2.4: Correlations of cost-effectiveness (all healthcare costs scenario) by cancer types, with (A) lifetime recurring medical costs and (B) 5-year relative survival. ..... 82

Figure 3.1: Diagrammatic representation of the evaluation process for ambulatory program eligibility ..... 99

Figure 3.2: Actual and projected number of hospitalisation episodes of FN in Australia ..... 100

Figure 3.3: Estimated cumulative (A) cost-averted and (B) bed days saved over 10 years by % identified as low-risk (LR) FN and by % eligible for ambulatory program (EA). ..... 101

Figure 4.1: QoL trajectory profiles and class membership for six-class model ..... 126

Figure S4.1: Relative risk ratio with 95% confidence intervals (multivariable multinomial logistic regression) of being in each trajectory vs. reference trajectory (Trajectory 5) for each covariate in the model. ..... 141

Figure 5.1: Flow diagram of patients included in the longitudinal analysis ..... 155

Figure 5.2: Long-term patterns of QoL utility value changes in total joint replacement (TKR) patients in (A) females and (B) males ..... 156

Figure S5.1: QoL utility value changes among TKR patients by HbA1c control ..... 163

Figure S5.2: QoL utility value changes among TKR patients by medication use ..... 164

Figure 6.1: (A) Variation in the pattern of QoL following TKR across groups (tertiles) categorised by baseline utility (B) Mean change in utility at 12 months across tertile groups. ..... 183

Figure 6.2: Kaplan-Meier survival curves (A) Survival differences by baseline utility (B) Survival differences by change in utility..... 184

Figure 6.3: Change in incremental QALYs against change in QoL HR across models185

Figure S6.1: Kaplan-Meier survival curve of the observed data..... 197

Figure S6.2: Predicted survival curves from various parametric survival models fitted to the observed data ..... 197

Figure S6.3: Cox-Snell residual plots..... 199

Figure S6.4: Variations in estimated life expectancies across ages and different levels of baseline utility simulated using each of the models. ..... 205

Figure 7.1: Mean monthly cost of care by malignancy type. ..... 221

Figure 7.2: Variations in the 1-year cumulative excess cost by sex and age groups.... 222

Figure S7.1: Excess cost of care ($CAD 2018) results from sensitivity analysis (iv) . 236

Figure S7.2: Kaplan-Meier survival curves comparing sepsis cases and matched no sepsis controls for (A) haematological and (B) solid tumour cancer. ..... 237

Figure S7.3: Mean monthly excess cost of care due to sepsis by malignancy type. .... 244

# Chapter 1 : Introduction

## 1.1. Health economics and medical decision making

In the last half century, global health care expenditures have risen steeply, rising approximately 7% annually in Australia [1]. This, combined with improvements in medical technology, growing consumer demand for health care, an ageing population and emergence of new diseases, have made it increasingly challenging for health care providers and policy makers to prioritise health care resource allocation. Against such constraints, it is crucial to maximise population health gains within limited available resources and to conduct evaluations in a rigorous, structured and evidence-based manner. Health economics provides the foundational economic theory for priority setting and economic evaluation offers a framework to quantify the resources required for an intervention and the relative health gains likely to be achieved. Economic evaluation involves comparing the costs and benefits of health interventions and strategies of competing alternatives, allowing for efficient and equitable decisions about the allocation of scarce resources [2]. It helps encapsulate both costs and outcomes into a single summary measure, the incremental cost-effectiveness ratio (ICER; Δcosts/Δoutcomes), which represents the economic value of an intervention compared to an alternative.

The two most common evaluation methods are cost-effectiveness and cost-utility analyses. Cost-effectiveness analysis allows the analysis of outcomes in any measure of effectiveness that is relevant and common to both comparators; for example, number of cancer cases averted in the comparative analysis of two cancer screening strategies or change in HbA1c in diabetic interventions. In cost-utility analysis, health effects in the form of quality-adjusted life years (QALYs) are used to capture impact on both quality (measured using preference-based quality-of-life instruments) and life extension benefits derived from the health intervention. As a result, the ICER expressed as cost per QALY allows for reasonable comparison across different types of interventions, which is useful in helping decision makers allocate scarce resources across competing healthcare programs.

Over the last few decades, the use of economic evaluation has become increasingly widespread [3-5], with at least 1,000 published annually in the recent decade [6, 7]. Economic evaluation is considered a fundamental component in the assessment of

treatment interventions (surgical procedures and medications), prevention programs (vaccination [8], health promotion and screening strategies [9]), medical diagnostics and delivery of healthcare services, particularly for countries with universal single payer health insurance systems. They play a critical role in health technology assessments (HTA), which are comprehensive review processes instituted by funding bodies to jointly assess the safety, effectiveness, cost-effectiveness and budget impact of health interventions and technologies.

The Australian Government Pharmaceutical Benefits Advisory Committee (PBAC) was the first in the world to put forward guidelines for mandatory assessment of the cost and value for money for pharmaceutical reimbursements in the early 90s [10], requiring demonstration of evidence on not just effectiveness but also cost-effectiveness to government. Since then, many international HTA agencies such as the National Institute of Health and Care Excellence (NICE) in the UK, Canadian Agency for Drugs and Technologies in Health (CADTH), Pharmaceutical Managements Agency (PHARMAC) in New Zealand, German National Institute for Quality and Efficiency in Health Care (IQWiG) and Zorginstituut Nederland (ZIN) in The Netherlands have also established national guidelines on how economic evaluations should be conducted and the resultant outcomes of such assessments play a prominent role in the decision for government subsidy of pharmaceuticals and medical services [11].

While understandably not all medical and health policy decisions are made based on the results of economic evaluations, they can help decision makers make informed choices on the most efficient use of available resources. Economic evaluation evidence has influenced and contributed to many areas of health policy making, relevant to all levels of the health care system. For example, cost-effectiveness analyses have helped shape clinical guidelines on the optimal age for colorectal screening [12, 13], frequency of screening for cervical cancer [14-16], national childhood vaccination strategies [17], which in turn influence and affect decisions in clinical practice. Cost-effectiveness results have also been used to challenge existing national guidelines and to help refine recommendations by identifying risk groups most likely to benefit, as in the case for the use of statin for primary or secondary prevention of coronary heart disease depending patient's risk factors [18].

Beyond employing economic evaluations when considering public investments for effective and costlier novel technologies, it has been argued that evaluations should also be applied to the disinvestment of interventions that offer low-value [19]. The concept of value-based care is gaining popularity and a number of countries are shifting towards a value-driven healthcare system [20-22] with a focus on improving outcomes and reducing costs [23]. This has necessitated broadening the remit of cost-effectiveness and cost-utility analyses to assess value in health care [24]. Further, the importance in delivering care that is of good value has also been emphasised at the clinician level as evidenced by the growth in value frameworks that have been developed in certain disease-specific disciplines by organisations such as the European Society of Medical Oncology, American Society of Clinical Oncology and American Heart Association [25-27]. These frameworks aim to integrate clinical benefits and cost to assist in selecting options that provides the best value of care, which is increasingly appreciated in an era where healthcare costs have grown significantly.

## 1.2. Limits and quality of economic evaluations

For economic evaluation to be useful to decisions makers, it needs to provide relevant, useful, robust and reliable information. To achieve this, methodological guidelines have been produced and should be followed. Between 1990 and 2010, there was a growing pool of at least 76 published reviews on economic evaluation methodologies [28]. The sheer volume of reviews conducted to assess the scientific rigor and adherence to recommendations highlights the significant effort in ensuring continuous improvement. Many are seeking to raise awareness about the importance of conducting and producing high-quality economic evaluations. However, findings consistently show that published evaluations have considerable methodological differences in the incorporation of costs, quality-of-life inputs, extrapolation techniques and assumptions, characterising uncertainty and in general, lack adherence to guidelines [5, 28-34]. Even within the same disease areas [35-37] or for the same interventions [38] discrepancies have been observed. Lack of trust and understanding in the methods of cost-effectiveness analyses can diminish credibility and result in resistance to their use in medical and policy decision making [39].

Encouragingly, calls for higher methodological quality [40-43] have been answered by the growing amount of literature focused on health economics methodologies [44-47], the development of national pharmacoeconomic guidelines [48], having clear publication and reporting standards [49-51] and the introduction of repositories for economic evaluations [52-54]. Studies have shown that the quality of economic evaluation studies have improved over time [55]. However, contributions to improve quality of data inputs and initiatives for consistency have been uneven, particularly on estimating cost and the standardisation of costing methods. A review on the costing methodologies of published cost-effectiveness analyses found that although improvements such as clearer reporting of methods were observed over time, considerable variations in types of costs included in analyses persist [56]. Reasons for this can be methodological (resource valuation approach, scope and breath of costs included), and related to the perspective taken. Although numerous guidelines for best practices exist, recommendations vary. For example, the NICE guidance [57] states that resource costs and savings should be considered from the perspective of the NHS and personal social services (health system perspective) and to limit the scope of costs considered to those related to the condition of interest. This varies considerably from the recommendations made by the Second Panel on Cost-Effectiveness in Health and Medicine [58] which advocates for both health system and societal perspectives, and suggests inclusion of a broader scope of cost categories such as unrelated health care costs resulting from the additional life-years produced by the intervention. As demonstrated by Lomas et al. [59], the extent of cost categories will not only affect incremental cost-effectiveness ratios (ICERs) but also the certainty. This has the potential to affect decisions made by policymakers with implications for valid comparisons across different types of interventions. Therefore, a clearer understanding of the consequences from inconsistent methodologies is required.

While there is research and guidance on the extrapolation of effectiveness of interventions within economic evaluations (e.g. survival), there is less clarity and agreement concerning the handling of costs. This lack of guidance on assessment and measurement of costs was highlighted by Drummond in 1992 [10] when the PBAC issued their first HTA guideline for pharmaceutical reimbursements. One example is the treatment of future cost in economic evaluations. There continues to be debate around the extent and types of future costs to include [60-65] and methods used to extrapolate [66]. Although there appears to be a growing consensus among international HTA agencies to include all future medical

costs [67, 68], variations in guidelines persist which can limit comparability or analyses and interpretation of results [69, 70]. While it is acknowledged that the lack of reliable cost estimates and/or the unavailability of costs data beyond the study period can be a limitation for inclusion [71-73], this issue is further compounded by the lack of guidance to appropriately extrapolate using available resources [66]. This is important considering cost represents a critical component of economic evaluations and assumptions made regarding the approach to extrapolation can have a significant impact on assessment of cost-effectiveness. There are important subsequent decision-making implications, such as the funding of new medications and technologies.

The proliferation of methods and instruments used to obtain patient preferences and value health states demonstrates the importance researchers have placed in validating and advancing techniques to improve methodological issues of measuring health. Patient-reported outcomes measures (PROMs) are instruments commonly used to measure outcomes and provide valuable information about the effectiveness of the intervention from the patient's perspective. Outcomes such as health-related quality-of-life are important components of economic evaluations as they are used to derive utilities to calculate quality-adjusted life years (QALYs), necessary for cost-utility analyses. These analyses and the use of cost per QALY metric plays a major role in policy decisions on the acquisition and use of health technologies. They are widely used and advocated by national institutions including NICE, CADTH and PBAC.

Patient-reported outcomes are commonly collected at intervals within the time frame of a clinical study, most commonly at the start (baseline) and at the end of the study. Therefore, extrapolation of utilities, oftentimes alongside life expectancy of patients for modelled analysis on a lifetime horizon is needed. This requires appropriate methods and assumptions in modelling quality-of-life values as the approach employed can influence evaluation results important to subsequent reimbursement decisions made by policy makers [74, 75]. Currently, there is limited guidance on the appropriate methodologies for extrapolating utilities and existing methods rely on use of assumptions in economic models [66]. While health economists are generally comfortable in making modelling assumptions often in the absence of data, the excessive use of assumptions or those that do not adequately capture the complexity of patients may undermine the value and relevance of results. Clinicians may be more accustomed to actual data (e.g. real-world

data). Therefore, opportunities to improve availability of data inputs and techniques of analysis can strengthen the rigor of economic evaluations.

Beyond methodological research and the use of economic analyses for efficient allocation, the recognition of the value of patient-reported outcomes in measuring quality of care and benchmarking of providers has prompted substantial efforts in the collection of such data. A good example of this the NHS England's National Patient Reported Outcomes Measures Program that has been routinely collecting patient-reported outcomes for selected surgeries since 2009. The information is used to monitor performance and inform commissioning decisions [76]. Increasingly, there have been calls to routinely integrate these measures into clinical practice to improve patient engagement to achieve better health outcomes with shared-decision making and patient-centred care [77-80]. The appeal to use PROMs to optimise patient outcomes is growing and will become increasingly important as healthcare systems are transitioning from volume- to value-based health care. This will mean a focus on sustainability of healthcare systems and outcomes may be tied to reimbursements [81]. As PROMS are increasingly integrated into clinical practice, there is a pressing need to make better use of collected data and translate patient-level collected data into valuable information to improve health outcomes and delivery of care [82-84].

Often results of cost-effectiveness analysis summarised based on the average for the total population are used to make population reimbursement decisions which may mask and overlook important underlying heterogeneity within the patient population. This can result in either health benefits forgone when an intervention is deemed not cost-effective on average or inefficiencies and suboptimal use of available resources when intervention may not be cost-effective to all within the population [85]. Heterogeneity relate to patient demographics, preferences and clinical characteristics, all of which have differing implications on baseline risk, treatment effect, health state utility and resource utilisation patterns [86]. Whilst patient heterogeneity is recognised as an important consideration in economic evaluations [87], it remains infrequently assessed [88] and can lead to inefficiencies in healthcare spending and limit maximisation of population gains [85, 89].

The benefits of exploiting heterogeneity through targeted care are evident in the growing movement towards personalised medicine, most prominent in cancer treatment strategies [90-95], acknowledging a key approach towards improving patient outcomes by ensuring

patients receive the best possible medical care for their needs. Further, gains made from individualised care can far outweigh decisions made based on population-level cost-effectiveness analysis. In an example by Basu and Meltzer [89], the authors showed the value of identifying cost-effective treatments for prostate cancer at the individual patient-level was 100 times greater than the value of identifying cost-effective treatments at the population level. Understanding and capturing heterogeneity can be complex and will require appropriate source of information (e.g. individual patient-level data) as well as specific guidelines for optimal identification and robust analytical strategies for cost-effectiveness at subgroup level which are currently inadequate [86, 96]. Initiatives to facilitate collection of data and leveraging appropriate data sources can help contribute to future methodological research in improving current approaches, promote a better understanding of real-world heterogeneity, and ultimately optimise patient outcomes, and ensure better overall societal healthcare resource allocation decisions.

Undoubtedly, greater consistency in the conduct of economic evaluations is essential if policy makers, healthcare providers and clinicians are to rely on these to make decisions on reimbursements, priority setting and to determine the best value care. Moving forwards, health decision makers are increasingly seeking real-world, generalisable evidences (beyond data collected from randomised clinical trials) to complement and support policy and clinical decisions [97-99]. At a broader level, demonstrated evidence of effectiveness, safety and cost-effectiveness may not always translate into real-world implementation and effective policy change [100, 101], therefore evidence of benefits of changing practice, particularly on a national scale, can be valuable to policy makers and health service providers in setting priorities and implementing policies.

## 1.3. Real-world, longitudinal data for health economics research and applications

Longitudinal data refers to the collection of data from the same group of subjects (commonly patients but can be entities such as households or hospitals) over a period of time. The collection of such data can be intentional for research purposes; for example, through longitudinal studies such The Longitudinal Study of Australian Children (LSAC) which follows a cohort of children to study their development and life course trajectories [102] and Framingham Heart Study for the study of cardiovascular diseases over time [103]. These large-scale studies, however, can be complex, time consuming and

expensive to conduct and limited by issues such as loss-to-follow-up and under-representation of minority population subgroups (e.g. migrants) limiting generalisability of results [104, 105].

Routinely collected administrative data typically used for reporting purposes or obtained from purpose-built databases such as registries can also be considered longitudinal in nature. These data can also be referred to as real-world data [99, 106, 107], broadly representing data generated from routine clinical practice such as hospitalisations, physician consultations, medical and prescriptions claims. The use of data from these sources for health research has become increasingly common, with the growing amount of research and published literature as well as public investments to establish data linkage centres and national registries [108, 109]. They are efficient sources of information as data are consistently and continuously collected based on patients' access to health services and can overcome issues around generalisability, recall bias and loss-to-up prevalent in primary data collection approaches [110-112].

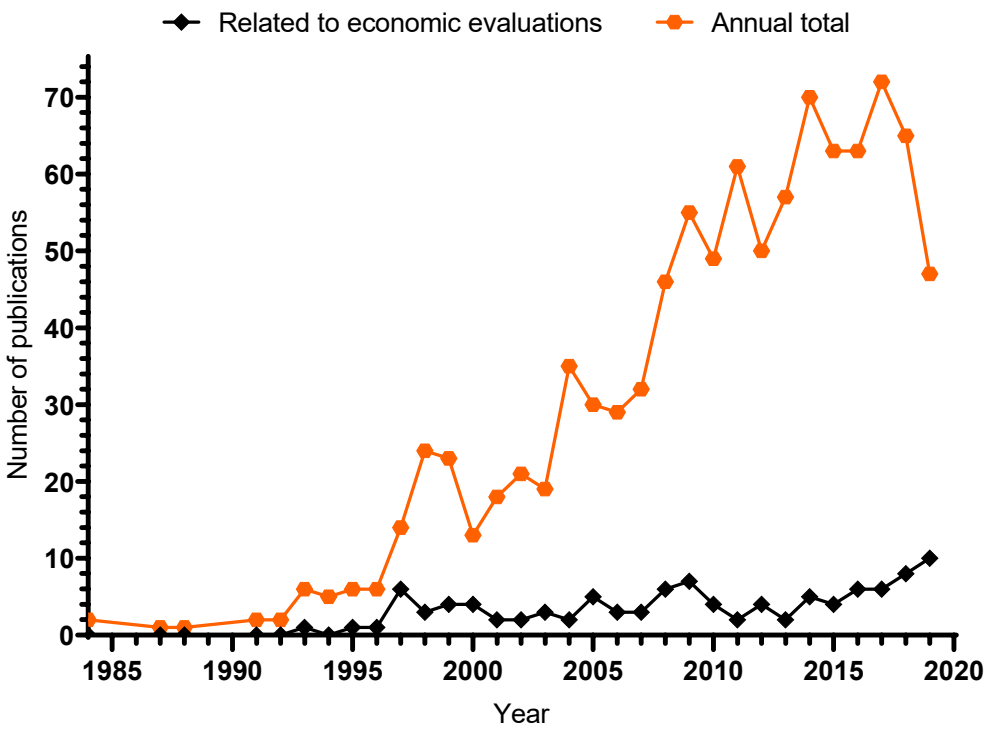
The strength of longitudinal data is that they allow critical longer-term insights into the health or care of the population (or individual), thus offering detailed and ordered information on health conditions, disease progression and patterns of care and changes over time. Such data therefore provides health economics researchers and evaluators opportunities to investigate and address many of the limitations described in Section 1.2. For instance, data generated from contact with the health care system provides researchers information about health care utilisation for any length of time or for any given year [113]. This flexibility can be useful for conducting cost analyses such as cost-of-illness studies to obtain both prevalence-based and incidence-based cost estimates for understanding the burden of the disease for priority setting and allocation considerations [114]. This also generates reliable cost inputs that can be used to populate predictive models and cost-effectiveness models. Further, administrative data on health service utilisation provides important real-world evidence that reflects current clinical practices thus providing clearer guidance when accounting for resource use beyond a trial setting and for undertaking extrapolations in economic models. Improvements in the availability of reliable data and validating modelling assumptions can improve the applicability of economic evaluations.

The population coverage offered by real-world, longitudinal data offers greater external validity by including patients often not represented in randomised control trials and can provide large patient numbers ideal for examining heterogeneity and rare events. It is a valuable source of capturing and understanding patient differences (demographics, clinical characteristics and preferences). Data can be used as a source of information to generate useful inputs to inform baseline event risks for modelling of disease progressions over time and can also capture health inequities, preferences and behaviours for various subpopulations [115-117]. This can offer insights into the variations of care and outcomes across a wider, representative population in real-world settings. This presents opportunities to study of the implications of sub-optimal care and develop strategies to improve the value of care and efficiency of the health system.

Information from real-world, longitudinal data are made available in various forms depending on data availability, accessibility and the purpose of their use. Data can be presented in aggregate form or at individual-level relating to a single patient (or entity). The richness of individual-level data can be further expanded with data linkage. Data collected on individuals from different sources can be brought together to create a powerful platform allowing researchers and policy makers a much larger picture and greater potential to conduct real-world research to better map care pathways, understand population health issues and improve outcomes [118].

These information-rich sources capture many useful health and economic outcomes such as survival, adverse events, patient-reported outcomes, resource utilisation and associated costs which can be leveraged to strengthen the rigour of economic evaluations. They offer enormous health economics research opportunities for better research design and analysis, which ultimately influences decisions on reimbursements, priority setting and patient outcomes. Although the use of longitudinal data in health economics research has grown tremendously in the past few decades, its application in economic evaluations remains sparse (Figure 1.1). Maximising the potential and applications of available health data can be a cost-effective and time-efficient way of generating evidence particularly when the infrastructure is already in place. Using data to influence policy is important, and more can be done to maximise the use of routinely collected administrative data to generate real-world evidence to guide effective and cost-effective evidence-based care.

Figure 1.1: Annual number of publications involving use of longitudinal data published in selected health economics journals between 1984 and 2019[1]




## 1.4. Overarching aim

This thesis aims to demonstrate the usefulness and practicality of applying real-world, longitudinal data in health economics research and evaluations. It features six individual health economics studies which explore longitudinal data in various forms – aggregate, individual-level and individual-level with population-linkage – and shows their value and contribution towards advancing economic evaluation methodologies and better decision making.

In this thesis, I showcase how different types of real-world, longitudinal data can be maximised as part of health economics research. These studies demonstrate a broad range of applications of longitudinal data and aim to make specific contributions in three key areas:

[1] Results from a search of the following terms (panel, longitudinal or fixed-effect) for publications related to longitudinal data and terms (cost-effectiveness, cost-utility or economic evaluation) to indicate relevance to economic evaluations. Health economics journals searched include Health Economics, Journal of Health Economics, Value in Health and Pharmacoeconomics.

I. Extrapolation of costs in economic models

II. Modelling and translating long-term outcomes, specifically health-related quality-of-life (QoL) outcomes

III. Generating real-world evidence to inform future economic evaluations and resource allocation considerations.

Table 1.1 summarises the health economics applications using various forms of longitudinal data presented in this thesis. Each of the studies answer specific research questions that contribute towards better informed decision making by generating and providing robust evidence for resource allocation considerations. They also test commonly applied economic evaluation assumptions and contribute towards advancing current modelling approaches. These studies, along with the methods employed and their key contributions, will be discussed in turn in the next section.

Table 1.1: Studies presented in this thesis and their health economic applications

**Longitudinal data**
Increasing level of data granularity and complexity

| | Chapter / Study | | Application |
|---|---|---|---|
| | **I : EXTRAPOLATION OF COSTS** | | |
| **Aggregate** | 2 | Incorporating future medical costs: Impact on CEA | • Assess implications of incorporating future medical costs<br>• Synthesise future cost inputs for economic model |
| | 3 | National cost savings from an ambulatory program for LR FN patients | • Leverage historical data for future trends |
| | **II : MODELLING & TRANSLATING OUTCOMES** | | |
| **Individual-level** | 4 | Using PROMs to guide patient-centred care and optimise outcomes | • Uncover heterogeneity of QoL outcomes<br>• Demonstrate value of care |
| | 5 | Co-morbidities and sex differences in long-term QoL outcomes among patients with and without diabetes | • Modelling QoL outcomes by patient subgroups |
| | 6 | Exploring the impact of QoL on survival | • Examine correlation between QoL and survival<br>• Assess implications on survival extrapolation |
| | **III : GENERATING REAL-WORLD EVIDENCE** | | |
| **Individual-level + Population-linked** | 7 | Economic burden of sepsis in cancer: Health care cost estimates from a population-based study | • Quantify cost of cancer care and excess (net) cost of sepsis |

CEA, cost-effectiveness analysis; FN, febrile neutropenia; LR, low-risk; PROMs, patient-reported outcome measures; QoL, quality-of-life

## 1.5. Chapter content

*Section I: Extrapolation of costs in economic models*

In Chapter 2, I examine the contended issue relating to the inclusion of future medical costs in economics evaluation. I provide an applied example using data from a clinical study to evaluate the cost-effectiveness of a sepsis intervention in cancer patients. The evaluation was conducted under three scenarios reflecting the different types of costs – no future cost, lifetime disease-related (cancer) costs and all future medical costs

including those unrelated to cancer. As cost data were not available beyond the study period, I make use of published regression equations derived from longitudinal data [119, 120] to obtain aggregated population lifetime cost estimates to populate the cost-effectiveness models. Cost estimates were derived by age, sex, cancer type and phase of cancer to account for heterogeneity among cancer patients and were included in a time-dependent Markov model structured to capture life course transitions (e.g. variations due to ageing and death). I find that incorporating future medical costs into the economic model increases the ICER. This is perhaps not surprising. However, the scenarios presented with and without future medical costs clearly demonstrate their potential to result in different policy decisions. The exclusion of future costs from an economic evaluation means that decisions made will not adequately reflect a healthcare system perspective and are not considered in conjunction with the potential impact the intervention has on healthcare budgets in the longer term [121]. Importantly, this study demonstrated that incorporating future medical costs in an economic evaluation in cancer patients was feasible through the use of publicly available data and structuring economic models to adequately reflect changes in costs over time.

In Chapter 3, I make use of publicly available aggregate-level data on national hospitalisation trends to extrapolate the findings from an economic evaluation of an ambulatory program for low-risk febrile neutropenia patients to inform broader uptake. In this study, in addition to demonstrating the cost-effectiveness of the program, annual data of febrile neutropenia hospital admissions collected and reported by the Independent Pricing Authority (IHPA) were leveraged to extrapolate the cost benefits. Failure or delayed implementation of safe and cost-effective programs can result in inefficiencies and waste of limited resources [122, 123]. Therefore, providing strong supportive evidence that demonstrates sustainability of the program and significant return-on-investment to the healthcare system may provide a strong case for institutions and policy makers for resource allocations considerations and bridge the gap between translation to research findings to implementation [124].

*Section II : Modelling and translating long-term outcomes, specifically health-related quality-of-life (QoL) outcomes*

Chapters 4, 5 and 6 are three published research studies focused on long-term quality-of-life outcomes of total knee replacement patients. In these studies, I use patient-level data

collected over a 10-year period extracted from the St. Vincent's Melbourne Arthroplasty Outcomes (SMART) Registry. Total knee replacement is generally considered to be an effective procedure as patients typically experience a significant improvement in their quality-of-life within the first year following surgery with the effects tending to plateau in subsequent years [125-127]. Although this pattern of recovery is well-known, outcomes of patients can differ [128-130], consequently effectiveness gained from surgery can vary considerably across patients.

In Chapter 4, I employ latent class growth analysis, a unique statistical technique to analyse routinely collected measures to explore variations in the long-term quality-of-life outcomes among a cohort of SMART Registry patients. By identifying distinct quality-of-life trajectories, I demonstrate the presence of significant heterogeneity in outcomes among total knee replacement patients and show that not all patients benefit from the procedure the same way. This, therefore, challenges a commonly applied utility extrapolation assumption; i.e. assuming utilities are homogenous with respect to patient characteristics and time. While total knee replacement is widely regarded as cost-effective, using the identified quality-of-life trajectories, I show the distinct variations in health gains (QALYs) from the intervention which raises the question if the expensive surgical intervention is cost-effective for all patients. This highlights the limitations of current practice of allocating resources based on population-averaged cost-effectiveness ratios [131] and the need for better incorporation of heterogeneity in economic evaluations in order to maximise health gains within resource constraints. I also demonstrate the potential of translating routinely collected patient-reported outcomes data to facilitate shared decision making and optimise patient outcomes by correlating quality-of-life trajectories with patient characteristics.

In recognising the significant heterogeneity in quality-of-life outcomes among total knee replacement patients, I proceed to verify this in Chapter 5 by examining whether quality-of-life trajectories differ between patients with and without diabetes. As outcome data are collected from the same individuals at repeated intervals over time, it is important to employ appropriate methods to analyse these longitudinal quality-of-life data to avoid misleading results [132]. To account for the longitudinal structure of the data and possible correlation between quality-of-life measures of individuals over time, I use multi-level regression to model these repeated measures to estimate utility changes over time and

make comparisons across both patient groups. I find that even after controlling for possible confounders such as age, sex, existing co-morbidities and socioeconomic status, patients with diabetes exhibit poorer outcomes following surgery compared to those without diabetes and these differences were sustained over time. This further highlights the differences among patient groups and the inadequacies of simplistic assumptions when modelling long-term outcomes such as utilities.

In Chapter 6, I examine the importance of the relationship between quality-of-life and mortality and its influence on survival estimates. There is a growing body of evidence that indicates patient-reported outcomes such as quality-of-life to be important predictors of mortality [133-138]. However, current health economic models rarely capture the correlation between quality-of-life and mortality when extrapolating survival. This is important as survival estimates are often translated into health outcomes such as life expectancy and QALYs to quantify health effects. Imprecise survival extrapolations could misinform policy decisions. I develop survival models to investigate the implications of neglecting this correlation and estimate the impact on incremental outcomes for a cohort of total knee replacement patients. I find that incremental QALYs differed by as much as 9.5% when quality-of-life variables were included in models when estimating survival, noting that even small differences in the denominator can lead to quite different cost-effectiveness results and can have an impact of decision making. With the increasing availability of patient-level data and collection of patient-reported outcomes, the new generation of disease progression models and modelled economic evaluations should consider accounting for this important correlation.

*Section III : Generating real-world evidence to inform future economic evaluations*

Populating economic models with accurate data can be challenging and inputs used are often compromised when original data is unavailable, as demonstrated in the evaluation of the sepsis protocol presented in Chapter 2. Learning from my evaluation experience, I recognise the value of reliable real-world evidence to inform future economic evaluations and the current knowledge gaps on the burden of sepsis, and thus motivated the following research study. The acute nature of infections often makes it difficult to capture the longer-term implications, thus resulting in our limited understanding of its true burden, both clinically and economically. In Chapter 7, I make use of a population-linked dataset on a large cohort of cancer patients identified from the Ontario Cancer Registry which I

successfully secured access to. This allowed me to study the pattern of healthcare service utilisation by cancer patients, when and why (including infection episodes), the type of care – hospital admissions, physician consultations, cancer clinic visits, type of treatment, long-term care – over the course of their cancer diagnosis and subsequent years. Leveraging on this important resource, I estimated the cost of care of cancer patients with and without sepsis and the excess cost due to sepsis. These cost estimates can be used in cost-effectiveness models for decisions on sepsis interventions and are useful in helping inform development of sepsis programs and policies across the cancer care continuum, which can include prevention, screening, treatment and end-of-life care.

## 1.6. Thesis structure

Following this introductory chapter, six papers are presented in Chapters 2 to 7 showcasing the use of longitudinal data across a range of health economic applications. Across these chapters, I demonstrate the quantum of work produced during my candidature using a wide range of health economics and longitudinal modelling methods, including decision-analytic modelling, survival analysis, economic evaluation, latent class growth analysis and multi-level modelling. I make contributions in three key areas relevant towards advancing economic evaluation methodologies and better-informed decision making and health policy design. A summary of the key contributions from each of the research studies presented in this thesis alongside the methods applied is provided in Table 1.2.

Table 1.2: Summary of methods employed and key contributions from each of the studies presented in this thesis

| Chapter / Study | | Methods of analysis | Key contributions | |
|---|---|---|---|---|
| | | | Methodology | Clinical and policy |
| **I : EXTRAPOLATION OF COSTS** | | | | |
| 2 | Incorporating future medical costs: Impact on CEA | • Cost-utility analysis<br>• Decision tree analysis<br>• Markov model | Demonstrate feasibility of appropriately including future medical costs | Provide evidence of cost-effectiveness of sepsis protocol and highlight potential differences in cost-effectiveness results |
| 3 | National cost savings from an ambulatory | • Cost-effectiveness analysis | Undertake evaluation beyond cost-effectiveness analysis | Offer strong evidence for national implementation of a cost-effective program |

| | | | | |
|---|---|---|---|---|
| | program for LR FN patients | • GLM regression<br>• Cost projections | | |
| **II : MODELLING & TRANSLATING OUTCOMES** | | | | |
| 4 | Using PROMs to guide patient-centred care and optimise outcomes | • Latent class growth analysis<br>• Multinomial logistic regression | Employ novel application of technique to uncover heterogeneity | Show important heterogeneity in longer-term outcomes and variations in the value of surgery for different patient groups |
| 5 | Co-morbidities and sex differences in long-term QoL outcomes | • Multi-level modelling | Demonstrate method to assess patterns of change of repeated QoL measures over time and generate utility values for cost-effectiveness analyses | Highlight notable differences in long-term QoL patterns among specific patient subgroups (diabetes, females) and need for tailored post-surgery management |
| 6 | Exploring the impact of QoL on survival | • Survival analysis<br>• Life table methods for life expectancy | Advance understanding of influence and consequence of correlation between QoL and mortality when extrapolating survival outcomes | Quantify impact of unaccounted correlation and heterogeneity on cost-effectiveness results |
| **III : GENERATING REAL-WORLD EVIDENCE** | | | | |
| 7 | Economic burden of sepsis in cancer patients | • Matching (case-control)<br>• Panel data manipulation<br>• Survival-adjusted estimation of costs | Generate short- and long-term cost estimates | Provide key insights on burden of sepsis and useful inputs for future economic evaluations and resource allocation decisions |

CEA, cost-effectiveness analysis; FN, febrile neutropenia; GLM, generalised linear model; LR, low-risk; PROMs, patient-reported outcome measures; QoL, quality-of-life

In Chapter 8, I conclude with a summary of the research findings, discussion on implications and translational value of findings, strengths and limitations, and provide suggestions for directions for future research.

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# SECTION I : Extrapolation of Costs

| Chapter / Study | | Methods of analysis | Key contributions | |
|---|---|---|---|---|
| | | | Methodology | Clinical and policy |
| **I : EXTRAPOLATION OF COSTS** | | | | |
| 2 | Incorporating future medical costs: Impact on CEA | + Cost-utility analysis<br>+ Decision tree analysis<br>+ Markov model | Demonstrate feasibility of appropriately including future medical costs | Provide evidence of cost-effectiveness of sepsis protocol and highlight potential differences in cost-effectiveness results |
| 3 | National cost savings from an ambulatory program for LR FN patients | + Cost-effectiveness analysis<br>+ GLM regression<br>+ Cost projections | Undertake evaluation beyond cost-effectiveness analysis | Offer strong evidence for national implementation of a cost-effective program |
| **II: MODELLING & TRANSLATING LONG-TERM OUTCOMES** | | | | |
| 4 | Using PROMs to guide patient-centred care and optimise outcomes | + Latent class growth analysis<br>+ Multinomial logistic regression | Employ novel application of technique to uncover heterogeneity | Show important heterogeneity in longer-term outcomes and variations in the value of surgery for different patient groups |
| 5 | Co-morbidities and sex differences in long-term QoL outcomes | + Multi-level modelling | Demonstrate method to assess patterns of change of repeated QoL measures over time and generate utility values for cost-effectiveness analyses | Highlight notable differences in long-term QoL patterns among specific patient subgroups (diabetes, females) and need for tailored post-surgery management |
| 6 | Exploring the impact of QoL on survival | + Survival analysis<br>+ Life table methods for life expectancy | Advance understanding of influence and consequence of correlation between QoL and mortality when extrapolating survival outcomes | Quantify impact of unaccounted correlation and heterogeneity on cost-effectiveness results |
| **III : GENERATING REAL-WORLD EVIDENCE** | | | | |
| 7 | Economic burden of sepsis in cancer patients | + Matching (case-control)<br>+ Panel data manipulation<br>+ Survival-adjusted estimation of costs | Generate short- and long-term cost estimates | Provide key insights on burden of sepsis and useful inputs for future economic evaluations and resource allocation decisions |

# Chapter 2 : Incorporating future medical costs: Impact on cost-effectiveness analysis in cancer patients

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## 2.1. Abstract


### Background

The inclusion of future medical costs in cost-effectiveness analysis remains a controversial issue. The impact of capturing future medical costs is likely to be particularly important in patients with cancer where costly lifelong medical care is necessary. The lack of clear, definitive pharmacoeconomic guidelines can limit comparability and has implications for decision-making.

### Objective

To demonstrate the impact of incorporating future medical costs through an applied example using original data from a clinical study evaluating the cost-effectiveness of a sepsis intervention in cancer patients.

### Methods

A decision analytic model was used to capture quality-adjusted life-years (QALYs) and lifetime costs of cancer patients from an Australian healthcare system perspective over a lifetime horizon. The evaluation considered three scenarios: 1) intervention-related costs (no future medical cost), 2) lifetime cancer costs and 3) all future healthcare costs. Inputs to the model include patient-level data from the clinical study, relative risk, cancer mortality and future medical costs sourced from published literature. All costs are expressed in 2017 Australian dollars and discounted at 5%. To further assess the impact of future cost on cancer heterogeneity, variation in survival and lifetime costs between cancer types and the implications for cost-effectiveness analysis was explored.

### Results

The inclusion of future medical costs increased incremental cost-effectiveness ratios (ICER) resulting in a shift from intervention being a dominant strategy (cheaper and more effective) to an ICER of $7,526/QALY. Across different cancer types, longer life expectancies did not necessarily result in greater lifetime healthcare costs. Incremental costs differed across cancers depending on the respective costs of managing cancer and survivorship thus resulting in variations in ICERs.

**Conclusions**

There is scope for including costs beyond intervention costs in economic evaluations. The inclusion of future medical costs can result in markedly different cost-effectiveness results, leading to higher ICERs in a cancer population, with possible implications for funding decisions.

## 2.2. Key points for decision makers

There remain inconsistencies in the recommendations across international pharmacoeconomic guidelines regarding the inclusion of future medical costs hence variations exist across economic evaluation literature.

There is value in the inclusion of future medical costs in economic evaluation to support decision-makers considerations relating to future healthcare budgets.

This study demonstrated the practicability of including future medical costs in an economic evaluation in cancer patients, which can be an important consideration for future cost-effectiveness analyses.

There is considerable heterogeneity in the ICERs across different cancer types and the type of future costs included do not impact all cancers consistently.

## 2.3. Introduction

The inclusion of future costs in cost-effectiveness analysis (CEA) is a contentious issue, particularly when costs are *unrelated* to the intervention being evaluated. Fundamentally, the aim of CEA is to aid decision-makers to optimally allocate scarce healthcare resources to maximise population health gains. To achieve this, appropriate costs and benefits need to be accounted for in order to determine if the benefits outweigh the costs. Much health economics research has contributed to a better understanding of quantifying and extrapolating outcomes (utilities, life years and quality-adjusted life years) in CEA to fully capture the lifetime benefits of an intervention. Therefore, it has been argued the same philosophy should be applied to costs (i.e. inclusion of all costs necessary to attain the lifetime benefits captured) for consistency [1, 2] and to achieve utility maximisation [3].

The inclusion of *related* medical costs, those that are a direct consequence of the intervention under study, is common practice in economic evaluations and the general agreement is that they should be accounted for. However, there is much debate around the inclusion of *unrelated* future medical costs. These are healthcare costs that are expected incur as a consequence of added life years resulting from the intervention; i.e. not directly related the intervention but conditional on survival due to the intervention. Therefore, the impact of future costs is most relevant to life-extending technologies where the omission of medical costs incurred in the additional surviving years could risk overstating the cost-effectiveness of these interventions compared to those that improve quality-of-life. This relative overstating of cost-effectiveness could ultimately result in loss of population health benefits [4]. Conversely, some have reasoned that omission of future costs[2] is unlikely to have any substantial impact as long as decisions are made based on consistent use of cost data [5, 6]. Costs in health economics are however linked to the context of a decision so that information about inputs, timing, technology and who the decision maker is are all critical to have accurately reflected [7]. Others have argued the case that to include future costs would result in inequitable outcomes; for example in patient populations where future medical costs inevitably includes expensive ongoing healthcare costs such as dialysis costs for chronic kidney disease patients [8, 9].

Although it appears that the growing consensus is to include all future medical costs [10, 11], variations in pharmacoeconomic guidelines persist. Many agencies involved with health technology assessment for reimbursement recommend that only costs related to the intervention studied should be included. For example, National Institute for Health and Care Excellence (NICE) in the UK recommends that "costs that are considered to be unrelated to the condition or technology of interest should be excluded" [12]. Likewise, in Australia, the Pharmaceutical Benefits Advisory Committee (PBAC) suggests similar recommendations [13]. However, this has been challenged by the recent recommendation of the second US Panel on Cost-effectiveness in Health and Medicine. They propose that all costs both present and future, whether related or unrelated, should be included in cost-effectiveness analyses [14]. In recent years, there has also been a change in national guidelines for technology appraisals to include all future costs such as those from the

[2] Note that in this article, the focus is on medical costs only. Future cost discussions do extend to non-medical costs which includes productivity and consumptions costs in the added life years. A comprehensive discussion around future costs including non-medical costs have been described elsewhere [18].

Netherlands [15]. Given the lack of agreement or clear methodological recommendations large variations in the incorporation of costs across CEAs is unsurprising and can limit the comparability and interpretation of results [16, 17].

The impact of capturing future medical costs is likely to be particularly important in patients with cancer as treatment costs are higher than many other diseases [19-21]. Costs are also rising rapidly with the availability of new technologies, particularly those that improve survivorship [22]. It is also important to recognise that the care of cancer patients does not only involve the treatment of primary disease, but also requires management of complications arising that can impact survival [23]. To most, it may seem obvious that the inclusion of more cost categories or future costs would necessarily increase the incremental cost-effectiveness ratio (ICER), particularly for life-prolonging interventions due to added life years. This has been demonstrated in a review of cancer-related CEAs for interventions that extend life expectancy where the authors retrospectively recalculated alternative ICERs based on assumptions regarding inclusion of future related and unrelated costs [17]. Further, none of the cost-effectiveness studies reviewed included *unrelated* future medical costs and one-third did not include medical costs *related* to the disease. ICERs can vary considerably depending on the costing methodology employed which can have important decision-making implications particularly in the funding of new cancer pharmacotherapies.

Cancer care costs are substantial at the time of diagnosis, and lifetime cancer care will continue to impact healthcare costs throughout the remaining life of the patient [24-27]. Furthermore, there can be important differences in treatment costs as this can vary depending on the time since diagnosis, stage and cancer type [26-29], resulting in variations in healthcare costs. Therefore, if future medical costs are to be incorporated into CEA, an improved understanding of economic evaluation methodology and the consequences for priority setting (i.e. the degree of variation in cost-effectiveness ratios for treatment of patients with different types of cancer) is needed.

The objective of this study is to demonstrate the impact of incorporating future medical costs through an applied example using original data from an Australian clinical study evaluating the impact of sepsis intervention in cancer patients (see Appendix 2 in Supplementary Materials for more details on sepsis management and an overview of the Australian healthcare system). To address this question, an economic evaluation

considering only intervention costs (no future medical cost) is undertaken and compared with evaluations that considered ongoing lifetime medical costs related and unrelated to cancer. As survival and lifetime costs between cancer types vary, the analysis was also conducted across different cancers to better understand the implications for CEA. Information from this study will assist decision making for clinicians and policymakers and also add to the understanding of how incorporation of future costs impacts resource allocation for cancer interventions.

## 2.4. Methods

### 2.4.1. Study setting

An economic evaluation of a hospital-wide sepsis pathway intervention (SP) in a cancer hospital was performed comparing the cost and outcomes of patients pre- and post-pathway intervention. The analysis was undertaken from the perspective of the healthcare system/payer. Details of the implementation study including identification of sepsis and non-sepsis cohorts, and the clinical outcomes have been described elsewhere [30, 31]. Briefly, the SP intervention supported nurse-initiated sepsis care, early medical review, and prompt antibiotic and fluid resuscitation and was implemented in Peter MacCallum Cancer Centre (PMCC), Melbourne Australia in March 2013. Two patient cohorts were compared; patients in the SP cohort (post-intervention) and non-SP cohort (pre-intervention). Detailed hospitalisation costs were available for 275 patients, 184 (86.8%) and 91 (82.0%) in the SP and non-SP cohorts respectively. Patient demographic and clinical characteristics are presented in Appendix 3 Table S2.1 in Supplementary Materials. For more details on the study setting and costing of the intervention see Appendix 3 and 4 in Supplementary Materials.

### 2.4.2. Overview of analysis

To demonstrate and quantify the implications of different assumptions regarding the incorporation of future medical costs on the cost-effectiveness of the SP intervention, the evaluation was conducted under three scenarios reflecting the different sets of costs incorporated in the analysis.

(1) Intervention-related costs - no future medical costs;

(2) Excess cancer costs - intervention and lifetime disease-related costs;

(3) All future costs - intervention, disease-related and all other health care costs

*Model structure*

A decision analytic model was developed to capture both the quality-adjusted life-years (QALYs) and lifetime costs of cancer patients. The lifetime model consists of two-parts; a decision tree and a cohort time-dependent Markov model to capture the long-term impact (lifetime modelling) of the SP intervention (Appendix 5 Figure S2.1 in Supplementary Materials). The decision tree represents the initial acute hospitalisation episode as observed and measured in the implementation study [31]. Survivors at 30-days enter the life-long Markov model that consists of a simple two-state model (Alive and Dead) to extrapolate full life expectancy. The combination of a decision tree and Markov model captures the short-term mortality of the initial episode reflecting the limited duration of most clinical studies and the subsequent risk of death of survivors by extrapolation of survival and costs over a 40-year lifetime time horizon [32, 33].

*Data inputs*

Cancer patients were assumed to be newly diagnosed and clinical effectiveness of the intervention (30-day mortality) as observed in the clinical study was applied similarly across cancer types. Future medical costs due to cancer (excess cancer costs) and other (unrelated) healthcare costs were sourced from New Zealand data published by Blakely et al [28, 34] providing reliable national estimates derived from large population-linked data. As robust Australian population cost estimates for lifetime medical costs were not available for the variety of cancers considered, this cost data was deemed to be most appropriate. Further, similarities between the Australian and New Zealand healthcare systems and in their hospital funding systems [35] makes this a reasonable source. Both countries also share treatment guidelines; for example [36]. Cancer costs were calculated based on coefficients published by the referenced source which provided specific costs for different cancer types and by time since diagnosis. This allowed the incorporation of detailed lifetime cost information into the model appropriate for the evaluation of future medical costs. The method of deriving specific cancer costs is described in Appendix 6 in Supplementary Materials. Death transition costs were included in the model reflecting

the substantial and elevated healthcare costs incurred in the months immediately prior to death.

All parameter inputs were entered as probability distributions to capture uncertainty as listed in Table 2.1. Data for the decision tree were sourced from the clinical implementation study reflecting the average survival probabilities and hospitalisation costs of both cohorts. The base-case analysis utilised mortality rates and lifetime cancer costs for all-cancers combined. A scale-up factor [37] was used to inflate the mortality rate, reflecting the impact of sepsis on patient mortality in a cancer specific population. This was calculated using relative risks sourced from a large cohort study examining excess mortality risk in sepsis patients [38] and were assumed to last up to two years following the sepsis episode concurrent to reported findings in Australia [39]. Excess mortality rates due to cancer were estimated from relative survival data sourced from the Australian Institute of Health and Welfare (AIHW) [40] which publishes national health statistics. The method of estimating mortality rate is described in Appendix 7 in Supplementary Materials.

To calculate QALYs, time spent in the Alive health state (i.e. life years gained) was multiplied by assigning sepsis specific utility value. Utilities up to 5 years post-sepsis were sourced from published studies evaluating long-term quality of life of critically ill patients with cancer or severe sepsis [41, 42].

*Analytical methods*

The model was run over a lifetime horizon with monthly cycles for a cohort with starting age 60 years reflecting the average age of patients in the implementation study. Half-cycle corrections were applied. Probabilistic sensitivity analysis (PSA) was undertaken by running 10,000 simulations of lifetime modelling for the two cohorts. A series of one-way sensitivity analyses were also undertaken to explore the implications of the assumptions made and data sources used in the model. Cost-effectiveness acceptability curves were used to present the uncertainty in cost-effectiveness. Net monetary benefit (NMB) was also calculated to further elucidate differences across costing scenarios and cancer types assuming a plausible threshold of $50,000 in Australia [43].

Both the costs and benefits were discounted at 5% annually as per Australian Pharmaceutical Benefits Advisory Committee recommendations [13] and were varied in

sensitivity analyses. All costs are expressed in 2017 Australian dollars adjusted using the Consumer Price Index and purchasing power parities from the Australian Bureau of Statistics [44] and Organisation for Economic Co-operation and Development (OECD) [45], respectively. Reporting follows the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) consolidated health economic evaluation reporting standards guideline [46] (Appendix 1 in Supplementary Materials).

As significant heterogeneity exists between cancer types, there is value in investigating cost-effectiveness within a disease [47]. Therefore, in addition to the base-case analysis (all cancers combined), the impact of future medical costs was similarly conducted for a number of the most commonly diagnosed cancers. All costs and mortality inputs (Appendix 5 Table S2.3 in Supplementary Materials) were cancer specific as obtained from sources referenced above. All original data were analysed using STATA statistical software (version 14.0, Texas, USA) and the CEA model was built using TreeAge Pro 2017 (Massachusetts, USA).

## 2.5. Results

### 2.5.1. Cost-effectiveness analysis

Comparisons of cost-effectiveness results for all three scenarios are presented in Table 2.2. Incremental costs and ICERs increased as more cost resource categories were included into the analysis. In scenario 1, when considering intervention-related costs only (no future medical cost), the SP was a dominant strategy (cheaper and more effective than the non-SP cohort). This changed for scenarios 2 and 3. In the all future healthcare cost scenario, the ICER increased to $7,526.09/QALY gained. The incorporation of future costs also had an impact on the probability of the SP implementation being cost-effective at willingness-to-pay (WTP) threshold below $25,000/QALY as shown in Figure 2.1.

A number of one-way sensitivity analyses were conducted to test the robustness of the model and results are presented in Figure 2.2. Overall, the model was most sensitive to changes in the time horizon. The model was also sensitive to the discount rate, assumptions on prevalence and ongoing risk of sepsis. For instance, in comparison to the base-case ICER, when time horizon was reduced to 5 years in the model, the intervention

became a dominant strategy and reducing the discount rate to 0% increased ICER to $10,992.87.

2.5.2. Analyses by cancer types and future costs

Figure 2.3 shows the breakdown of lifetime costs and QALYs across different types of cancer. Intervention-related costs, composed predominantly of hospitalisation costs (blue bars) were higher for the non-SP cohort than SP cohort, therefore the intervention appeared to be a dominant strategy across all cancer types when no future costs were taken into account. With the inclusion of future costs, total lifetime healthcare costs varied depending on the type of cancer (Figure 2.3). As more cost sets were incorporated into the analysis, incremental costs increased and differed across cancers depending on the cost of managing the respective cancers and survivorship. The full set of results can be found in Appendix 8 Table S2.4 in Supplementary Materials. The cost-effectiveness of SP intervention varied depending on the type of cancer and a similar trend of increasing ICER was observed as future medical costs were included into the CEA analysis. Correspondingly, NMBs varied across cancer types and were substantially lower when future medical costs were included in the analysis (Appendix 8 Figure S2.2 in Supplementary Materials).

Figure 2.4 shows the cost-effectiveness acceptability curves with all costs included across different cancer types compared to the base-case (all cancers combined). Heterogeneity across cancer types is evident and this had an impact on decision uncertainty. For example, at a WTP of $50,000/QALY, the probability of SP intervention being cost-effective varied from 0.54 (leukaemia) to 0.70 (myeloma) to close to 1 for cancers such as breast, melanoma, prostate, colorectal and Hodgkin's lymphoma.

## 2.6. Discussion

This study demonstrated that the incorporation of future medical costs in the economic evaluation of a sepsis intervention in cancer patients can produce different cost-effectiveness results that may affect decisions made by policymakers. The CEA results based on intervention-related costs only showed that SP is highly likely to be a cost-saving dominant intervention. However, when extrapolated to lifetime with future medical costs, the intervention was no longer a dominant strategy but rather had an ICER

of $7,526/QALY gained. Although the sepsis intervention remains cost-effective by Australian standards [43], the scenarios presented with and without future medical costs clearly demonstrate their impact and potential to result in different policy decisions depending on WTP thresholds.

Future costs are likely to have substantial impact for life-extending interventions where survivors will require continuous and/or future medical attention that can translate into substantial ongoing healthcare costs. This has been demonstrated in disease areas such as type 1 diabetes [48], chronic heart failure [49] and chronic kidney disease [8, 50]. This is similarly important in cancer patients who require lifelong medical care and surveillance, further adding to the burden on the patient and healthcare system. The exclusion of these costs mean that decisions made using the cost-effectiveness ratios will not adequately reflect a healthcare system perspective and are not considered in conjunction with the potential impact these interventions will have on healthcare budgets longer term [51]. For countries that do not explicitly incorporate future cost in funding decisions, it is still important to recognise the impact of these costs. If decision makers are to use cost-effectiveness analyses to efficiently allocate resources within a fixed healthcare budget, then excluding future medical costs from analysis will not fully achieve this aim due to systematic biases that can arise from exclusion [4, 10].

The difference in the resultant ICER due to the inclusion or exclusion of future healthcare costs could be large enough to influence decisions based on a fixed threshold as demonstrated by van Baal et al [4]. When future costs are incorporated in our economic model, the impact is an increase in the ICER ranging from 92% to 290%. This change is similar to the impact observed in a review of cancer-related CEAs [17] that reported an average of 292% increase in ICER when incorporating future cost. A wide range of impacts have also been observed in other disease models (for example, a 57% decrease in Type 1 diabetes intervention [48] and 1776% increase in end-stage renal disease care [50] reflecting the broad range of methods and cost inputs. The extent of the impact of future costs will not only affect the resultant ICERs but the certainty under which decisions have to be made [52]. Additionally, as value-of-information analysis is increasingly becoming an important component in pharmacoeconomic assessments, further uncertainty generated from the inclusion of additional cost components have also shown to increase the expected value of perfect information (EVPI) [49] which may result

in the need to invest extra resources to eliminate all uncertainty in adopting the intervention. Given the large degree of variation observed, a much better understanding and consistency of how economic evaluations should be undertaken is warranted.

As cancer patients are unlikely to be a homogenous population, using cancer specific inputs to extrapolate both outcomes and costs through lifetime modelling provided a better differentiation across cancer types compared to averaging inputs across all cancer patients. Importantly, results from the analysis showed that the impact of future cost differ across cancer types due to two aspects; cost of managing cancer and relative survival. Longer life expectancies did not necessarily result in greater lifetime healthcare costs (Figure 2.3). High ICERs were observed for cancers such as leukaemia, myeloma and brain were driven by high ongoing cancer costs and lower relative survival indicating immediate trade-offs between costs of intervening and level of benefits attainable.

These results have demonstrated that the distinct cancer characteristics matter resulting in different cost-effectiveness results in subgroups according to the cancer type. Incorporating heterogeneity in economic evaluations has been controversial due to ethical considerations as subgrouping may lead to equity constraints in the provision of healthcare to certain populations. However, it is acknowledged that there is value in incorporating heterogeneity in economic evaluations [47, 53, 54]. Whilst it was useful to establish, these results are not intended to exclude certain groups from treatment as decisions on resource allocations are based on numerous factors other than cost-effectiveness such as clinical effectiveness and equity/ethical considerations, all of which need to be clear, transparent and acceptable. Therefore, there is value in incorporating heterogeneity in cost-effectiveness analyses to allow for better decision making [47, 55] and an understanding of how savings are being generated.

The ambiguity of what is *related* and *unrelated* medical costs has led to inconsistencies in the conduct of cost-effectiveness analyses and interpretation of results [8, 16]. This study has demonstrated the important implication the type of costs included has on the ICER (Figure 2.1) and depending on the types of costs considered, it could have more impact on some cancers compared to others (Appendix 8 Figure S2.3 and S2.4 in Supplementary Material). In practice, how costs are classified is subject to the discretion of the analyst and it is often difficult to distinguish these costs [52, 56]. Alternative suggestions to overcome this conundrum is to ignore the distinction between related or

unrelated particularly if all future medical costs are to be included in the economic evaluation of life-extending technologies [57, 58]. As national guidelines are standards for performing economic evaluations in healthcare, it is therefore pertinent to advocate for clearer and consistent pharmacoeconomic guidelines around costing methodologies.

### 2.6.1. Limitations

The economic model represents a necessary simplification in capturing excess cancer mortality rates and lifetime healthcare costs. Despite this limitation, the model estimated a life expectancy of 20.05 and 13.51 for non-septic breast and colon cancer patients respectively which is comparable to the published life expectances calculated from the US Surveillance, Epidemiology, and End Results (SEER) registries [59]. Similarly, for lifetime cancer costs, estimates obtained were within the ranges of those published internationally [60, 61]. Simplifying assumptions were made to ensure comparable scenarios across different cancer types to better understand the impact of future costs. However, it is acknowledged that analysis by cancer stage and sepsis severity could be an important consideration that has not been adequately captured in this study thus warranting future research. It would be important to better understand the impact of sepsis and the intervention across various types and severity of cancer patients.

The lack of precise or reliable cost estimates can be problematic and the unavailability of cost data beyond the study period (for example, post-hospitalisation) is often cited as a limitation [62-64]. While it is agreed that incorporating future medical costs into economic evaluations is not an easy task to accurately quantify and disaggregate, this analysis adds to the growing literature of economic evaluations that include future costs and has demonstrated the practicality of doing so. In countries like The Netherlands where guidelines mandate the inclusion of such costs, resources to facilitate the inclusion of such costs have been developed and made publicly available [65]. The increasing availability of access to individual-level population-linked data from routine collection of health-related data has availed researchers to capture healthcare resource use and provide health system costs estimates by disease type, age, sex and proximity to death [26-28, 34, 66]. Another commonly employed approach to account for future medical costs is to use average health expenditure per person by age and sex [67, 68]. The availability of such sources demonstrates the feasibility to include reasonable cost estimates into economic evaluations. Furthermore, Meltzer and Johansen [69] argues for the inclusion of rough

estimates rather than the complete omission of such costs to avoid significant biases in cost-effectiveness results favouring life-extending technologies over those which improve quality-of-life.

## 2.7. Conclusion

This CEA provides evidence for potential bias in ICER results if future medical costs of surviving patients are not included in an economic evaluation. The impact of inclusion (excess cancer costs or all other healthcare costs) and non-inclusion of future medical costs in the analysis are clearly distinguished providing an important example for the economic evaluation methods literature. The analysis demonstrates cost-effectiveness for cancer types showing the heterogeneity in cost-effectiveness results which will be an important input into treatment, planning and policy decisions.

## 2.8. Tables and figures

Table 2.1: Data input for lifetime model

| **Decision tree** | | | | | | |
|---|---|---|---|---|---|---|
| | **SP cohort** | | **Non-SP cohort** | | | |
| **Variable** | **Mean** | **SE** | **Mean** | **SE** | **Distribution** | **Source** |
| Hospitalisation cost | | | | | | |
| Survived [a] | 34,998.94 | 2262.65 | 43,118.74 | 4168.72 | Gamma | [31] |
| Died [a] | 36,207.10 | 8029.32 | 43,723.60 | 9164.93 | Gamma | [31] |
| Sepsis pathway cost | 141.83 | 70.92 [f] | - | - | Gamma | [g] |
| Probability of death at 30-days | 0.09 | 0.02 | 0.20 | 0.04 | Beta | [31] |
| **Markov model [b]** | | | | | | |
| **Variable** | **Mean** | **SE** | | | **Distribution** | **Source** |
| Relative risk of death due to sepsis | | | | | | |
| 31-90 days | 2.27 | 1.19 | | | Log normal | [38] |
| 91-180 days | 1.74 | 1.24 | | | Log normal | |
| 181-365 days | 1.43 | 1.19 | | | Log normal | |
| 1-2 years | 0.99 | 1.16 | | | Log normal | |
| Prevalence of sepsis | 0.02 | 0.01 [f] | | | Beta | [70] |
| Utilities (post-hospitalisation) | | | | | | |
| Month 1 | 0.41 | 0.02 | | | Beta | [42] |
| Month 3 | 0.56 | 0.02 | | | Beta | |
| Month 6 | 0.60 | 0.02 | | | Beta | |
| Month 12 | 0.67 | 0.02 | | | Beta | |
| Month 18 | 0.67 | 0.02 | | | Beta | |
| Month 42 | 0.64 | 0.04 | | | Beta | [41] |
| Month 60+ | 0.68 | 0.04 | | | Beta | |
| | **Male** | | **Female** | | | |
| | **Mean** | **SE** | **Mean** | **SE** | | |
| Excess mortality due to cancer [c] | | | | | | [40] |
| 0-1 year | 0.206 | 0.103 [f] | 0.190 | 0.095 [f] | Beta | |
| 1-5 years | 0.042 | 0.021 [f] | 0.041 | 0.021 [f] | Beta | |
| 5-10 years | 0.019 | 0.009 [f] | 0.016 | 0.008 [f] | Beta | |
| 10-15 years | 0.014 | 0.007 [f] | 0.010 | 0.005 [f] | Beta | |
| 15-20 years | 0.010 | 0.005 [f] | 0.006 | 0.003 [f] | Beta | |

| | | | | | | |
|---|---|---|---|---|---|---|
| Future medical costs [e] | | | | | | |
| Cancer-related | | | | | | [28] |
| 1-5 months | 3,399.04 | 196.03 | 3,873.83 | 241.36 | Gamma | |
| 6-11 months | 1,139.37 | 68.07 | 1,298.54 | 83.57 | Gamma | |
| 12-23 months | 425.97 | 23.65 | 485.48 | 29.48 | Gamma | |
| 24+ months | 191.24 | 6.64 | 217.96 | 9.32 | Gamma | |
| Pre-death [d] | 60,356.59 | 3,522.63 | 68,788.26 | 4,339.95 | Gamma | |
| | | | | | | |
| All other healthcare | | | | | | [34] |
| Recurring monthly | 186.42 | 93.21 [f] | 169.17 | 84.58 [f] | Gamma | |
| Pre-death [d] | 30,305.00 | 15,152.50 [f] | 33,065.00 | 16,532.50 [f] | Gamma | |

*SE* standard error, *SP* sepsis pathway.

[a] Patients who survived or died at 30-days

[b] Inputs for the Markov model applies to both the SP and non-SP cohorts

[c] Calculated from relative survival rates published in [40]

[d] Pre-death cost incurred in the 12 months prior to death

[e] Lifetime excess healthcare cost post-hospitalisation

[f] In the absence of reported measure of uncertainty around these estimates, standard error (SE) is assumed to be half the mean [71]

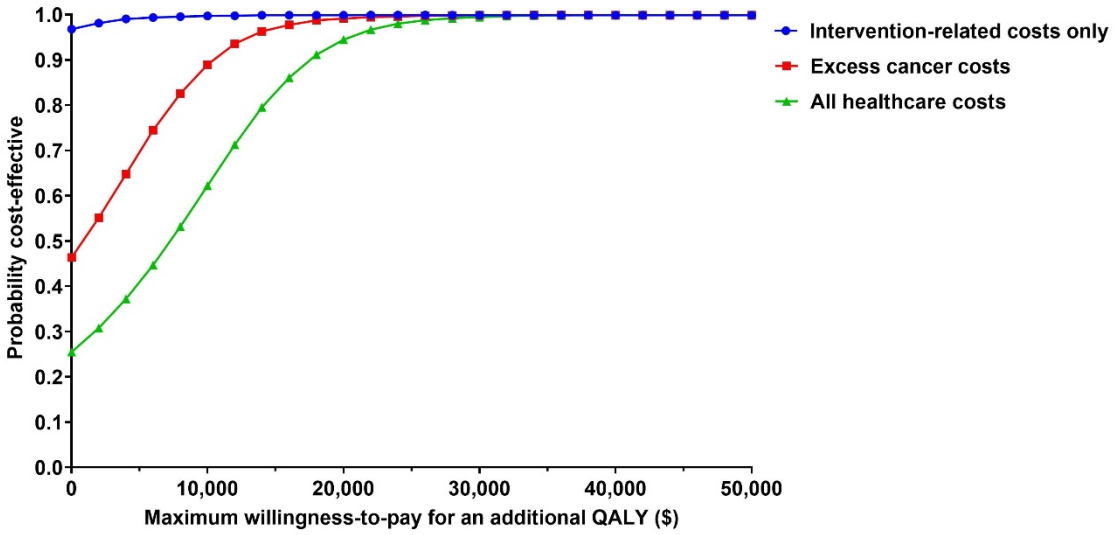
[g] Detailed costing methodology described in Appendix 4 in Supplementary Materials

Table 2.2: Incremental cost-effectiveness results

| | **SP cohort** | **Non-SP cohort** | **Difference** | **ICER** | **% of simulated ICERs in SE quadrant** |
|---|---|---|---|---|---|
| QALY gained | 4.87 | 4.27 | 0.60 | | |
| <u>Cost scenarios</u> | | | | | |
| Intervention-related | 35,247 | 43,240 | -7,993 | SP dominates | 96 |
| Excess cancer costs | 104,585 | 104,056 | 529 | 884 | 46 |
| All healthcare costs | 136,934 | 132,430 | 4,505 | 7,526 | 25 |

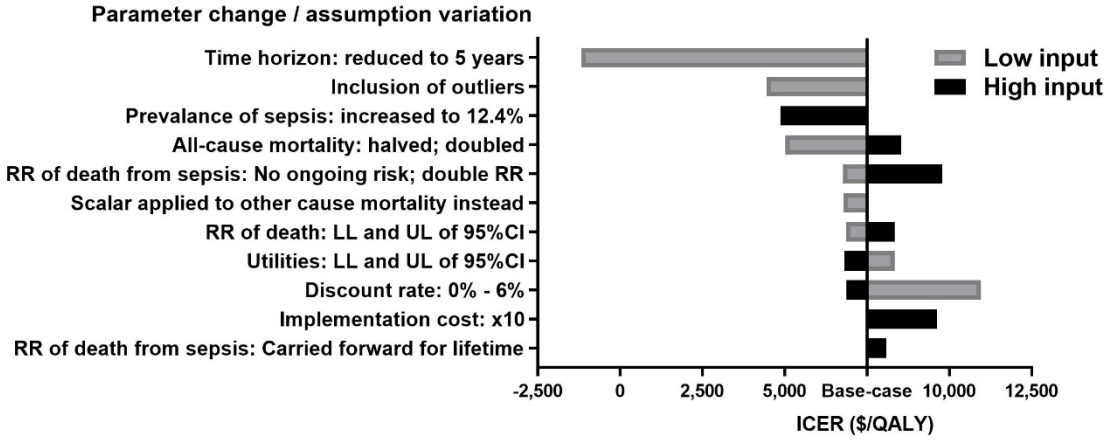
*ICER* incremental cost-effectiveness ratio, *QALY* quality-adjusted life year, *SE* south-east, *SP* sepsis pathway.

Figure 2.1: Cost-effectiveness acceptability curve for all cancers combined (base-case) reflecting the impact of costs included in analysis.



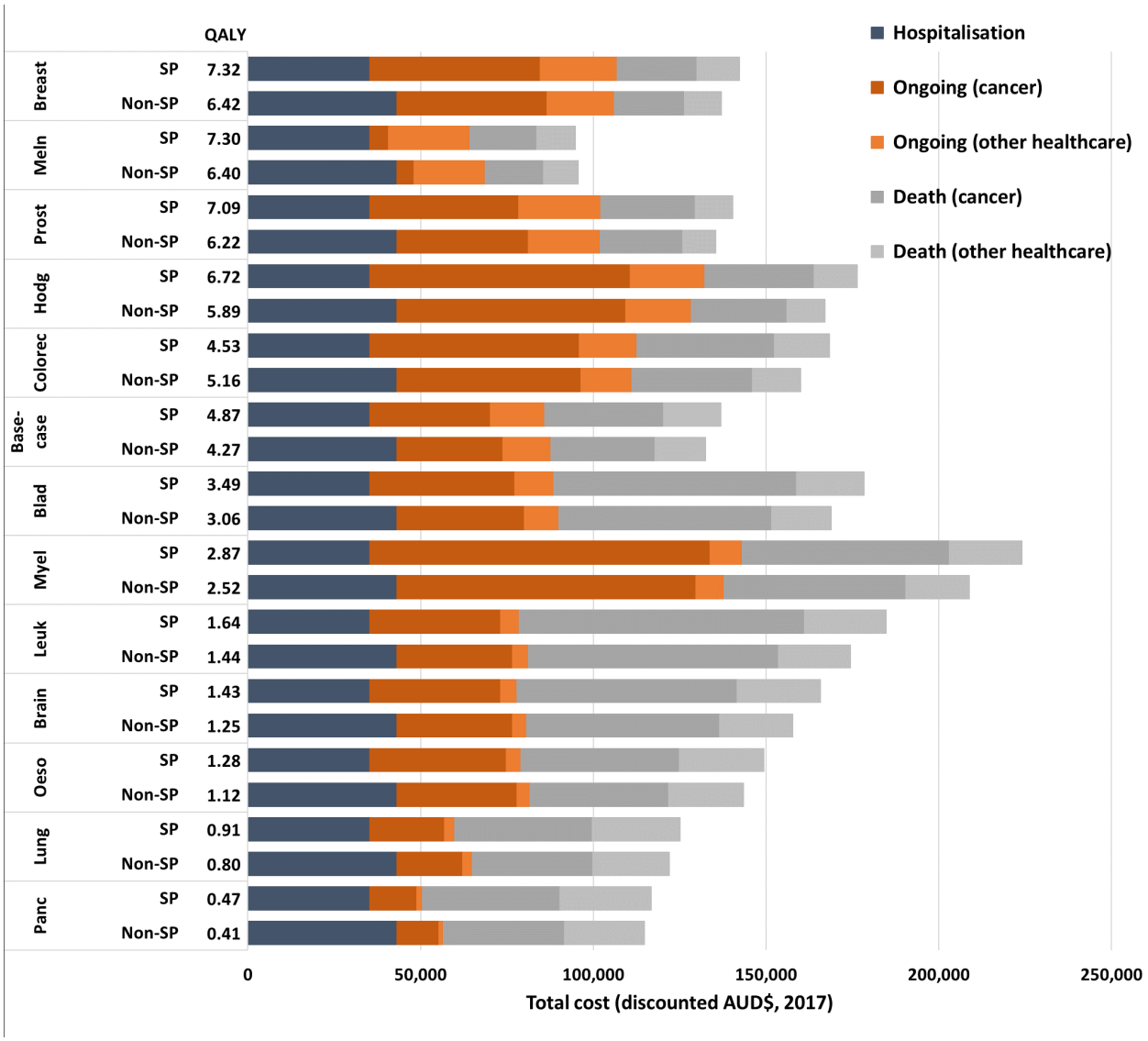

*QALY* quality-adjusted life-year

Figure 2.2: Tornado diagram showing the impact of different variables and assumptions on cost per QALY from one-way sensitivity analysis (base-case).



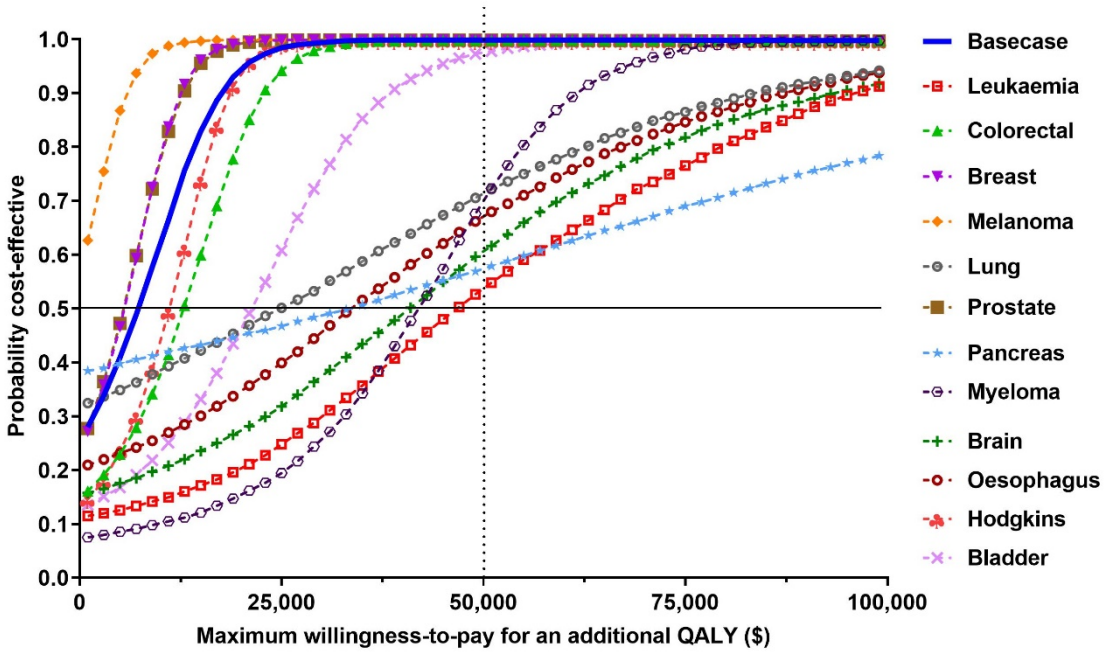

*CI* confidence interval, *LL* lower limit, *QALY* quality-adjusted life-year, *RR* relative risk, *UL* upper limit

Figure 2.3: Breakdown of lifetime costs and QALYs across different cancer types. Base-case represents all cancers combined.




*Blad* bladder, Colrec colorectal, *Hodg* Hodgkin's lymphoma, *Leuk* leukaemia (AML), *Meln* melanoma, *Myel* myeloma, *Oeso* oesophagus, *Panc* pancreas, *Prost* prostate, *QALY* quality-adjusted life years, *SP* sepsis pathway.

Figure 2.4: Cost-effectiveness acceptability curves across various cancer types for all healthcare costs scenario (all future medical costs).




*QALY* quality-adjusted life years

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## 2.10. Supplementary materials

### Appendix 1

**CHEERS Checklist**
**Items to include when reporting economic evaluations of health interventions**

| Section/item | Item No | Recommendation | Reported on page No/ line No |
|---|---|---|---|
| **Title and abstract** | | | |
| Title | 1 | Identify the study as an economic evaluation or use more specific terms such as "cost-effectiveness analysis", and describe the interventions compared. | Title |
| Abstract | 2 | Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions. | Abstract; Para 1-5 |
| **Introduction** | | | |
| Background and objectives | 3 | Provide an explicit statement of the broader context for the study.<br>Present the study question and its relevance for health policy or practice decisions. | Introduction; Para 1-6 |
| **Methods** | | | |
| Target population and subgroups | 4 | Describe characteristics of the base case population and subgroups analysed, including why they were chosen. | Methods; Para 1, 9<br>Appendix 2 in Supplementary Materials |
| Setting and location | 5 | State relevant aspects of the system(s) in which the decision(s) need(s) to be made. | Methods; Para 1<br>Appendix 2 & 3 in Supplementary Materials |
| Study perspective | 6 | Describe the perspective of the study and relate this to the costs being evaluated. | Methods; Para 1 |

| Section/item | Item No | Recommendation | Reported on page No/ line No |
|---|---|---|---|
| Comparators | 7 | Describe the interventions or strategies being compared and state why they were chosen. | Methods; Para 1, 2<br>Appendix 2 in Supplementary Materials |
| Time horizon | 8 | State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate. | Methods; Para 3 |
| Discount rate | 9 | Report the choice of discount rate(s) used for costs and outcomes and say why appropriate. | Methods, Para 8 |
| Choice of health outcomes | 10 | Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed. | Methods; Para 1, 3, 4, 5, 6 |
| Measurement of effectiveness | 11a | *Single study-based estimates:* Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data. | NA |
| | 11b | *Synthesis-based estimates*: Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data. | Methods; Para 3-9<br>Appendix 4, 5 & 6 in Supplementary Materials |
| Measurement and valuation of preference based outcomes | 12 | If applicable, describe the population and methods used to elicit preferences for outcomes. | NA |
| Estimating resources and costs | 13a | *Single study-based economic evaluation:* Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs. | Methods; Para 3, 4<br>Appendix 3 & 5 in Supplementary Materials |

| Section/item | Item No | Recommendation | Reported on page No/ line No |
|---|---|---|---|
| | 13b | *Model-based economic evaluation:* Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs. | Methods ; Para 4 & 5<br>Appendix 5 in Supplementary Materials |
| Currency, price date, and conversion | 14 | Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate. | Methods; Para 8 |
| Choice of model | 15 | Describe and give reasons for the specific type of decision-analytical model used. Providing a figure to show model structure is strongly recommended. | Methods; Para 3<br>Appendix 4 (Fig. S2.1) in Supplementary Materials |
| Assumptions | 16 | Describe all structural or other assumptions underpinning the decision-analytical model. | Methods; Para 3-9 |
| Analytical methods | 17 | Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty. | Methods; Para 3-9<br>Appendix 4, 5 & 6 in Supplementary Materials |
| **Results** | | | |
| Study parameters | 18 | Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to | Methods; Para 3-9 ( Table 2.1) |

| Section/item | Item No | Recommendation | Reported on page No/ line No |
|---|---|---|---|
| | | represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended. | Appendix 4 (Table S2.3) in Supplementary Materials |
| Incremental costs and outcomes | 19 | For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios. | Results; Para 1, 3 (Table 2.2, Fig 2.3) |
| Characterising uncertainty | 20a | *Single study-based economic evaluation:* Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact of methodological assumptions (such as discount rate, study perspective). | NA |
| | 20b | *Model-based economic evaluation:* Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions. | Results; Para 2, 4 (Figure 2.1, 2.2, 2.4) |
| Characterising heterogeneity | 21 | If applicable, report differences in costs, outcomes, or cost-effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information. | Results; Para 3, 4 (Figure 2.1, 2.2, 2.4)<br>Appendix 7 (Table S2.4) in Supplementary Materials |
| **Discussion** | | | |
| Study findings, limitations, generalisability, and current knowledge | 22 | Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalisability of the findings and how the findings fit with current knowledge. | Discussion; Para 1-8 |

| Section/item | Item No | Recommendation | Reported on page No/ line No |
|---|---|---|---|
| **Other** | | | |
| Source of funding | 23 | Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other non-monetary sources of support. | Information provided via the submission system |
| Conflicts of interest | 24 | Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations. | Information provided via the submission system |

For consistency, the CHEERS Statement checklist format is based on the format of the CONSORT statement checklist.

## Appendix 2

### Sepsis management in cancer patients in Australia

Cancer patients can present with sepsis in many different settings in the hospital; inpatient, outpatient, during radiotherapy or chemotherapy, aphaeresis or to the emergency department. The presence of neutropenia and/or immunocompromise are recognised risk factors for sepsis and are generally included in clinical guidelines for sepsis. Approaches to standardise sepsis management though bundles of care have led to improved awareness, patient management and outcomes [1, 2]. There is no national standardised approach for sepsis in Australia, although there are some high-profile programs such as the NSW CEC Sepsis Kills program, and the Think Sepsis Act Fast initiative in Victoria which was adapted from the whole of hospital cancer sepsis pathway implemented in Peter MacCallum Cancer Centre (PMCC) [3]. The sepsis pathway intervention implemented in PMCC employed a whole-of-systems approach to improve recognition and resuscitation of sepsis in cancer patients across their treatment journey. The hospital-wide intervention supported nurse-initiated sepsis care, early medical review, and prompt antibiotic and fluid resuscitation. The associated antimicrobial recommendations included recommendations for neutropenic fever (less than 50% of cancer patients with sepsis in this), as well as other common infections such as post-surgical infections and pneumonia.

### Australian health system

The Australian healthcare system is a hybrid model; a mix of both public and private. The government provides universal access via Medicare to basic healthcare needs for all Australians in public healthcare institutions, including hospitals. Medicare is funded through taxation and government-imposed levy [4]. Australians can access cancer services through Medicare for:

(1) free treatment in public hospitals and cancer centres;

(2) free or subsidised out-of-hospital medical services (GP and specialist services) and diagnostic and pathology services;

(3) low cost ($40.30 general population or $6.50 concessional [5]) approved pharmaceuticals including many chemotherapy and anti-cancer drugs.

Healthcare is also provided in the private sector which includes hospital care, allied health care such as physiotherapy and dental. Individuals can purchase private health insurance for extended healthcare coverage to access these services.

In Australia, cost-effectiveness analyses are routinely used as part of Health Technology Assessment to inform funding and reimbursement decisions for medical services and pharmaceuticals.

**Health system financing**

The Australian health system is funded by all levels of government. Funding for tertiary hospital services is shared between the Federal and State governments and is funded via activity-based funding arrangements. This means that funding is dependent on the services provided and the mix patients treated. The average cost of public hospital separations is determined based on the Australian Refined Diagnostic Related Group (AR-DRG). Countries such as France [6] and New Zealand [7] also allocate funding via the DRG system. Primary and specialist care services and medicines are primarily funded by the Federal government with set fees that are reimbursed.

At the hospital level, patient-level cost data consists of direct and indirect costs based on resources and services associated with each inpatient admission; for instance, imaging and pathology services and medical. Medical costs usually include costs of all medical and surgical staff and supplies used in medical units of the hospital. Hospital staff are renumerated based on agreed standard rates of salary for medical staff.

## Appendix 3

### Study Setting

An economic evaluation of a hospital-wide sepsis clinical pathway in a cancer hospital was performed comparing the cost and outcomes of patients pre- and post-pathway implementation. The analysis was undertaken from the perspective of the healthcare system/payer. The setting was the Peter MacCallum Cancer Centre (PMCC), a 100 inpatient-bed tertiary cancer hospital providing haematology, medical oncology, cancer surgery and radiation oncology services. Details of the implementation study and the clinical outcomes have been described elsewhere [3, 8]. Briefly, the SP supported nurse-initiated sepsis care, early medical review, and prompt antibiotic and fluid resuscitation and was implemented in PMCC in March 2013. Patients were included in the SP cohort if they had hospital ICD-10 codes for sepsis and relevant identification from the antimicrobial approvals system used for stewardship (Guidance, Melbourne Health) for periods between March and December 2013. To compare with a similar population who did not receive the SP, a pre-implementation cohort (non-SP) were identified using similar methods presented between March and December 2012. The implementation study included a total of 323 patients (212 in SP and 111 in non-SP).

### Patient Characteristics

Detailed hospitalisation costs were available for 275 patients, 184 (86.8%) and 91 (82.0%) in the SP and non-SP cohorts respectively. Three surgical patients had costs greater than $300,000 and were considered serious outliers and were excluded from analysis. Patient demographic and clinical characteristics are presented in Appendix 2 Table S2.1 in Supplementary Materials. Patients in the SP cohort were older (61.13 vs. 57.94 years, p=0.082), and more had surgery in the 30 days prior to the sepsis episode (15.93% vs. 6.67%, p=0.032). All other baseline characteristics were similar between the two cohorts.

Table S2.1: Description of patient characteristics between cohorts

| **Characteristics** | **SP cohort** (N = 182) | **Non-SP cohort** (N = 90) | **p-value** |
|---|---|---|---|
| Surgical (%) | 35 (19.23%) | 10 (11.11%) | 0.090 |
| Non-surgical [a] (%) | 147 (80.77%) | 80 (88.89%) | |
| Age (mean, SD) | 61.13 (13.5) | 57.94 (15.5) | 0.0824 |
| Female (%) | 75 (41.2%) | 36 (40.0%) | 0.849 |

| | | | |
|---|---|---|---|
| Heart rate (mean, SD) | 103.74 (17.72) | 107.64 (19.38) | 0.0983 |
| Systolic BP (mean, SD) | 119.06 (23.46) | 118.0 (22.21) | 0.7214 |
| Respiratory rate (mean, SD) | 21.20 (4.66) | 23.17 (21.41) | 0.2376 |
| Temperature (mean, SD) | 38.26 (0.87) | 38.66 (4.81) | 0.2741 |
| Neutrophil count (mean, SD) | 5.5 (7.91) | 5.03 (6.33) | 0.6278 |
| Neutropenia (%) | 71 (39.01%) | 42 (47.19%) | 0.200 |
| Surgery in the last 30 days (%) | 29 (15.93%) | 6 (6.67%) | 0.032 |

*BP* blood pressure, *SD* standard deviation, *SP* sepsis pathway.

[a] Non-surgical defined as haematology, medical oncology and radiation oncology patients

**Clinical Effectiveness**

Patients in the SP cohort demonstrated significantly lower rates of ICU admission (18.68% vs. 36.67%, $p<0.05$) and 30-day all-cause mortality (8.79% vs. 20.0%, $p<0.05$). Detailed key outcomes were previously reported in the implementation study [3].

## Appendix 4

The cost of implementing the SP protocol consisted of staff costs quantified by accounting for time spent by the different levels of staff involved in the development and implementation of the SP (Table S2.2). This was broadly categorised into three main phases which included reviewing the feasibility of the pathway, staff education and training, and implementation. The total cost consisted largely of staff cost and the bulk was for the implementation phase which required an infectious disease physician and a nurse project officer to manage the program. 30% was added to staff costs to account for overhead costs. These costs were assumed to incur only in the first year of implementation covering 500 sepsis cases. After one year, the cost of the pathway is assumed to be fully integrated into the ongoing framework of continuing medical education for all staff. The estimated total implementation cost of the SP at PMCC was $70,916.54 over one year at a cost per patient of approximately $141.83.

Table S2.2: Estimated costs to implement SP protocol in PMCC

| Key phases | Role | Staff involved | Number of staff | Time per staff (hours) | Wage per hour ($) [a] | Total cost ($) |
|---|---|---|---|---|---|---|
| *Staff resource* | | | | | | |
| Sepsis Working Party | Reviewing feasibility of pathway | Senior nurse | 7 | 6 | 45.66 | 1,862.45 |
| | | Specialist ID | 2 | 6 | 125.35 | 1,460.70 |
| | | Registrar ID | 1 | 6 | 68.32 | 398.08 |
| | | Senior pharmacist | 1 | 6 | 52.93 | 308.40 |
| Training and Education | Nursing and medical team education sessions; including cannulation training, Nurses' forum | Senior nurse (cannulation) | 8 | 2 | 45.66 | 709.50 |
| | | Senior nurse project officer (forum) | 8 | 3 | 48.41 | 1,128.32 |
| | | Senior nurse project officer (team education) | 1 | 5.33 | 48.41 | 250.74 |
| | | Specialist ID | 1 | 3 | 125.35 | 365.18 |
| | | Registrar ID | 1 | 3 | 68.32 | 199.04 |
| Implementation | Pathway form design, communication and liaison & project management | Senior pharmacist | 1 | 20 | 52.93 | 1,028.00 |
| | | Specialist ID | 1 | 69.33 | 125.35 | 8,439.62 |
| | | Grade 5 nurse project officer | 1 | 780 | 48.41 | 36,670.40 |
| **Total staff cost** | | | | | | **54,392.76** |
| **Total staff cost (+ 30% overhead cost)** | | | | | | **70,710.59** |
| *Other administrative resource* | Printing of hospital documentation and education materials | | | | | 205.95 |
| **Total implementation cost** | | | | | | **70,916.54** |

*ID* infectious disease, *PMCC* Peter MacCallum Cancer Centre, *SP* sepsis pathway

[a] Source of cost from Peter McCallum Cancer Centre (PMCC) new staff webpage [1] and from the main investigator of the SP implementation team.

## Appendix 5

Figure S2.1: TreeAge model for lifetime modelling

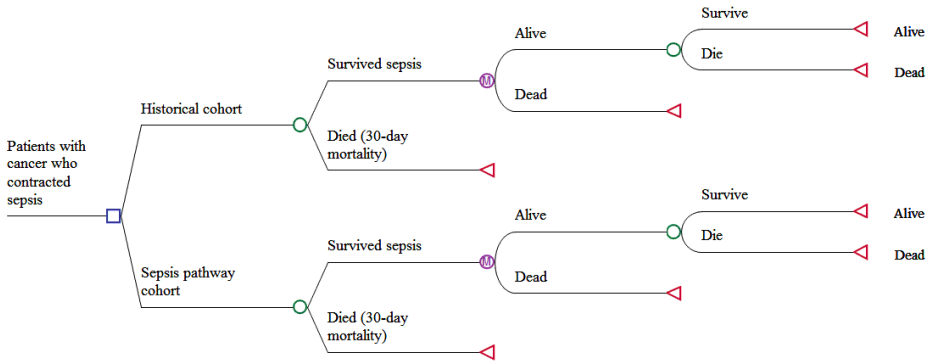



Table S2.3: Data inputs for cancer sub-group analyses

| Variable | Male Mean | SE [b] | Female Mean | SE [b] | Distribution | Source |
|---|---|---|---|---|---|---|
| **Markov model [a]** | | | | | | |
| *Excess mortality due to cancer* | | | | | | [9] |
| **Leukaemia (AML)** | | | | | | |
| *0-1 year* | 0.83471 | 0.417355 | 0.7962879 | 0.398144 | Beta | |
| *1-5 years* | 0.10723 | 0.053614 | 0.1065460 | 0.053273 | Beta | |
| *5-10 years* | 0.018204 | 0.009102 | 0.0224099 | 0.011205 | Beta | |
| *10-15 years* | 0.006711 | 0.003356 | 0.0117377 | 0.005869 | Beta | |
| *15-20 years* | 0 | 0 | 0.0115258 | 0.005763 | Beta | |
| **Colorectal** | | | | | | |
| *0-1 year* | 0.1485 | 0.07425 | 0.16134 | 0.080672 | Beta | |
| *1-5 years* | 0.05279 | 0.026397 | 0.04513 | 0.022565 | Beta | |
| *5-10 years* | 0.02041 | 0.010203 | 0.01538 | 0.007688 | Beta | |
| *10-15 years* | 0.008373 | 0.004186 | 0.006505 | 0.003252 | Beta | |
| *15-20 years* | 0.002415 | 0.001207 | 0.0004 | 0.0002 | Beta | |
| **Breast [c]** | | | | | | |
| *0-1 year* | 0.03149 | 0.015745 | 0.02122 | 0.010612 | Beta | |
| *1-5 years* | 0.03321 | 0.016605 | 0.01974 | 0.009872 | Beta | |
| *5-10 years* | 0.02716 | 0.013582 | 0.01366 | 0.006828 | Beta | |
| *10-15 years* | 0.02466 | 0.01233 | 0.011103 | 0.005551 | Beta | |
| *15-20 years* | 0.014299 | 0.00715 | 0.009209 | 0.004604 | Beta | |
| **Melanoma** | | | | | | |
| *0-1 year* | 0.03563 | 0.017814 | 0.01816 | 0.009082 | Beta | |
| *1-5 years* | 0.02019 | 0.010093 | 0.01131 | 0.005657 | Beta | |
| *5-10 years* | 0.00837 | 0.004186 | 0.00486 | 0.002429 | Beta | |
| *10-15 years* | 0.003429 | 0.001715 | 0.00201 | 0.001005 | Beta | |
| *15-20 years* | 0.003633 | 0.001816 | 0.001003 | 0.000501 | Beta | |
| **Lung** | | | | | | |
| *0-1 year* | 0.95972 | 0.47986 | 0.76357 | 0.381785 | Beta | |
| *1-5 years* | 0.22356 | 0.11178 | 0.1967 | 0.09835 | Beta | |

| | | | | | | |
|---|---|---|---|---|---|---|
| *5-10 years* | 0.07479 | 0.037397 | 0.06076 | 0.030381 | Beta | |
| *10-15 years* | 0.048414 | 0.024207 | 0.036544 | 0.018272 | Beta | |
| *15-20 years* | 0.019523 | 0.009761 | 0.023307 | 0.011653 | Beta | |
| | | | | | | |
| **Prostate [d]** | | | | | | |
| *0-1 year* | 0.0141 | 0.007049 | - | - | Beta | |
| *1-5 years* | 0.01047 | 0.005235 | - | - | Beta | |
| *5-10 years* | 0.01131 | 0.005657 | - | - | Beta | |
| *10-15 years* | 0.017112 | 0.008556 | - | - | Beta | |
| *15-20 years* | 0.01516 | 0.00758 | - | - | Beta | |
| | | | | | | |
| **Pancreas** | | | | | | |
| *0-1 year* | 1.272966 | 0.636483 | 1.298283 | 0.649142 | Beta | |
| *1-5 years* | 0.281299 | 0.14065 | 0.271736 | 0.135868 | Beta | |
| *5-10 years* | 0.069628 | 0.034814 | 0.062668 | 0.031334 | Beta | |
| *10-15 years* | 0.018204 | 0.009102 | 0.023532 | 0.011766 | Beta | |
| *15-20 years* | 0 | 0 | 0 | 0 | Beta | |
| | | | | | | |
| **Myeloma** | | | | | | |
| *0-1 year* | 0.196015 | 0.098007 | 0.205795 | 0.102897 | Beta | |
| *1-5 years* | 0.130785 | 0.065393 | 0.130018 | 0.065009 | Beta | |
| *5-10 years* | 0.108601 | 0.0543 | 0.110677 | 0.055339 | Beta | |
| *10-15 years* | 0.069345 | 0.034672 | 0.083406 | 0.041703 | Beta | |
| *15-20 years* | 0.028774 | 0.014387 | 0.047144 | 0.023572 | Beta | |
| | | | | | | |
| **Brain** | | | | | | |
| *0-1 year* | 0.636767 | 0.318383 | 0.693147 | 0.346574 | Beta | |
| *1-5 years* | 0.198311 | 0.099155 | 0.160592 | 0.080296 | Beta | |
| *5-10 years* | 0.055151 | 0.027575 | 0.039203 | 0.019601 | Beta | |
| *10-15 years* | 0.030863 | 0.015432 | 0.023757 | 0.011878 | Beta | |
| *15-20 years* | 0.014514 | 0.007257 | 0.020407 | 0.010203 | Beta | |
| | | | | | | |
| **Oesophagus** | | | | | | |
| *0-1 year* | 0.707246 | 0.353623 | 0.776529 | 0.388264 | Beta | |
| *1-5 years* | 0.192991 | 0.096496 | 0.16926 | 0.08463 | Beta | |
| *5-10 years* | 0.046386 | 0.023193 | 0.056738 | 0.028369 | Beta | |
| *10-15 years* | 0.012801 | 0.006401 | 0.036065 | 0.018032 | Beta | |
| *15-20 years* | 0 | 0 | 0.03969 | 0.019845 | Beta | |
| | | | | | | |
| **Hodgkin's Lymphoma** | | | | | | |
| *0-1 year* | 0.074724 | 0.037362 | 0.064005 | 0.032003 | Beta | |
| *1-5 years* | 0.014299 | 0.00715 | 0.01516 | 0.00758 | Beta | |
| *5-10 years* | 0.009418 | 0.004709 | 0.009838 | 0.004919 | Beta | |
| *10-15 years* | 0.006298 | 0.003149 | 0.009628 | 0.004814 | Beta | |
| *15-20 years* | 0.009209 | 0.004604 | 0.004245 | 0.002122 | Beta | |
| | | | | | | |
| **Bladder** | | | | | | |
| *0-1 year* | 0.235722 | 0.117861 | 0.382726 | 0.191363 | Beta | |
| *1-5 years* | 0.079499 | 0.03975 | 0.087391 | 0.043696 | Beta | |
| *5-10 years* | 0.035586 | 0.017793 | 0.031565 | 0.015782 | Beta | |
| *10-15 years* | 0.021072 | 0.010536 | 0.019082 | 0.009541 | Beta | |
| *15-20 years* | 0.013228 | 0.006614 | 0.004041 | 0.00202 | Beta | |

| | **Male** | | **Female** | | | |
|---|---|---|---|---|---|---|
| | **Mean** | **SE** | **Mean** | **SE** | **Distribution** | **Source** |

| | | | | | | |
|---|---|---|---|---|---|---|
| *Future medical costs* [e] | | | | | | |
| Cancer-related | | | | | | [10] |
| **Leukaemia (AML)** | | | | | | |
| *1-5 months* | 5,957.52 | 506.13 | 5,935.14 | 546.42 | Gamma | |
| *6-11 months* | 2,436.68 | 215.75 | 2,427.57 | 232.03 | Gamma | |
| *12-23 months* | 1,585.71 | 128.73 | 1,579.83 | 140.83 | Gamma | |
| *24+ months* | 924.98 | 45.09 | 921.58 | 56.58 | Gamma | |
| *Pre-death* [f] | 111,617.50 | 8,724.92 | 111,201.50 | 9,576.36 | Gamma | |
| **Colorectal** | | | | | | |
| *1-5 months* | 7,185.04 | 581.91 | 6,051.33 | 524.93 | Gamma | |
| *6-11 months* | 2,367.46 | 193.62 | 1,993.75 | 172.77 | Gamma | |
| *12-23 months* | 867.21 | 69.91 | 730.33 | 62.64 | Gamma | |
| *24+ months* | 302.62 | 14.18 | 254.86 | 14.26 | Gamma | |
| *Pre-death* [f] | 82,793.44 | 6,568.75 | 69,725.87 | 5,899.96 | Gamma | |
| **Breast** [c] | | | | | | |
| *1-5 months* | 4,109.61 | 389.71 | 4,109.61 | 389.71 | Gamma | |
| *6-11 months* | 1,659.80 | 150.53 | 1,659.80 | 150.53 | Gamma | |
| *12-23 months* | 461.25 | 38.78 | 461.25 | 38.78 | Gamma | |
| *24+ months* | 191.44 | 8.93 | 191.44 | 8.93 | Gamma | |
| *Pre-death* [f] | 62,491.53 | 7,075.82 | 62,491.53 | 7,075.82 | Gamma | |
| **Melanoma** | | | | | | |
| *1-5 months* | 730.12 | 90.54 | 495.58 | 67.13 | Gamma | |
| *6-11 months* | 115.70 | 14.64 | 78.54 | 10.85 | Gamma | |
| *12-23 months* | 80.57 | 9.48 | 54.70 | 7.14 | Gamma | |
| *24+ months* | 21.37 | 1.63 | 14.51 | 1.38 | Gamma | |
| *Pre-death* [f] | 59,558.90 | 11,805.45 | 40,425.56 | 8,307.35 | Gamma | |
| **Lung** | | | | | | |
| *1-5 months* | 5,181.20 | 659.87 | 4,990.65 | 656.11 | Gamma | |
| *6-11 months* | 1,377.98 | 188.40 | 1,327.33 | 186.78 | Gamma | |
| *12-23 months* | 827.50 | 111.62 | 797.12 | 111.01 | Gamma | |
| *24+ months* | 462.37 | 36.82 | 445.41 | 38.80 | Gamma | |
| *Pre-death* [f] | 51,425.64 | 4,953.10 | 49,537.57 | 5,061.47 | Gamma | |
| **Prostate** [d] | | | | | | |
| *1-5 months* | 1,445.77 | 221.74 | | | Gamma | |
| *6-11 months* | 776.64 | 119.07 | | | Gamma | |
| *12-23 months* | 137.76 | 20.42 | | | Gamma | |
| *24+ months* | 36.05 | 2.97 | | | Gamma | |
| *Pre-death* [f] | 70,466.46 | 19,683.17 | | | Gamma | |
| **Pancreas** | | | | | | |
| *1-5 months* | 4,046.87 | 1,003.05 | 4,251.21 | 1,080.69 | Gamma | |
| *6-11 months* | 1,584.91 | 426.20 | 1,665.05 | 457.77 | Gamma | |
| *12-23 months* | 984.15 | 261.32 | 1,034.07 | 281.48 | Gamma | |
| *24+ months* | 451.39 | 69.99 | 474.33 | 78.86 | Gamma | |
| *Pre-death* [f] | 47,959.46 | 8,937.53 | 50,390.73 | 9,827.31 | Gamma | |
| **Myeloma** | | | | | | |
| *1-5 months* | 6,013.67 | 758.30 | 6,261.91 | 851.55 | Gamma | |
| *6-11 months* | 3,829.33 | 476.48 | 3,986.64 | 531.00 | Gamma | |
| *12-23 months* | 1,779.27 | 224.00 | 1,852.44 | 249.86 | Gamma | |

| | | | | | | |
|---|---|---|---|---|---|---|
| *24+ months* | 1,277.52 | 92.86 | 1,330.21 | 117.45 | Gamma | |
| *Pre-death*[f] | 93,915.62 | 11,150.36 | 97,779.39 | 12,543.41 | Gamma | |
| | | | | | | |
| **Brain** | 8,663.50 | 1,619.02 | 8,679.16 | 1,676.63 | Gamma | |
| *1-5 months* | 2,344.12 | 470.22 | 2,348.46 | 485.38 | Gamma | |
| *6-11 months* | 643.89 | 132.34 | 645.13 | 136.73 | Gamma | |
| *12-23 months* | 373.86 | 42.99 | 374.61 | 47.27 | Gamma | |
| *24+ months* | 81,888.84 | 11,635.16 | 82,045.71 | 12,357.93 | Gamma | |
| *Pre-death*[f] | 8,663.50 | 1,619.02 | 8,679.16 | 1,676.63 | Gamma | |
| | | | | | | |
| **Oesophagus** | | | | | | |
| *1-5 months* | 9,780.89 | 2,469.10 | 8,617.66 | 2,286.49 | Gamma | |
| *6-11 months* | 2,808.39 | 740.56 | 2,473.76 | 678.13 | Gamma | |
| *12-23 months* | 949.06 | 243.50 | 835.53 | 222.28 | Gamma | |
| *24+ months* | 444.18 | 65.97 | 391.22 | 64.85 | Gamma | |
| *Pre-death*[f] | 62,566.79 | 11,959.32 | 55,096.66 | 11,257.80 | Gamma | |
| | | | | | | |
| **Hodgkin's lymphoma** | | | | | | |
| *1-5 months* | 5,715.04 | 1,137.68 | 6,322.59 | 1,318.74 | Gamma | |
| *6-11 months* | 1,296.63 | 260.39 | 1,434.58 | 301.93 | Gamma | |
| *12-23 months* | 761.39 | 140.01 | 842.50 | 164.36 | Gamma | |
| *24+ months* | 377.96 | 36.05 | 418.27 | 48.34 | Gamma | |
| *Pre-death*[f] | 75,274.04 | 14,078.83 | 83,285.74 | 16,431.66 | Gamma | |
| | | | | | | |
| **Bladder** | | | | | | |
| *1-5 months* | 6,315.75 | 976.93 | 5,606.96 | 918.03 | Gamma | |
| *6-11 months* | 2,003.62 | 314.16 | 1,778.86 | 295.30 | Gamma | |
| *12-23 months* | 720.67 | 105.63 | 639.89 | 100.47 | Gamma | |
| *24+ months* | 242.27 | 17.90 | 215.12 | 20.04 | Gamma | |
| *Pre-death*[f] | 114,509.90 | 16,160.83 | 101,666.40 | 15,376.88 | Gamma | |
| | | | | | | |
| All other healthcare costs [g] | | | | | | [11] |
| *Recurring monthly* | 186.42 | 93.21[f] | 169.17 | 84.58 [f] | Gamma | |
| *Pre-death*[f] | 30,305.00 | 15,152.50[f] | 33,065.00 | 16,532.50[f] | Gamma | |

*AML* acute myeloid leukaemia, *SE* standard error

[a] Inputs for the Markov model applies to both the SP and non-SP cohorts

[b] In the absence of reported measure of uncertainty around these estimates, SE is assumed to be half the mean [12].

[c] Proportion of males = 0.0089

[d] Proportion of males = 1.0

[e] Lifetime excess healthcare cost due to cancer

[f] Pre-death cost incurred in the 12 months prior to death

[g] Applied to all cancer types

## Appendix 6

### Deriving future medical costs due to cancer (excess cancer cost)

Future medical costs due to cancer (excess cancer costs) were sourced from data published by Blakely et al [10] providing robust national estimates derived from large population-linked data. Cancer costs were calculated based on coefficients published by the referenced source's Supplemental Digital Content Table 2 to obtain age and sex specific costs for different cancer types and by time since diagnosis and instructions for calculations. These coefficients allow for calculations of costs for different combinations of age, sex and phase hence allowed the incorporation of detailed lifetime cost information into the model appropriate for the evaluation of future medical costs.

Below is an example of how excess costs were calculated for a 60-year-old male with pancreas cancer at 7 months since diagnosis. The table below represents the relevant coefficients obtained from the above referenced source [10]. The authors have specified that age has been centered at 62.5 and excess cost (per person per month) is reflected in 2011 New Zealand dollars.

| | **Pancreas** | |
|---|---|---|
| **Parameter** | **Est.** | **s.e.** |
| Intercept | 5.6653 | 0.1522 |
| Females | 0.0476 | 0.0601 |
| Year | 0.0808 | 0.0217 |
| Age | -0.5993 | 0.115 |
| Age2 | -0.0642 | 0.0125 |
| Age3 | -0.0153 | 0.0044 |
| 6-11 Post | 1.3357 | 0.2041 |
| Age×6-11 Post | 0.3849 | 0.1549 |

Using the above coefficients, costs for our above example can be calculated by:
$\exp(5.6653 + (-0.25*-0.5993) + (-0.25^2*-0.0642) + (-0.25^3*-0.0153) + 1.3357 + (-0.25*0.3849)$
=$1,153.81

This value was converted to Australian dollars using published OECD purchasing power parity rates [13] and inflated to 2017 dollars using Consumer Price Index [14]. Variances around cost estimates were generated by 5000 random draws using STATA statistical software (version 14.0, Texas, USA). This was similarly calculated for all other cancers

included in the analysis and included in the model for cancer sub-group analysis as shown in Table S2.3 Appendix 5 above.

This resource was deemed to be the most reliable due to the unavailability of robust Australian population cost estimates for lifetime medical and the diverse variety of cancers that were considered in this analysis. Furthermore, Australian and New Zealand healthcare systems are very similar and share some cancer treatment guidelines; for example [15]. Death transition costs were included in the model reflecting the substantial and elevated healthcare costs incurred in the months immediately prior to death.

## Appendix 7

### Estimation of life years gained for cancer patients with sepsis

The ongoing mortality rate of cancer patients who have had sepsis was estimated using:

$1- \{[ (1 - EMR) *\theta ] * (1 - q_x)$

where EMR is the excess mortality rate due to cancer, θ is the scale-up factor adjusting for mortality due to sepsis and $q_x$ is the mortality rate of the Australian general population. The all-cause mortality rate of the general population was used as an approximate estimation of mortality due to other causes besides cancer in this population as deaths due to cancer in the overall population would be small. [16]

The increased risk of mortality due to sepsis is accounted for by adjusting the mortality rate of cancer patients through the scale-up factor, θ, estimated as [17]:

$\theta = RR / [RR * p + ( 1 + p )]$

where RR is the relative risk of mortality due to sepsis and p is the prevalence of sepsis among cancer population.

Excess mortality rate for each of the cancer types were calculated from relative survival published by the Australian Institute of Health and Welfare [9] using:

Relative survival = exp(-EMR * time)

**Appendix 8**

Table S2.4: Incremental cost-effectiveness results across cancer types

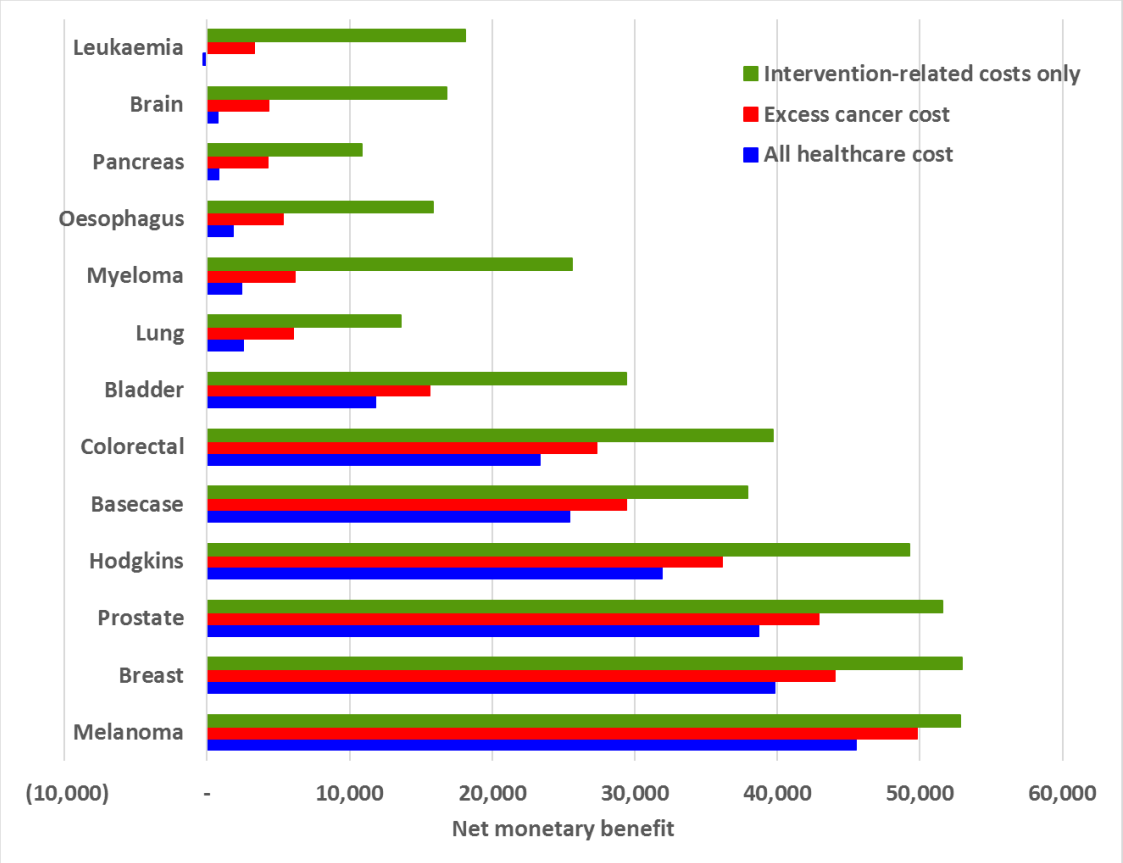
| **Sub-group analysis by cancer type** | **SP cohort** | **Non-SP cohort** | **Difference** | **ICER ($/QALY)** |
|---|---|---|---|---|
| **Leukaemia** | | | | |
| *QALY gained* | 1.62 | 1.42 | 0.20 | |
| No future cost | 35,246.97 | 43,239.71 | -7,992.74 | SP dominates |
| Excess cancer costs | 155,692.66 | 148,882.25 | 6,810.42 | 33,736.39 |
| All healthcare costs | 184,781.16 | 174,395.68 | 10,385.48 | 51,446.01 |
| **Colorectal** | | | | |
| *QALY gained* | 5.16 | 4.53 | 0.63 | |
| No future cost | 35,246.97 | 43,239.71 | -7,992.74 | SP dominates |
| Excess cancer costs | 135,789.09 | 131,424.89 | 4,364.20 | 6,881.97 |
| All healthcare costs | 168,430.58 | 160,054.63 | 8,375.95 | 13,208.14 |
| **Breast** | | | | |
| *QALY gained* | 7.32 | 6.42 | 0.90 | |
| No future cost | 35,246.97 | 43,239.71 | -7,992.74 | SP dominates |
| Excess cancer costs | 107,793.67 | 106,870.19 | 923.48 | 1,026.91 |
| All healthcare costs | 142,286.13 | 137,123.42 | 5,162.71 | 5,740.98 |
| **Melanoma** | | | | |
| *QALY gained* | 7.30 | 6.40 | 0.90 | |
| No future cost | 35,246.97 | 43,239.71 | -7,992.74 | SP dominates |
| Excess cancer costs | 60,078.58 | 65,019.44 | -4,940.86 | SP dominates |
| All healthcare costs | 94,858.41 | 95,524.72 | -666.31 | SP dominates |
| **Lung** | | | | |
| *QALY gained* | 0.91 | 0.80 | 0.11 | |
| No future cost | 35,246.97 | 43,239.71 | -7,992.74 | SP dominates |
| Excess cancer costs | 96,683.05 | 97,125.10 | -442.05 | SP dominates |
| All healthcare costs | 121,999.12 | 125,042.54 | 3,043.42 | 27,183.91 |
| **Prostate** | | | | |
| *QALY gained* | 7.09 | 6.22 | 0.87 | |
| No future cost | 35,246.97 | 43,239.71 | -7,992.74 | SP dominates |
| Excess cancer costs | 105,677.47 | 105,014.08 | 663.39 | 760.90 |
| All healthcare costs | 140,419.52 | 135,486.23 | 4,933.30 | 5,658.46 |

| | | | | |
|---|---|---|---|---|
| **Pancreas** | | | | |
| *QALY gained* | 0.47 | 0.41 | 0.06 | |
| No future cost | 35,246.97 | 43,239.71 | -7,992.74 | SP dominates |
| Excess cancer costs | 88,848.65 | 90,253.58 | -1,404.93 | SP dominates |
| All healthcare costs | 114,722.61 | 116,746.41 | 2,023.80 | 35,410.03 |
| **Myeloma** | | | | |
| *QALY gained* | 2.87 | 2.52 | 0.35 | |
| No future cost | 35,246.97 | 43,239.71 | -7,992.74 | SP dominates |
| Excess cancer costs | 193,635.18 | 182,161.51 | 11,473.67 | 32,543.01 |
| All healthcare costs | 224,008.23 | 208,801.61 | 15,206.62 | 43,130.84 |
| **Brain** | | | | |
| *QALY gained* | 1.43 | 1.25 | 0.18 | |
| No future cost | 35,246.97 | 43,239.71 | -7,992.74 | SP dominates |
| Excess cancer costs | 136,873.62 | 132,376.12 | 4,497.49 | 25,577.98 |
| All healthcare costs | 165,762.72 | 157,714.66 | 8,048.06 | 45,770.60 |
| **Oesophagus** | | | | |
| *QALY gained* | 1.28 | 1.12 | 0.16 | |
| No future cost | 35,246.97 | 43,239.71 | -7,992.74 | SP dominates |
| Excess cancer costs | 120,682.44 | 118,174.89 | 2,507.55 | 15,996.84 |
| All healthcare costs | 149,412.04 | 143,373.53 | 6,038.51 | 38,522.51 |
| **Hodgkin's lymphoma** | | | | |
| *QALY gained* | 6.72 | 5.89 | 0.83 | |
| No future cost | 35,246.97 | 43,239.71 | -7,992.74 | SP dominates |
| Excess cancer costs | 142,181.30 | 137,031.47 | 5,149.83 | 6,237.08 |
| All healthcare costs | 176,384.07 | 167,030.62 | 9,353.46 | 11,328.19 |
| **Bladder** | | | | |
| *QALY gained* | 3.49 | 3.06 | 0.43 | |
| No future cost | 35,246.97 | 43,239.71 | -7,992.74 | SP dominates |
| Excess cancer costs | 147,408.66 | 141,616.37 | 5,792.28 | 13,517.61 |
| All healthcare costs | 178,374.72 | 168,776.60 | 9,598.11 | 22,399.37 |

*ICER* incremental cost-effectiveness ratio, *QALY* quality-adjusted life-year, *SP* sepsis pathway

Figure S2.2: Net monetary benefit (NMB) for different costing scenarios across cancer types.

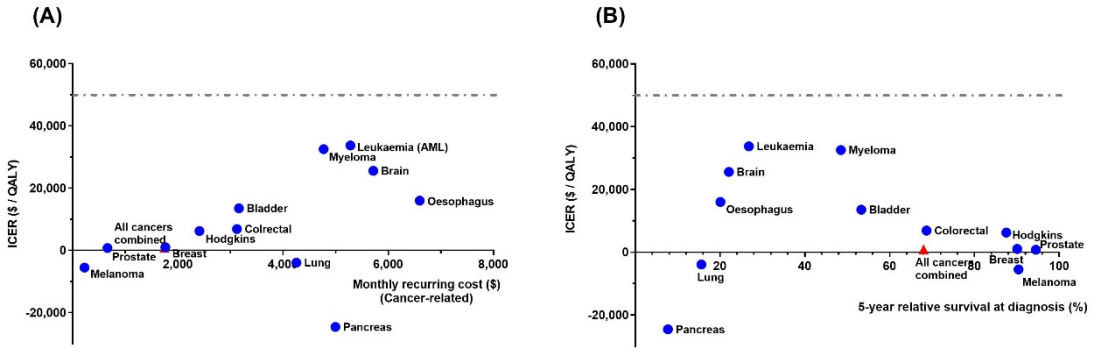
NMB calculated using NMB = ΔE λ - ΔC where ΔE is the QALYs gained, λ is the willingness-to-pay at $50,000 and ΔC is the incremental cost.




*QALY* quality-adjusted life-year

Figure S2.3: Correlations of cost-effectiveness (cancer costs only scenario) by cancer types, with (A) lifetime recurring medical costs and (B) 5-year relative survival.

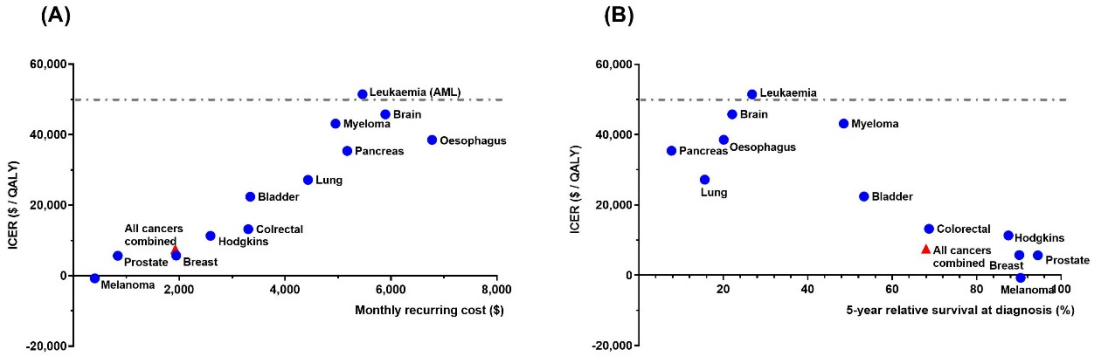
Dotted line indicating a willingness-to-pay threshold of $50,000 per QALY. All cancers combined = base-case as indicated by the red triangle.




*QALY* quality-adjusted life-year

Figure S2.4: Correlations of cost-effectiveness (all healthcare costs scenario) by cancer types, with (A) lifetime recurring medical costs and (B) 5-year relative survival.

Dotted line indicating a willingness-to-pay threshold of $50,000 per QALY. All cancers combined = base-case as indicated by the red triangle.




*QALY* quality-adjusted life-year

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# Chapter 3 : National cost savings from an ambulatory program for low-risk febrile neutropenia patients in Australia

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## 3.1. Abstract


### Objective

The management of low-risk febrile neutropenia (FN) patients through ambulatory programs has demonstrated comparative safety and effectiveness to inpatient strategies. However, there is limited evidence of benefits of changing practice particularly on a national scale. The aim of the study was to estimate costs and benefits of the program over a 10-year time horizon.

### Methods

A comparative cost analysis from health system perspective comparing costs and length of stay (LOS) of patients enrolled in an ambulatory program to a historical cohort who did not receive the program. Generalised linear models were used for analysis and bootstrapped to account for uncertainty. National data of identified FN admissions were used to inform future projections, with varying proportions of low-risk patients and eligibility for ambulatory program.

### Results

The overall LOS for patients in ambulatory cohort was 1.9 days (95% CI,1.0-2.8) shorter, a 50% reduction in inpatient bed-day. Whilst patients in ambulatory cohort incurred additional costs due to care received outside hospital ($828.03 (SD,124.3)), the mean total cost incurred remained substantially lower compared to historical cohort ($2,979 (95%CI,772-5,391). On a national scale, this could translate into $62.7 million in costs-averted and 41,347 bed-days saved over ten years if the low-risk prediction rate and eligibility for ambulatory programs remained at currently observed rate.

### Conclusions

The wider implementation of a safe and effective ambulatory program to manage low-risk FN patients can result in significant return-on-investment for the healthcare system by eliminating avoidable costs due to unnecessary lengthy hospital admissions.

## 3.2. Key question summary

1. What is known about the topic?

There is strong evidence demonstrating outpatient treatment of low-risk FN patients to be an effective and cost-effective strategy compared to continued inpatient hospitalisation.

2. What does this paper add?

This study demonstrates the sustainability of the ambulatory program in ensuring cost benefits and inpatient bed through real-life implementation data. It also provides evidence of the substantial cost and bed days potentially averted when the cost savings and difference in length of stay are estimated on a national scale over a 10-year time horizon.

3. What are the implications for practitioners?

The management of low-risk FN patients through ambulatory or outpatient programs is safe and effective approach. There is strong evidence demonstrating the likely cost savings and considerable bed-days saved which can be reallocated to meet other medical demands.

## 3.3. Introduction

Febrile neutropenia (FN) is a common and potentially life-threatening complication for cancer patients undergoing chemotherapy which necessitates prompt treatment. Historically, this involved in-hospital management with broad spectrum intravenous (IV) antibiotics [1]. However, it is recognised that FN patients are a heterogenous population, where only a small proportion of FN patients are at high risk of complications or death [2]. Therefore, not all FN patients necessarily require inpatient care The Multinational Association of Supportive Care in Cancer (MASCC) risk index [2] is validated clinical tool that has been successfully used to identify FN patients with a low risk of complications. Clinical studies have shown that low-risk FN patients can be successfully treated with oral instead of IV antibiotics without compromising patient's safety [3, 4]. The management of these patients through ambulatory or outpatient programs has also demonstrated comparative safety and effectiveness compared with inpatient management strategies [5-7]. In addition to having a shorter length of hospital stay, the benefits of

outpatient care include improved health-related quality of life [8, 9], reduced risk of hospital-acquired infections and lower costs [10-13].

There is consistent evidence demonstrating outpatient treatment of low-risk FN patients to be a cost-effective strategy compared to continued inpatient hospitalisation [12, 14]. Whilst the advantages of ambulatory programs are evident, there remain inconsistencies in the practices in managing these patients [15-17]. Patient willingness, suitability of home environment, and/or prevailing medical condition have been identified as possible reasons for the low uptake [16, 18]. Clinician acceptance has also been recognised as a potential barrier [19]. Although much is known about the potential barriers that could explain the slow uptake, there is limited evidence of the potential benefits of changing practice particularly on a national scale. A better understanding of the implications of different management strategies are increasingly important to inform healthcare resource allocation decisions in a budget constrained environment.

This study builds upon an existing evaluation of an ambulatory program implemented at the Peter MacCallum Cancer Centre (PMCC), a tertiary cancer centre in Australia. The PMCC ambulatory program for FN patients is a nurse-led model of care with MASCC risk assessment performed for patients presenting with FN. Patients were recruited into the program following 3 stages of evaluation: (1) risk stratification using the MASCC risk index (low risk defined as score $\geq 21$), (2) suitability for switching from intravenous to oral antibiotics and (3) suitability for early discharge, after at least one dose of IV antibiotics and 24-hour observation. Patients in the ambulatory program are discharged with a course of oral antibiotics, followed up by ambulatory care nurses and reviewed by an infectious disease physician within one week post-discharge. Figure 3.1 shows a representation of the evaluation process. In its first year of implementation, the early discharge of eligible low-risk FN patients reduced inpatient length of stay from 4.0 to 1.1 days, resulting in 72.5 inpatient bed days saved across 25 patients and this translated into a net cost reduction of $71,895 after accounting for implementation and operational costs. 4 out of 25 patients (16%) required readmission and no deaths were reported. A detailed description of the program including its implementation, safety and cost in the first year has been reported by Teh et al. [11].

The aims of this study are to demonstrate the sustainability of the program in ensuring cost benefits, and to model the potential cost averted and inpatient bed days saved over

10 years if the program is rolled out nationwide. Information from this study will assist decision making for clinicians and policymakers by providing estimates of the economic impact of introducing ambulatory care programs as standard of care across Australia to manage low-risk FN patients.

## 3.4. Methods

*Cost analysis*

A cost analysis from the healthcare perspective was performed comparing patient's costs and length of hospital stay. Patients were prospectively enrolled in the ambulatory program between March 2014 and February 2017. These patients were compared to a historical cohort of retrospectively identified consecutive FN patients from February to July 2011 who were assessed to be low-risk using the MASCC risk index, fulfilled eligibility criteria to switch to oral antibiotics and be discharged into a theoretical ambulatory program [11]. These patients were identified from medical records. Patients in the historical cohort were subjected to the standard of care prior to the implementation of the ambulatory program which was hospital admission of all FN patients with a course of IV antibiotics until resolution of fever and neutropenia. Inpatient admission costs were calculated based on each patient's Australian Refined Diagnosis Related Group (AR-DRG) [20] and length of stay.

Ambulatory care costs were estimated based on the components of resource used. This included staff time spent on home nursing visits, follow-up phone call by nurse co-ordinator, consultation to develop appropriate follow-up protocol by infectious disease physician, physician and nurse time required to review the patient in a specialist clinic, two sets of blood tests, and patient discharge information pack. Patients in the ambulatory cohort were also discharged with a prescription for a one-week standard course of antibiotics. These patients were followed-up for the duration of the ambulatory program (7 days) and re-admitted patients were treated with IV antibiotics and their length of stay recorded.

Generalised linear models (GLM) were used to analyse cost and length of stay. For costs, distribution family of Gamma was determined using the Modified Parks Test and its log link determined using Pearson correlation, Pregibon and Modified Homer & Lemeshow

tests and for length of stay, Poisson distribution with log link was used [21, 22]. Age, sex and cancer types were included in the models to control for possible baseline imbalances. The choice of models was also based on Akaike Information Criterion (AIC). To account for sampling uncertainty, sensitivity analysis was undertaken using bootstrapping with 1000 replications using the recycled predictions method [22].

*Projected cost and bed days averted*

National data of all FN hospital admissions among cancer patients aged 15 and above between 2009 to 2014 were obtained from the Independent Hospital Pricing Authority (IHPA), a national government agency responsible for collecting and reporting hospital use and expenditure data. The selection criteria for FN patients as described by Lingaratnam et al. [23] was used. The data captured all FN inpatient episodes, irrespective of risk types and were used to inform on future trends for hospital presentation with FN.

The proportion of low-risk FN patients varies internationally. A review of the 10-year of MASCC index reported low-risk prediction rates in the range of 70-75% across several international studies [13] whereas Australian studies evaluating early discharge strategies indicated a 56-65% low-risk prediction with up to 41% of these episodes subsequently converted to ambulatory care [15, 24]. Inpatient bed days and cost averted over 10 years were therefore calculated using bootstrapped results with proportions of low-risk (LR) ranging from 50-80% and 30-60% eligibility for ambulatory program (EA).

All costs are expressed in 2017 Australian dollars adjusted using the Consumer Price Index from the Australian Bureau of Statistics [25] and discounted at 5% annually as per Australian recommendations [26]. All data were analysed using STATA statistical software (version 14.0, Texas, USA).

*Ethics approval*

The study was approved by the Peter MacCallum Cancer Centre Ethics Committee.

## 3.5. Results

Between March 2014 and February 2017, 50 low-risk FN patients were enrolled into the ambulatory program (25 patients in first year, 25 patients in years 2 and 3). The baseline characteristics of patients in the ambulatory and historical cohorts are described in Table

3.1. Both cohorts were well balanced except for gender where there was a lower proportion of males in the ambulatory program compared to the historical cohort (p=0.016). Of the 50 patients in the ambulatory cohort, 5 hospital re-admissions (10%) were recorded and no deaths reported. Time to re-admission was approximately 1.4 days (SD, 0.7).

*Cost analysis*

A breakdown of the components, program protocol, quantity or time required as well as costs of resource used for the ambulatory program is provided in Table 3.2. The mean cost of providing ambulatory care outside of hospital over a one-week period was $828.03, (SD, 124.3) per patient.

A comparison of length of stay and total cost between the two cohorts is presented in Table 3.3. Patients in the ambulatory cohort had a significantly shorter length of initial hospital admission of 2.1 days (95% CI, 1.3-2.9; p<0.001). 4 patients were re-admitted to the same hospital and their average length of stay ranged from 0.7 to 5.6 days. Overall, patients in the ambulatory cohort had a total length of hospital stay of 1.9 days (SD, 1.7). This was 1.9 days (95% CI, 1.0-2.8; p<0.001) shorter than patients in the historical cohort indicating a 50% reduction in inpatient bed utilisation as a result of the early discharge protocol. Mean total cost incurred by the ambulatory cohort remained lower than the historical cohort. The cost difference between the two cohorts was $2,839 (95% CI, 949-4730; p=0.004).

Bootstrapped results from both GLM regressions are presented in Table 3.3. These estimates closely reflect those from the direct comparison analysis. However, the bootstrapped results for total cost difference yielded a wider 95% confidence interval.

*National projections*

Data obtained from IHPA showed an average increase of FN hospitalisation episodes by approximately 4% annually, increasing from 7,350 in 2010 to 8,708 in 2015. Assuming this increase remains constant over the next 10 years, it is estimated that by 2020 and 2025 the number of FN episodes would increase to 10,318 and 12,012, respectively. Figure 3.2 shows the actual and projected number of hospitalisation episodes of FN in Australia.

The estimated cumulative bed days and cost averted over 10 years would vary depending on the low-risk prediction rates as well as proportion of low-risk patients eligible for the ambulatory program. Figure 3.3 reflects the ranges of cost-averted and bed days saved over 10 years if the ambulatory program were to continue to produce a cost saving of $2,979 per patient. Based on the best available Australian evidence [15, 24], a scenario reflecting a LR prediction rate of 60% and 40% EA, the estimated discounted total cost averted over 10 years would be $62.7 million (95%CI, 16.2-113.4). This cost is associated with a cumulative total of 41,347 (95%CI, 21137-62130) bed days saved.

## 3.6. Discussion

The ambulatory program to manage low-risk FN patients in an outpatient setting at PMCC represents a real-world implementation of the program with proven effectiveness and has demonstrated sustained cost-benefit to the health system since it was implemented in 2014. The safety of patients was not compromised with an overall re-admission rate of 10% and no deaths reported. On average, the ambulatory program cost $828 per patient for care provided in their homes and follow-up consultations. Despite this, the mean total cost of the ambulatory cohort was $2,979 (per patient) lower compared to care delivered to the historical cohort, even after taking into account re-admission costs. This cost saving was mainly driven by the shorter length of hospital stay due to early discharge.

In Australia, the cost of managing FN is considerable. In 2015, it was estimated that there were 8,708 inpatient episodes of FN among cancer patients, totalling an estimated $251 million (data provided from IHPA). This estimate captures all FN episodes irrespective of risk type and equated to $28,801 per episode with an average length of stay of 14.8 days. This is similarly observed in the US, where a large study conducted in 2010 assessing the economic burden of FN-related hospitalisation among cancer patients showed a mean hospitalisation cost of US$18,880 [31]. The lower cost observed in the US study is likely due to the inclusion of less severe cancer groups (leukaemia and myeloma were excluded) hence the shorter length of stay. Nonetheless, the mean cost per day of hospitalisations were comparable. It is evident that the economic burden of hospitalisations related to FN is significant and is not unique to Australia. It is also widely recognised that a large proportion of FN patients are of low-risk [13-15], therefore there is scope to reduce the national average length of stay of FN patients and alleviate the cost

burden through the implementation of effective and safe strategies such as early discharge programs for low-risk FN patients.

For the first time, this study has demonstrated the substantial cost and bed days potentially averted when the cost savings and difference in length of stay are estimated at a national scale. Most cost studies have primarily focused on the delivery of ambulatory care and its comparison to an existing standard of care (inpatient strategy). The strengths of the present study include real-life implementation data and the use of national statistics to inform future projections. The estimated total cost and bed days averted over 10 years is $62.7million and 41,347 respectively if the low-risk prediction rate and proportion converted to ambulatory programs remained at the current rate as indicated by local studies. Despite the wide 95% confidence intervals, the ambulatory program remains a cheaper and more effective option compared to inpatient management of these low-risk patients and is likely to translate well to other centres nationally.

This cost analysis adds to the growing literature that have demonstrated outpatient treatment strategies to manage low-risk FN patients to be a cost-effective approach compared to inpatient management. Although this study was conducted in the Australian setting, similar early discharge programs have been implemented elsewhere therefore these results could be applied internationally. In this study, a mean reduction of 2 inpatient days and potential cost-savings of $2,979 per patient (40% reduction in cost) were observed. A randomised-controlled single centre study conducted in the UK has also reported a 2-inpatient day reduction and outpatient treatment was 44% cheaper [14], while a US study reported a larger difference of 4.4 days and a 49% cost reduction [8]. Potential cost-savings were estimated to be up to 55% in an economic modelling analysis in the Canadian setting [12]. As such, the potential cumulative bed days and cost averted could possibly be larger in these countries.

It is acknowledged that such ambulatory programs would require significant initial investments to ensure successful implementation, which include institutional support for the required infrastructure, a committed multi-disciplinary team and well-defined protocols to manage patient monitoring and follow-up [32]. Furthermore, funding to ensure sustainability of a program often also requires sound evidence and justification. The projected cost-savings demonstrated at a national scale in this study provides a strong case for institutions and healthcare policy makers in making resource allocation decisions

for the ambulatory program. Additionally, efficiencies in running the program could also translate into higher adoption rates thus greater cumulative cost and bed-days saved; for example, a 10% increase in the proportion eligible for the ambulatory program above the current 40% would result in an additional $15.7 million and 10,337 bed-days saved (Figure 3.3).

It is recognised that the study has several limitations. The small sample size of this study is an important limitation subject to biases and inadequate statistical power. Although the estimated cost and bed-day averted are consistent with findings in the literature [8, 12, 14, 15], it is acknowledged that there is a large amount of uncertainty around the extrapolated estimates based on small sample size. As such, the wide confidence intervals should be taken into account when interpreting the results. It is also acknowledged that the use of a historical cohort can have an impact on the economic analysis as changes in practice can change over time affecting resource use. However, hospitalisation costs were calculated based on each patient's AR-DRG and length of stay hence likely to overcome this issue. Although there was a disproportionate distribution by gender, results from the regression analysis (GLM) did not indicate any significant differences between males and females on the cost and length of stay outcomes. There was a drop in the number of patients recruited for the ambulatory program in the second and third year (n=25) compared to first (n=25). While this can be largely ascribed to the discontinuity in funding a dedicated nurse to help with patient recruitment after the first year, other factors such as patient/physician willingness, medical concerns and psychosocial factors could potentially also have an influence [15, 16, 24]. In light of the substantial potential savings in terms of costs and bed days demonstrated in this study, considerations to allocate resources to implement and support the continuity of an ambulatory program to manage low-risk FN patients is warranted.

## 3.7. Conclusions

The economic burden of hospitalisations related to FN is significant. The management of low-risk patients through ambulatory or outpatient programs is a safe and effective approach. Further, there have been consistent evidence to demonstrate the likely cost savings. A national roll-out of an ambulatory program across Australia could result in up to $62.7 million cost-averted and 41,347 bed days saved over ten years if the low-risk

prediction rate and proportion converted to ambulatory programs remained at the current rate.

## 3.8. Tables and figures

Table 3.1: Characteristics of patients across the two cohorts

| **Patient characteristics** | **Ambulatory cohort n=50** | **Historical cohort n=27** | **p-value** |
|---|---|---|---|
| Mean age (SD) | 49.2 (15.7) | 50.1 (18.2) | 0.8185 |
| Male (%) | 19 (38.0) | 18 (66.7) | 0.016 |
| Malignancy type (%) | | | 0.982 |
| Haematological | 11 (22.0) | 6 (22.2) | |
| Solid organ | 39 (78.0) | 21 (77.8) | |

Table 3.2: Components and associated costs of ambulatory program

| Components | Timing of provision | Quantity/Time required | Unit cost | Mean utilisation [h] | Source |
|---|---|---|---|---|---|
| Discharge information pack | On discharge | 1 pack per patient | $3.75 /patient [a] | 1 pack | |
| Antibiotic prescription | On discharge | 1-week supply of medication | $38.65 /prescription [b] | 1 prescription | [27] |
| Pathology (blood tests) | On discharge and home visit 1 (Day 1) | 2 sets as per protocol | $69.30 /set [c] | 2 sets | [28] |
| Home nursing service | Home visit 1 & 2 (Day 1 and 2) | 2 x 45-minute reviews | $168.30 /45-min review [d] | 1.98 reviews | |
| Infectious Disease physician | Day 3 | 30-minute protocol development and phone advice | $188.50 /hour [e] | 0.45 hours | [29] |
| Nurse co-ordinator | Day 3 | 2 hours: Co-ordinate program and patient follow-up via phone | $57.29 /hour [f] | 1.8 hours | [30] |
| Infectious Disease physician | Between Day 5 and 7 | 45-minute outpatient clinic | $188.50 /hour [e] | 0.68 hours | [29] |
| Hospital re-admissions | | Based on patient-level data | $1,863.94 /day [g] | 2.11 days | |

[a] Calculated based on market price
[b] Prescription for amoxicillin-clavulanic acid (875/125mg BD) and ciprofloxacin (750mg BD)
[c] Medicare Benefit Scheme (MBS) item numbers 65070 & 66512
[d] Based on hospital administrative records
[e] Based on hourly rates of a Year 2 specialist + 30% overhead cost
[f] Based on hourly rates of a Registered nurse grade 4A Year 2 +30% overhead cost
[g] Based on mean inpatient cost of ambulatory cohort
[h] Average resource used per patient

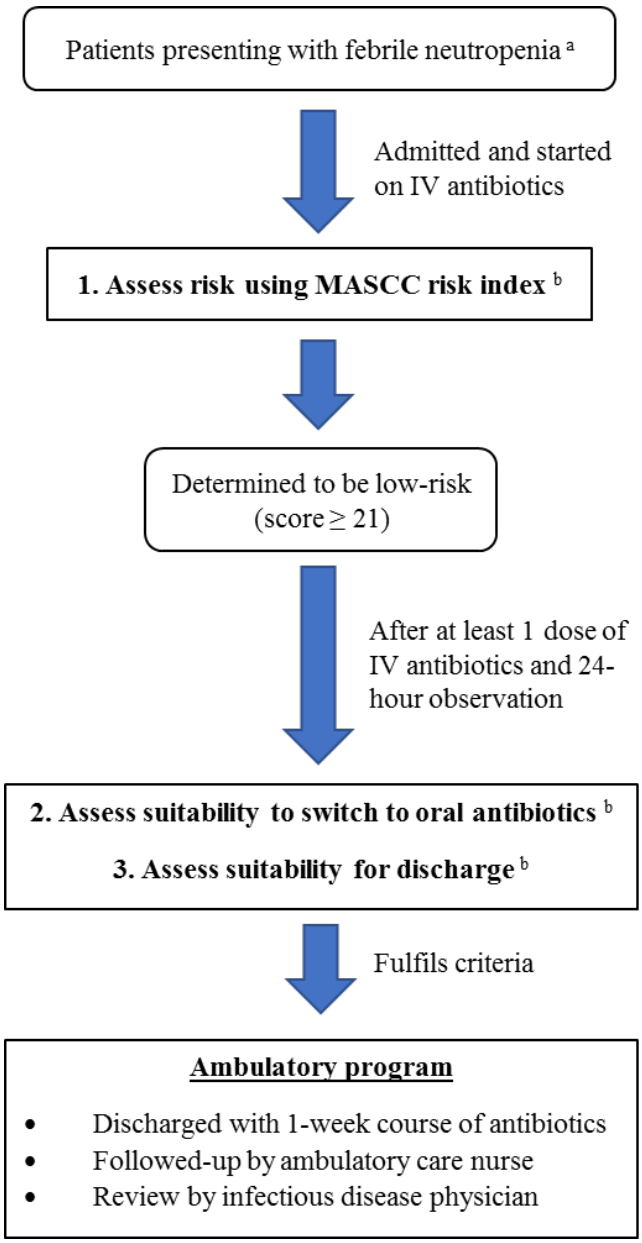
Table 3.3: Comparison of length of stay and total cost between cohorts

| | **Ambulatory cohort Mean (SD)** n=50 | **Historical cohort Mean (SD)** n=27 | **Difference (95% CI)** | **p-value** |
|---|---|---|---|---|
| **Length of stay (days)** | | | | |
| Initial hospital admission | 1.7 (1.5) | 3.8 (2.1) | 2.1 (1.3-2.9) | <0.001 |
| Re-admission [a] | 2.1 (2.3) | - | | |
| Total length of stay | 1.9 (1.7) | 3.8 (2.1) | 1.9 (1.0-2.8) | <0.001 |
| Bootstrapped (SE) [b] | 1.92 (0.23) | 3.89 (0.43) | 1.96 (1.00-2.95) | |
| **Cost ($)** | | | | |
| Initial hospital admission | 3293.3 (3106.1) | 7354.0 (4907.9) | 4060.7 (2239. 7-5881.7) | <0.001 |
| Ambulatory care cost | 828.0 (124.3) | - | | |
| Re-admission | 3933.3 (3782.3) | - | | |
| Total cost | 4514.7 (3374.8) | 7354.0 (4906.9) | 2839.3 (948.9-4729.7) | 0.004 |
| Bootstrapped (SE) [b] | 4493.65 (463.57) | 7472.58 (1034.17) | 2978.93 (771.85-5390.96) | |

[a] Based on 4 patient re-admissions. One patient was re-admitted to a different hospital therefore length of stay was undetermined. Missing data was imputed with mean length of re-admission

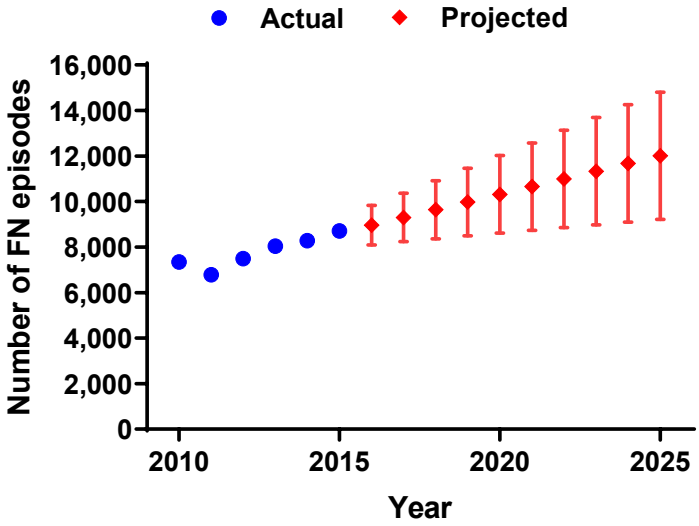
[b] Results from GLM regressions, bootstrapping with 1000 replications

Figure 3.1: Diagrammatic representation of the evaluation process for ambulatory program eligibility




[a] Febrile neutropenia defined as fever of ≥ 38.3 °C or ≥ 38.0 °C on two occasions and an absolute neutrophil count of < 1.0 × 109 cells/L
[b] Assessment using MASCC risk assessment and eligibility screening tool published in Teh et al. [11]

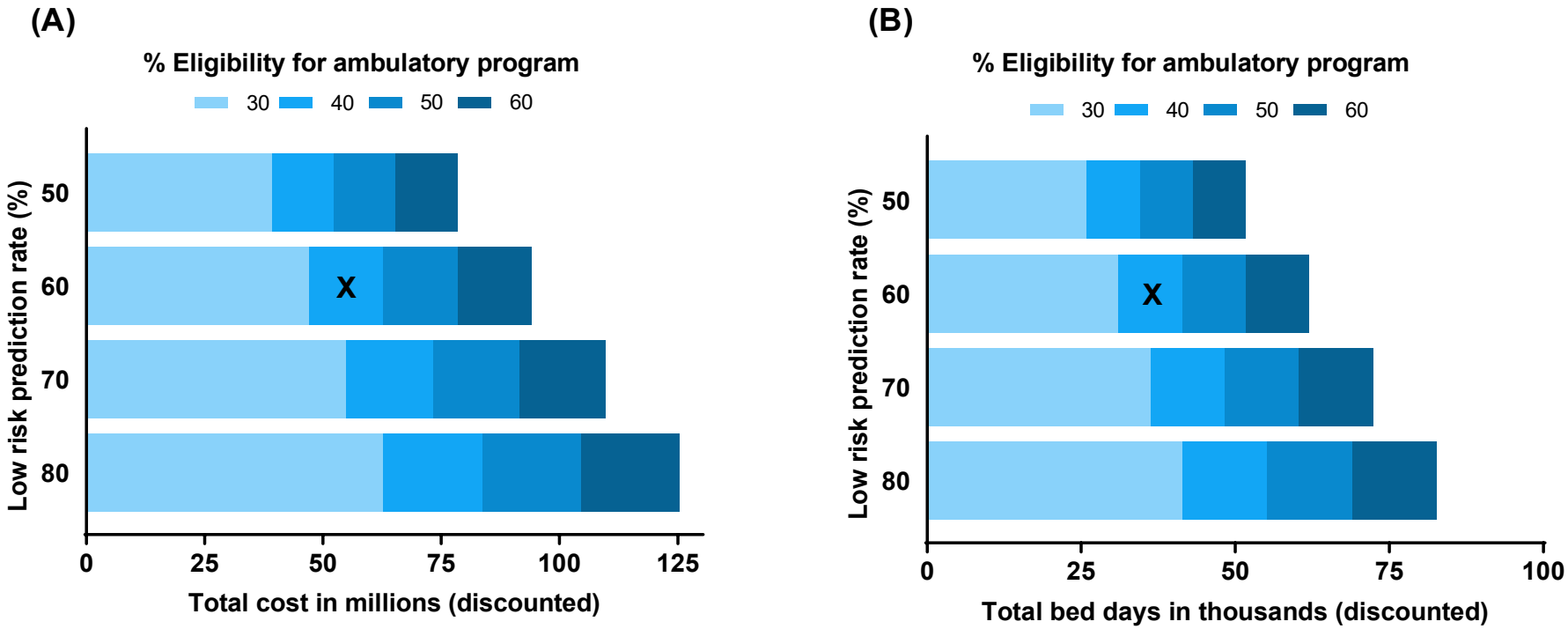
Figure 3.2: Actual and projected number of hospitalisation episodes of FN in Australia




*FN* febrile neutropenia

Figure 3.3: Estimated cumulative (A) cost-averted and (B) bed days saved over 10 years by % identified as low-risk (LR) FN and by % eligible for ambulatory program (EA).

Marker 'X' represents estimates based on best available Australian evidence.



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# SECTION II : Modelling Long-Term Outcomes

| | Chapter / Study | Methods of analysis | Key contributions: Methodology | Key contributions: Clinical and policy |
|---|---|---|---|---|
| | **I : EXTRAPOLATION OF COSTS** | | | |
| 2 | Incorporating future medical costs: Impact on CEA | + Cost-utility analysis<br>+ Decision tree analysis<br>+ Markov model | Demonstrate feasibility of appropriately including future medical costs | Provide evidence of cost-effectiveness of sepsis protocol and highlight potential differences in cost-effectiveness results |
| 3 | National cost savings from an ambulatory program for LR FN patients | + Cost-effectiveness analysis<br>+ GLM regression<br>+ Cost projections | Undertake evaluation beyond cost-effectiveness analysis | Offer strong evidence for national implementation of a cost-effective program |
| | **II: MODELLING & TRANSLATING LONG-TERM OUTCOMES** | | | |
| 4 | Using PROMs to guide patient-centred care and optimise outcomes | + Latent class growth analysis<br>+ Multinomial logistic regression | Employ novel application of technique to uncover heterogeneity | Show important heterogeneity in longer-term outcomes and variations in the value of surgery for different patient groups |
| 5 | Co-morbidities and sex differences in long-term QoL outcomes | + Multi-level modelling | Demonstrate method to assess patterns of change of repeated QoL measures over time and generate utility values for cost-effectiveness analyses | Highlight notable differences in long-term QoL patterns among specific patient subgroups (diabetes, females) and need for tailored post-surgery management |
| 6 | Exploring the impact of QoL on survival | + Survival analysis<br>+ Life table methods for life expectancy | Advance understanding of influence and consequence of correlation between QoL and mortality when extrapolating survival outcomes | Quantify impact of unaccounted correlation and heterogeneity on cost-effectiveness results |
| | **III : GENERATING REAL-WORLD EVIDENCE** | | | |
| 7 | Economic burden of sepsis in cancer patients | + Matching (case-control)<br>+ Panel data manipulation<br>+ Survival-adjusted estimation of costs | Generate short- and long-term cost estimates | Provide key insights on burden of sepsis and useful inputs for future economic evaluations and resource allocation decisions |

# Chapter 4 : Patient-reported outcome measures (PROMs): Can they be used to guide patient-centered care and optimise outcomes in total knee replacement?

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## 4.1. Abstract


### Purpose

As patient-reported outcome measures (PROMs) are increasingly integrated into clinical practice, there is a need to translate collected data into valuable information to guide and improve the quality and value of patient care. The purpose of this study was to investigate health-related quality-of-life (QoL) trajectories in the five years following total knee replacement (TKR) and the patient characteristics associated with these trajectories. The feasibility of translating QoL trajectories into valuable information for guiding patient-centered care was also explored.

### Methods

Data on patients who underwent TKR between 2006 and 2011 from a single-institution registry were extracted including patient-reported QoL (captured using the Short Form Survey (SF-12) instrument) up to 5 years post-surgery. QoL trajectories were modelled using latent class growth analysis. Quality-adjusted life-years (QALYs) were calculated to illustrate longer term health benefit. Multinomial logistic regression analyses were performed to examine the association between trajectory groups and baseline patient characteristics.

### Results

After exclusions, 1,553 patients out of 1,892 were included in the analysis. Six unique QoL trajectories were identified; with differing levels at baseline and improvement patterns post-surgery. Only 18.4% of patients were identified to be in the most positive QoL trajectory (low baseline, large sustainable improvement after surgery) associated with the greatest gain in QALY. These patients were likely to be younger, have no co-morbidities and report greater pain at pre-surgery than most in other QoL trajectories.

### Conclusions

Our findings demonstrate the importance of underlying heterogeneity in QoL trajectories, resulting in variable QALY gains. There is scope in translating routinely collected PROMs to improve shared decision making allowing for more patient engagement.

However, further research is required to identify suitable approaches of its implementation into practice to guide clinical care and maximize patient outcomes.

## 4.2. Key points for decision makers

- There is strong evidence indicating important heterogeneity in QoL trajectories in TKR patients indicating not all patients benefit from the surgical procedure in the same way.

- Knowledge of the combination of characteristics that predisposes a patient to trajectories with poor health gains can be useful in anticipating possible outcomes and mitigating such risks.

- Associating patient-reported outcomes such as QoL to patient characteristics can facilitate delivery of individualized health care as it allows patient engagement in shared decision making to help optimize outcomes.

## 4.3. Introduction

The value of patient-reported outcomes measures (PROMs) to evaluate outcomes after surgery is gaining recognition and the need to integrate these into clinical practice is becoming increasingly important [1-6]. For surgical interventions such as total knee replacement (TKR), patient-reported outcomes generally include pain, function and health-related quality-of-life (QoL). Patients typically experience a significant improvement in these outcomes within the first year following surgery and the effects tend to plateau in subsequent years [7-11]. Although this pattern of recovery is well-known, it is unclear if it can be universally applied because up to 20% of TKR patients do not gain clinically meaningful improvement following surgery [12, 13]. Recent research on longer-term functional outcomes identified a subgroup with delayed functional gains [14] which indicates that longer-term recovery patterns, and consequently effectiveness gained from surgery, differ considerably across patients. Therefore, it is important to better understand the longer-term implications of TKR, particularly in patients who experience poorer outcomes and whether these patients can be identified early to optimize their outcomes.

There is growing evidence that QoL is an important predictor of outcomes such as complications, hospitalisation and mortality [15-18]. This suggests that a better understanding of patients' QoL trajectories can reveal important information on disease progression and outcomes. QoL PROMs have the additional benefit of capturing the necessary information for cost-effectiveness analysis allowing decision makers to compare the value of health interventions and prioritize resource allocation. Further, associating patterns of QoL with patient characteristics may help identify groups for whom TKR may be of higher or lower value. This can help facilitate the rational deployment of TKR to those who stand to benefit the most while targeting others for more appropriate alternative interventions or management strategies. This is important as healthcare systems are transitioning from volume- to value-based health care as a means of improving sustainability of the healthcare system whilst also optimizing patient outcomes and experience [19, 20]. This is particularly relevant for surgical interventions such as TKR, which are performed in high volumes annually and are associated with considerable health care costs, amounting to $11.8 billion in 2014 in the US alone [21].

In this study, we aimed to identify unique QoL trajectory groups for TKR patients from routinely collected PROMs, demonstrate the distinct variations in health gains and explore the individual characteristics related to group membership, using a rich data source with 5 years QoL data. By quantifying health gains using quality-adjusted life years (QALYs), a commonly used outcome in economic evaluations such as cost-effectiveness analyses, we demonstrate the feasibility of how QoL trajectories can be translated into valuable information for guiding patient-centered care. This will also provide a better understanding of the value of surgery across different trajectory groups.

## 4.4. Material and Methods

### 4.4.1. Data

The St. Vincent's Melbourne Arthroplasty Outcomes (SMART) Registry prospectively captures clinical and patient-reported outcomes in all patients undergoing elective hip and knee replacement at the study institution in Melbourne, Australia. The study institution is a tertiary referral centre for joint replacement surgeries and receives state-wide referrals. Registry data collection started in 1998 and to date, has recorded over 10,000 procedures with approximately 800 registered annually [11, 22, 23]. This dataset is ideal to answer

the research question regarding longer term trajectories as at least 5 years of annual follow-up data are available. This included patients who had TKR between January 1, 2006 and December 31, 2011. Individuals were excluded if they had missing baseline QoL score, no QoL scores at all subsequent time points, underwent early revision or died within 2 years of surgery. Our analysis included patients with at least two QoL scores. For individuals that underwent bilateral knee surgery during the study period, only the most recent TKR was included in the analysis. Sensitivity analyses were conducted to assess the effect of our exclusion criteria.

Baseline data on patients were prospectively collected and included baseline socio-demographic and patient characteristics such as age, gender, body mass index (BMI), smoking status, co-morbidity measures such as Charlson Co-morbidity Index (CCI) and American Society of Anesthesiologist (ASA) Physical Status Classification. Cultural and linguistic diversity was measured via the need for an interpreter, socioeconomic status was measured via the Socio-Economic Index for Areas (SEIFA) [24] and geographical accessibility index (ARIA+) [25] reflected rurality. Clinical variables included bilateral knee surgery, Kellgren-Lawrence scale [26] describing radiographic severity of osteoarthritis and the Knee Society Scores (KSS) [27] subscales for pain and function.

#### 4.4.2. Quality-of-life measurements

Patients completed the 12-item Short Form Survey (SF-12) prior to surgery and annually post-operatively. Baseline and annual QoL scores up to 5 years post-surgery were considered for analysis. SF-12 responses were transformed into utility values using a published algorithm [28]. A utility value is a general index of wellbeing used for economic evaluation where 1 is equivalent to ‘full health’ and 0 is equivalent to being ‘dead’ with scoring algorithms based on public preferences for health states.

#### 4.4.3. Statistical analysis

*Latent class trajectory analysis*

Latent class growth analysis (LCGA) was used to identify subgroups of patients according to their trajectory of QoL (described using utility values) pre-surgery and up to 5 years following TKR. LCGA is a semi-parametric technique used to classify distinct

subgroups that follow a similar pattern of change over time hence appropriate for analyzing longitudinal data [29]. This means that patients exhibiting similar patterns of QoL are grouped forming sets of homogenous classes. LCGA is able to accommodate missing data such that patients with missing QoL values at several time points are not excluded from the analysis thus minimizing the exclusion of patients [30, 31].

*Identifying trajectory groups*

As the number of potential trajectories is unknown, a series of models considering 1 to 8 classes were estimated. The censored normal model was selected as the most appropriate for the available data. The Bayes Information Criteria (BIC) is a commonly used criteria to assess model fit, where higher BIC values indicate better model fit [32]. The choice for optimal model was guided by a combination of factors including our research objective, goodness-of-fit statistics Akaike's Information Criteria (AIC), model interpretability, posterior group-membership probability diagnostics [31, 32]. The latter set of diagnostics included ensuring all groups displayed average group posterior probabilities above 0.7 [29] and odds of correct classification (OCC) were greater than 5 [32]. Patients were assigned to the trajectories which they had the highest posterior probability of membership.

*Estimating QALYs*

Quality-adjusted life-year (QALY) is a common metric used to measure health benefit and incremental outcomes are of interest for economic analysis to quantify the value of interventions [33]. QALYs for each QoL trajectories were calculated using patient-level utility values using the area under the curve method [34]. To quantify the effectiveness (health benefit) gained from the intervention, QALYs gained (incremental QALYs) were calculated for each patient assuming the patient experienced no change from baseline utility if the patient had not had a TKR [10, 35-38].

*Multinomial logistic regression analysis*

Based on assigned trajectories, multinomial logistic regression analysis weighted by probability of class membership was performed to examine the association between trajectory groups and baseline patient characteristics. The multivariable model included variables identified as potentially important discriminators of class membership in the

univariable multinomial logistic regression analyses (those displaying associations at P<0.10). Tests for collinearity were conducted with variance inflation factor (VIF) greater than 10 and tolerance of less than 0.1 considered to indicate the presence of multi-collinearity. The trajectory group with the highest incremental QALYs was used as reference category against which other trajectory groups were compared. All analyses were conducted using Stata SE14 (StataCorp, College Station, TX, USA), employing Traj plugin for LCGA.

## 4.5. Results

### 4.5.1. Study population

1,553 TKR patients were included in the analysis after 339 cases were excluded based on: missing baseline QoL (n=3), no follow-up QoL (n=36), early death (n=14), early revision (n=32) and bilateral surgeries where the most recent surgery was already included (n=254). Table 4.1 displays the baseline patient characteristics who were on average 70.1 years (SD,8.5) and 67.4% were female and mean QoL utility of 0.56 (SD,0.11) pre-operatively. Of those included, complete QoL data from baseline and across all 5 years were available for 1,218 patients (78%).

### 4.5.2. Model selection

The model with six classes was chosen to achieve a balance between model parsimony and adequately identifying distinct QoL patterns to demonstrate heterogeneity within the cohort to provide insights on the longer-term QoL outcomes and the potential value of surgical intervention across different patient groups. The 6-class model produced six distinct QoL trajectories (Figure 4.1) and met all diagnostic tests criteria. The probability of membership for allocated class ranged between 0.78 and 0.85 and displayed OCC above the minimum value of 5 (full results can be found in Supplementary Material Tables S4.1 and S4.2). The addition of excluded individuals in the sensitivity analysis produced similar results.

### 4.5.3. Characterization of classes

The trajectories were characterized by 3 main phases; pre-surgery, post-operative improvement (period between pre-surgery and Year 1) and maintenance (after Year 1).

Table 4.2 provides the description for each of the trajectories, total and incremental QALYs gained over the 5-year period.

Total QALYs of the trajectory with lowest QoL (Trajectory 1) was 2.62 (SD, 0.19) and the number of QALYs increased with higher utility values for subsequent trajectories. In terms of effectiveness gained from TKR, incremental QALYs were lowest for Trajectory 1 (0.16 (SD,0.35)) and greatest gain for trajectory 5 (1.42 (SD,0.40)). Although patients in Trajectory 6 had the greatest number of QALYs, estimated incremental gains from TKR were small at 0.39 (SD, 0.37) compared to most other trajectories.

### 4.5.4. Characterization of patients across trajectory groups

Baseline patient socio-demographic and clinical characteristics were compared across the 6 QoL trajectories and are provided in Supplementary Material Table S4.3. Patient characteristics differed across trajectories. The mean age of patients in Trajectories 3 and 5 was lower than in other trajectories. There was a higher proportion of females in trajectories reporting poorer QoL. Trajectory 1 had the largest proportion of patients reporting severe baseline pain (71.3%) and lowest baseline KSS function (26.7 (SD,19.8)) compared to others.

Although there was a low chance of collinearity (tolerance range between 0.79 and 0.98; mean VIF=1.14) when all variables were included, to achieve a parsimonious model, only patient characteristics displaying associations of $P<0.10$ from the univariable regression models (Supplementary Material Table S4.4) were included in the final multivariable model. These were age, gender, BMI, interpreter, CCI, ASA, rurality, baseline KSS pain and function. Results from multivariable multinomial logistic regression are presented in Table 4.3 (Supplementary Material Figure S4.1), showing the relative risk of belonging in the respective trajectory for each patient characteristic.

Compared to patients with the greatest incremental QALY (Trajectory 5), patients with the lowest gains from TKR (Trajectory 1) are more likely to have co-morbidities, high ASA score, need an interpreter, more likely to report lower KSS function score (poorer mobility) and less likely to be in rural residence. Patients with moderate, sustained gains in Trajectory 2 are more likely to be older, female, require an interpreter, have co-morbidities, less likely to be in a rural residence, more likely to report lower KSS function

score and are less likely to report severe pain compared to those with large gains (Trajectory 5). Patients exhibiting slow progressive improvement (Trajectory 3) were found to be more likely to have co-morbidities and report mild than moderate/severe pain compared to those whose improvement peaked earlier (Trajectory 5). Compared to Trajectory 5, patients in Trajectory 4 were older, have co-morbidities, and less likely to report moderate/severe pain. Patients consistently reporting high QoL (Trajectory 6) were likely to be older, less likely to report moderate/severe pain and more likely to report higher KSS function score compared to Trajectory 5. A summary of these findings is presented in Table 4.4.

## 4.6. Discussion

Using latent class growth analysis, we identified 6 distinct QoL trajectories indicating the presence of significant heterogeneity in QoL outcomes among TKR patients. Although most patients exhibited a trajectory profile that is commonly reported in the literature (improvement within 1 year followed by a plateau), the distinct difference observed in this study is that patients had variable gains following surgery and not all patients maintained the improvement. This highlights that patients will not universally achieve large QoL improvement following TKR as is commonly reported in the literature. Trajectory 5 (large sustainable improvement after surgery) was identified to be the most positive QoL trajectory with the greatest gain in QALYs. However, only 18.4% of the patients were classified in this trajectory and were likely to be younger, have no co-morbidities and report greater pain at pre-surgery than most in other QoL trajectories.

While much research has focused on identifying potential risk factors and integrating these to improve medical decision making, associating patient-reported outcomes such as QoL to these patient characteristics can facilitate delivery of individualized health care as it allows patient engagement in shared decision making to help optimize outcomes [20, 39]. The unique QoL trajectories identified in this study clearly show variations in the benefits of TKR; one-year post-surgery and in the longer term, and the combination of patient characteristics associated with each trajectory. Whilst there are limitations in employing the current findings to deterministically identify patient subgroup most likely to have poor outcomes, knowledge of the combination of characteristics (Table 4.4) that predisposes a patient to trajectories with poor health gains (for example, trajectories 1, 2

and 6) can be useful in anticipating possible outcomes and mitigating such risks. This may include managing pre-surgery expectations [40], personalizing self-management plans [41], careful planning in managing co-morbidities to optimize patients prior to surgery [42] and tailoring pre-surgery management through mindfulness training to maximize outcomes in these patients [43].

There is also potential to use this information to improve post-surgical management to optimize care. Correlating patient characteristics with patient-reported QoL responses can help clinicians track progress and identify patients who are unlikely to obtain the maximum effectiveness from the treatment; for example, elderly female patients with moderate pain pre-surgery who consistently report low QoL may not benefit fully from the standard prescribed post-surgical management and may require an individualized approach. This gives both the patients and providers opportunity to engage and plan follow-up consultations based on goals and expectations for physical [44-46] or mental health [43] therapies to improve outcomes. Recognizing the variability in health trajectories could also enable patients to have realistic expectations, to better understand their clinical course and facilitate discussions with their surgeons [1]. This allows for the opportunity to tailor the evolving care post-surgery on an as-needed basis. While understanding the patient characteristics associated with these trajectories is important, it is acknowledged that beyond these characteristics, psychological factors such as pain-related beliefs and psychological distress can also influence TKR outcomes [47-49] and should be considered alongside.

To date, trajectory analysis on TKR patients have mostly focused on pain and function trajectories and have also demonstrated heterogeneity within the TKR population; commonly identifying the presence of a subgroup with poor pain and/or function outcomes comprising between 14% and 23% of the study cohort [11, 50, 51]. While it is unclear if patients with a low QoL trajectory (Trajectory 1) were non-responders or those reporting poor pain/function outcomes after surgery, some similarities in the characteristics of these patients were observed. Patients in Trajectory 1 had higher BMI, were more likely to be co-morbid, report severe pain, have low mental and physical well-being (Supplementary Material Table S4.3) which are consistent with the predictors of non-responders [22] or poor pain and function outcomes [11, 50]. For these patients, the prescribed standard surgical treatment and follow-up plans are unlikely to be adequate,

thus resulting in poor patient outcomes and low value care. Therefore, by maximizing the use of PROMs to better understand potential QoL trajectories, clinicians can be better informed on how they may plan to manage subgroups with these characteristics and assign patients to more appropriate level of surveillance and better supportive care or alternative rehabilitation programs to optimize the outcomes of those who are truly experiencing low QoL long-term after surgery.

This study showed that improvement in QoL following surgery was observed to be the greatest among younger patients; Trajectory 5 and Trajectory 3 albeit over a longer period. Although the observed associations were statistically significant, they were relatively weak, and this could be due to the small number of patients under the age of 60 (approximately 12% of sample). Historically, younger patients are considered as less appropriate candidates compared to elderly patients due to the higher risk for revision [52]. This is likely related to duration of prostheses survivorship and higher levels of activity among younger patients [53]. While revision risk is an important consideration, the current study provides additional insights. It may be useful for clinical practice to consider the potential benefits and value to be gained from the intervention when making surgical recommendations, particularly in younger patients [54]. Post-marketing surveillance and advances in technology have led to improvements in prostheses survivorship which have now reached 90% at 20 years and even 82% at 25 years [55]. Therefore, having to wait for advanced age to be suitable for surgery may represent a missed opportunity to improve an individual's well-being and labor force productivity.

As PROMs including QoL are increasingly recognized as an important consideration in clinical care, it is important these are routinely captured pre- and post-surgery using relevant tools to evaluate the effectiveness and value of intervening [56]. These findings also reinforce the need to encourage PROMs collection beyond the one-year post-surgery mark as delayed improvers (Traj 3) or diverging trends (e.g. Traj 4 and 5) can be indicators of sub-optimal care. Beyond routine collection of PROMs, there also needs to be considerations in integrating these into shared decision-making tools and identifying suitable approaches to implement these in practice to better guide clinical care and improve the value of surgery. Additionally, risk stratification is an important approach in advancing research [57], thus the ability to identify homogenous subgroups based on a

combination of characteristics amongst a heterogenous cohort can be useful in selecting the right patients for trials of novel interventions allowing for a more targeted approach.

Because of the rapidly growing rates of utilization and large costs associated with TKR, the judicious use of scarce healthcare resources is ever more important to ensure sustainability for health insurers and health systems. Further, the appropriateness of the surgery in selected patients has also been called into question where studies showed up to one-third of TKRs were deemed to be inappropriate procedures [58, 59]. Therefore, it is important to target those whom we can maximize outcomes and improve value of care. We find patients reporting good QoL prior to surgery (Trajectory 6) were among those with small gains. Though it is uncertain if these patients have merely adapted to their condition hence report higher levels of QoL than others with the same condition [60], it may be important to understand the rationale for surgical intervention in these patients. While TKR is widely regarded as a cost-effective procedure in general, this raises the question if TKR is necessarily cost-effective for all patients. Some groups of patients may require additional care and healthcare services demands to improve their outcomes. This may be relevant to patients exhibiting poor long-term QoL outcomes with small gains in health benefit such as those in Trajectories 1, 2 and 6, which in combination contributes to a significant proportion (55%) of the cohort. Therefore, further research to quantify the healthcare needs and assess the cost-effectiveness across these sub-groups would be helpful in understanding the true value of surgery amongst the group of heterogenous TKR patients.

#### 4.6.1. Limitations

Several limitations should be considered when interpreting these results. The generalizability of the findings could be limited as patients were from a single-center. However, the demographics of patients in this study closely reflect those reported in our National Joint Replacement Registry [61]. It is acknowledged that changes to modifiable characteristics such as comorbidity over time can affect QoL trajectories [62]. However, it is difficult to ascertain the extent of this in the current study unless such information is also captured over time. QoL assessments can be subject to biases known as response shifts where patients could change the way they evaluate themselves and respond to surveys over time [63]. While studies have shown that changes in health outcomes were underestimated when response shifts were not accounted for in TKR patients [64, 65],

another has shown that despite adjusting for large response shifts, it did not change the authors' clinical interpretation of the results [66]. In the context of our study where all patients were surveyed in the same manner across time, it is unlikely to change the conclusions drawn from our analysis. It is noted that our assumption of no change from baseline made in the calculation of incremental QALYs may result in an overestimation of QALYs as a result of regression to the mean [67]. Conversely, deterioration in QoL due to aging or absence of surgery may also result in an underestimation. The application of our assumption follows published economic evaluations [10, 34, 35, 37, 38]. Variables such as co-morbidity, ASA, KL scores and socio-economic indicators (SEIFA) were dichotomized to avoid small cell sizes which could reduce the sensitivity of our analysis.

## 4.7. Conclusion

There is strong evidence indicating important heterogeneity in QoL trajectories in TKR patients resulting in variable gains in QoL and QALYs across different trajectory groups. This indicates not all patients benefit from the surgical procedure in the same way. With the growing recognition to support patient-centered care, PROMs may have a particular usefulness when employed alongside patient characteristics for tracking and guiding clinical care to maximize patient outcomes and justifying costs of surgical intervention. Future research should focus on identifying approaches of its implementation into clinical practice.

## 4.8. Tables and figures

Table 4.1: Baseline characteristics

| | No. | (%) |
|---|---|---|
| Total number of patients | 1553 | |
| **Patient characteristics** | | |
| Age, mean (SD) | 70.1 | 8.5 |
| Female | 1047 | 67.4 |
| BMI, mean (SD) | 32.8 | 6.0 |
| Aetiology | | |
| Osteoarthritis | 1456 | 93.8 |
| Other [a] | 97 | 6.3 |
| Bilateral surgery | 382 | 24.6 |
| Smoker | | |
| No | 1065 | 68.6 |
| Ex | 381 | 24.5 |
| Yes | 107 | 6.9 |
| Interpreter | 231 | 14.9 |
| CCI | | |
| 0 | 875 | 56.3 |
| 1+ | 678 | 43.7 |
| ASA | | |
| 1/2 | 901 | 58.0 |
| 3/4 | 652 | 42.0 |
| KL | | |
| <4 | 757 | 48.7 |
| 4 | 796 | 51.3 |
| SEIFA deciles | | |
| 1-5 | 562 | 36.2 |
| 6-10 | 991 | 63.8 |
| Rural residence | 263 | 16.9 |
| **Patient-reported outcomes** | | |
| KSS pain [b] | | |
| Mild | 88 | 5.7 |
| Moderate | 596 | 38.4 |
| Severe | 869 | 56.0 |
| KSS function [b], mean (SD) | 36.0 | 20.5 |
| SF-12, mean (SD) | | |
| PCS | 23.1 | 8.0 |
| MCS | 45.6 | 16.1 |
| Utility | 0.56 | 0.11 |

[a] Other aetiology includes rheumatoid arthritis and avascular osteonecrosis.

[b] KSS pain scores were categorised as follows; none (50), mild occasional (45) mild on stairs (40), mild on walking (30), moderate occasional (20), moderate continual (10) and severe pain as (0) points. KSS function score assesses walking, stair ability and use of walking aids and ranges for 0 to 100 with a higher score indicating better function.

Abbreviations: ASA, American Society of Anesthesiologist; BMI, body mass index; CCI, Charlson Co-morbidity Index; KL, Kellgren-Lawrence scale; MCS, mental component score; PCS, physical component score; SEIFA, Socio-Economic Index for Areas; KSS, Knee Society Score.

Table 4.2: Description of each QoL trajectories by phases and estimated QALYs over 5-years

| | **Traj 1** | **Traj 2** | **Traj 3** | **Traj 4** | **Traj 5** | **Traj 6** |
|---|---|---|---|---|---|---|
| **Phases** | | | | | | |
| Pre-surgery QoL | Low | Low | Low | Low | Low | High |
| Post-surgery QoL improvement at year 1 | Small | Moderate | Moderate | Large | Large | Moderate |
| Maintenance of trajectory after year 1 | Maintained | Maintained | Improving | Declined | Maintained | Maintained |
| **Measure of health gains** | | | | | | |
| Total QALY (SD) [a] | 2.62 (0.19) | 3.15 (0.17) | 3.55 (0.20) | 3.80 (0.19) | 4.20 (0.20) | 4.42 (0.20) |
| Incremental QALY (SD) [a b] | 0.16 (0.35) | 0.42 (0.46) | 0.75 (0.47) | 0.85 (0.43) | 1.42 (0.40) | 0.39 (0.37) |

[a] Complete case analysis

[b] QALYs gained as a result of TKR assuming patient experienced no change from baseline utility if the patient not had a TKR

Abbreviations: QALY, quality-adjusted life-years; QoL, quality-of-life; Traj, trajectory

Table 4.3: Multivariable multinomial logistic regression showing relative risk (RRR) of belonging in each of the trajectory groups compared to Trajectory 5 (highest incremental QALYs/health gains)

| | Trajectory 1 | | | Trajectory 2 | | | Trajectory 3 | | | Trajectory 4 | | | Trajectory 6 | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Variable** | **RRR** | **95% CI** | **P Value** | **RRR** | **95% CI** | **P Value** | **RRR** | **95% CI** | **P Value** | **RRR** | **95% CI** | **P Value** | **RRR** | **95% CI** | **P Value** |
| Age | 1.00 | 0.98-1.03 | 0.73 | 1.03 | 1.01-1.05 | 0.004 | 1.00 | 0.97-1.03 | 0.90 | 1.03 | 1.01-1.06 | 0.001 | 1.04 | 1.01-1.07 | 0.02 |
| Female | 1.30 | 0.88-1.91 | 0.19 | 1.46 | 1.04-2.06 | 0.03 | 1.17 | 0.72-1.91 | 0.52 | 1.33 | 0.91-1.94 | 0.14 | 0.70 | 0.41-1.17 | 0.17 |
| BMI | 1.02 | 0.99-1.05 | 0.29 | 1.02 | 0.99-1.05 | 0.17 | 1.01 | 0.98-1.05 | 0.46 | 1.03 | 1.00-1.06 | 0.07 | 0.98 | 0.94-1.02 | 0.35 |
| Interpreter | 2.61 | 1.49-4.59 | 0.001 | 2.22 | 1.30-3.78 | 0.003 | 1.76 | 0.84-3.70 | 0.14 | 1.56 | 0.84-2.87 | 0.16 | 1.00 | 0.35-2.87 | 0.99 |
| CCI | | | | | | | | | | | | | | | |
| 0 | 1 [Reference] [a] | | | 1 [Reference] [a] | | | 1 [Reference] [a] | | | 1 [Reference] [a] | | | 1 [Reference] [a] | | |
| ≥1 | 2.71 | 1.85-3.95 | <.001 | 2.15 | 1.53-3.03 | <.001 | 1.99 | 1.25-3.17 | 0.004 | 1.84 | 1.25-2.69 | 0.002 | 1.07 | 0.62-1.84 | 0.82 |
| ASA score | | | | | | | | | | | | | | | |
| 1/2 | 1 [Reference] [b] | | | 1 [Reference] [b] | | | 1 [Reference] [b] | | | 1 [Reference] [b] | | | 1 [Reference] [b] | | |
| 3/4 | 2.10 | 1.44-3.08 | <.001 | 1.29 | 0.92-1.81 | 0.15 | 1.33 | 0.84-2.12 | 0.22 | 1.32 | 0.90-1.95 | 0.15 | 0.71 | 0.39-1.29 | 0.26 |
| Rural residence | 0.47 | 0.28-0.80 | 0.005 | 0.66 | 0.44-0.99 | 0.04 | 0.68 | 0.37-1.23 | 0.20 | 1.02 | 0.67-1.56 | 0.91 | 0.96 | 0.54-1.73 | 0.90 |
| KSS pain | | | | | | | | | | | | | | | |
| Mild | 1 [Reference] [a] | | | 1 [Reference] [a] | | | 1 [Reference] [a] | | | 1 [Reference] [a] | | | 1 [Reference] [a] | | |
| Moderate | 0.41 | 0.14-1.15 | 0.09 | 0.46 | 0.19-1.09 | 0.08 | 0.29 | 0.10-0.86 | 0.03 | 0.33 | 0.14-0.79 | 0.01 | 0.23 | 0.09-0.59 | 0.003 |
| Severe | 0.60 | 0.22-1.68 | 0.33 | 0.38 | 0.16-0.91 | 0.03 | 0.33 | 0.11-0.95 | 0.04 | 0.25 | 0.10-0.61 | 0.002 | 0.12 | 0.04-0.34 | <.001 |

| | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| KSS function [c] | 0.98 | 0.97-0.98 | <.001 | 0.99 | 0.98-1.00 | 0.008 | 1.00 | 0.98-1.01 | 0.53 | 1.00 | 0.99-1.01 | 0.53 | 1.03 | 1.01-1.04 | <.001 |

[a] Overall P Value < 0.001

[b] Overall P Value = 0.001

[c] Per point increase in KSS function score. The score assesses walking, stair ability and use of walking aids and ranges for 0 to 100 with a higher score indicating better function.

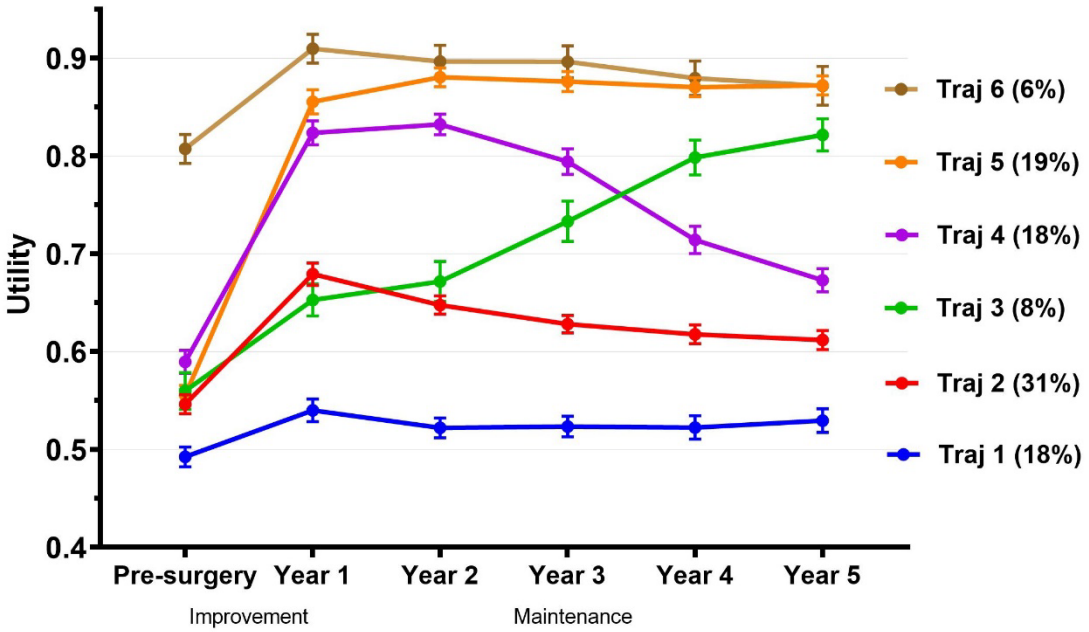
Abbreviations: ASA, American Society of Anesthesiologist; BMI, body mass index; CCI, Charlson Co-morbidity Index; KSS, Knee Society Score; RRR, relative risk ratio

Table 4.4: Patient characteristics associated with each of the trajectories compared to Trajectory 5 (highest incremental QALYs/health gains).

| Trajectory 1 | Trajectory 2 | Trajectory 3 | Trajectory 4 | Trajectory 6 |
|---|---|---|---|---|
| | Older<br>Female | | Older | Older |
| High ASA score (3 and above) | | | | |
| Need interpreter | Need interpreter | | | |
| Have co-morbidities | Have co-morbidities | Have co-morbidities | Have co-morbidities | |
| Less likely to be in rural residence | Less likely to be in rural residence | | | |
| Report lower (below 40) KSS function score [a] | Report lower (below 40) KSS function score [a] | | | Report higher (above 40) KSS function score [a] |
| | Less likely to report severe pain [a] | Less likely to report moderate/severe pain [a] | Less likely to report moderate/severe pain [a] | Less likely to report moderate/severe pain [a] |

[a] KSS pain scores were categorised as follows; none (50), mild occasional (45) mild on stairs (40), mild on walking (30), moderate occasional (20), moderate continual (10) and severe pain as (0) points. KSS function score assesses walking, stair ability and use of walking aids and ranges for 0 to 100 with a higher score indicating better function.

Figure 4.1: QoL trajectory profiles and class membership for six-class model




Traj 6 – High baseline, moderate sustained improvement (6%)

Traj 5 – Low baseline, large sustained improvement (19%)

Traj 4 – Low baseline, large unsustained improvement (18%)

Traj 3 – Low baseline, moderate improving (8%)

Traj 2 – Low baseline, moderate sustained improvement (31%)

Traj 1 – Low baseline, small sustained improvement (18%)

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## 4.10. Supplementary materials

Table S4.1: Comparison of fit statistics for models containing 1 to 8 classes

| No. of classes | BIC | AIC | Min PP | Max PP | Proportion in each class (%) | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |
| 1 | 4142.2 | 4155.6 | | 1.00 | 100 | | | | | | | |
| 2 | 5842.0 | 5868.7 | 0.96 | 0.96 | 52.6 | 47.4 | | | | | | |
| 3 | 6087.1 | 6127.2 | 0.85 | 0.94 | 31.7 | 35.1 | 33.2 | | | | | |
| 4 | 6149.8 | 6203.3 | 0.81 | 0.87 | 18.8 | 33.2 | 26.5 | 21.5 | | | | |
| 5 | 6233.6 | 6300.4 | 0.76 | 0.88 | 17.8 | 10.9 | 32.6 | 15.7 | 22.9 | | | |
| 6 [a] | 6279.0 | 6359.2 | 0.78 | 0.85 | 18.4 | 29.6 | 9.1 | 17.8 | 18.6 | 6.5 | | |
| 7 | 6291.3 | 6384.9 | 0.69 | 0.82 | 15.1 | 9.4 | 25.8 | 17.6 | 15.2 | 10.9 | 6.1 | |
| 8 | 6299.5 | 6406.5 | 0.68 | 0.83 | 5.1 | 10.8 | 27.4 | 12.2 | 16.4 | 15.4 | 6.6 | 6.1 |

[a] Model selected

Abbreviations: AIC, Akaike Information Criteria; BIC, Bayes Information Criteria; PP, average posterior probability of class membership

Table S4.2: Group membership probability diagnostics for models containing 1 to 8 classes

| No. of classes | QoL trajectory # | No. in each trajectory | Average posterior probability | Odds of correct classification | Probability of group membership | Total probability |
|---|---|---|---|---|---|---|
| 2 | 1 | 817 | 0.964 | 24.154 | 0.526 | 0.525 |
| | 2 | 736 | 0.963 | 28.631 | 0.474 | 0.475 |
| 3 | 1 | 492 | 0.899 | 19.248 | 0.317 | 0.315 |
| | 2 | 545 | 0.849 | 10.416 | 0.351 | 0.351 |
| | 3 | 516 | 0.935 | 28.835 | 0.332 | 0.333 |
| 4 | 1 | 292 | 0.839 | 22.482 | 0.188 | 0.191 |
| | 2 | 516 | 0.825 | 9.485 | 0.332 | 0.327 |
| | 3 | 411 | 0.807 | 11.606 | 0.265 | 0.265 |
| | 4 | 334 | 0.873 | 25.004 | 0.215 | 0.217 |
| 5 | 1 | 276 | 0.845 | 25.206 | 0.178 | 0.182 |
| | 2 | 170 | 0.763 | 26.190 | 0.109 | 0.120 |
| | 3 | 507 | 0.815 | 9.068 | 0.326 | 0.310 |
| | 4 | 244 | 0.776 | 18.564 | 0.157 | 0.162 |
| | 5 | 356 | 0.884 | 25.749 | 0.229 | 0.226 |
| 6 [a] | 1 | 286 | 0.849 | 25.395 | 0.181 | 0.183 |
| | 2 | 481 | 0.815 | 9.601 | 0.315 | 0.301 |
| | 3 | 121 | 0.785 | 34.208 | 0.097 | 0.112 |
| | 4 | 279 | 0.817 | 19.505 | 0.186 | 0.180 |
| | 5 | 292 | 0.780 | 18.385 | 0.162 | 0.160 |
| | 6 | 94 | 0.822 | 72.466 | 0.060 | 0.064 |
| 7 | 1 | 234 | 0.818 | 25.283 | 0.151 | 0.152 |
| | 2 | 146 | 0.692 | 21.692 | 0.094 | 0.107 |
| | 3 | 400 | 0.726 | 7.653 | 0.258 | 0.240 |
| | 4 | 273 | 0.816 | 20.735 | 0.176 | 0.170 |
| | 5 | 236 | 0.757 | 17.362 | 0.152 | 0.148 |
| | 6 | 169 | 0.775 | 28.253 | 0.109 | 0.120 |
| | 7 | 95 | 0.819 | 69.333 | 0.061 | 0.063 |
| 8 | 1 | 79 | 0.825 | 88.222 | 0.051 | 0.063 |
| | 2 | 168 | 0.681 | 17.582 | 0.108 | 0.118 |
| | 3 | 425 | 0.777 | 9.264 | 0.274 | 0.248 |
| | 4 | 190 | 0.694 | 16.281 | 0.122 | 0.125 |
| | 5 | 254 | 0.821 | 23.381 | 0.164 | 0.161 |
| | 6 | 239 | 0.756 | 17.050 | 0.154 | 0.146 |
| | 7 | 103 | 0.725 | 37.029 | 0.066 | 0.076 |
| | 8 | 95 | 0.823 | 71.223 | 0.061 | 0.063 |

[a] Model selected

Table S4.3: Patient profiles by QoL trajectories (Traj)

| | Traj 1 | | Traj 2 | | Traj 3 | | Traj 4 | | Traj 5 | | Traj 6 | | P Value [a] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | No. | (%) | No. | (%) | No. | (%) | No. | (%) | No. | (%) | No. | (%) | |
| | 286 | 18.42 | 481 | 30.97 | 121 | 7.79 | 279 | 17.97 | 292 | 18.80 | 94 | 6.05 | |
| **Patient characteristics** | | | | | | | | | | | | | |
| Age, mean | | | | | | | | | | | | | <.001 |
| (SD) | 70.4 | 9.0 | 71.1 | 8.8 | 68.5 | 8.7 | 70.6 | 7.4 | 68.1 | 8.4 | 70.2 | 8.0 | |
| Female | 206 | 72.0 | 348 | 72.4 | 81 | 66.9 | 186 | 66.7 | 184 | 63.0 | 42 | 44.7 | <.001 |
| BMI, mean | | | | | | | | | | | | | |
| (SD) | 33.7 | 6.7 | 33.0 | 6.1 | 32.9 | 5.8 | 32.9 | 5.5 | 32.3 | 5.8 | 30.7 | 4.5 | 0.001 |
| Aetiology | | | | | | | | | | | | | 0.55 |
| Osteoarthritis | 264 | 92.3 | 449 | 93.4 | 112 | 92.6 | 262 | 93.9 | 278 | 95.2 | 91 | 96.8 | |
| Other [b] | 22 | 7.7 | 32 | 6.7 | 9 | 7.4 | 17 | 6.1 | 14 | 4.8 | 3 | 3.2 | |
| Bilateral | | | | | | | | | | | | | |
| surgery | 57 | 19.9 | 118 | 24.5 | 28 | 23.1 | 84 | 30.1 | 68 | 23.3 | 27 | 28.7 | 0.101 |
| Smoker | | | | | | | | | | | | | 0.31 |
| No | 193 | 67.5 | 337 | 70.1 | 85 | 70.3 | 184 | 66.0 | 202 | 69.2 | 64 | 68.1 | |
| Ex | 66 | 23.1 | 108 | 22.5 | 26 | 21.5 | 82 | 29.4 | 75 | 25.7 | 24 | 25.5 | |
| Yes | 27 | 9.4 | 36 | 7.5 | 10 | 8.3 | 13 | 4.7 | 15 | 5.1 | 6 | 6.4 | |
| Interpreter | 66 | 23.1 | 91 | 18.9 | 16 | 13.2 | 32 | 11.5 | 21 | 7.2 | 5 | 5.3 | <.001 |
| CCI | | | | | | | | | | | | | <.001 |
| 0 | 127 | 44.4 | 252 | 52.4 | 64 | 52.9 | 158 | 56.6 | 209 | 71.6 | 65 | 69.2 | |
| 1+ | 159 | 55.6 | 229 | 47.6 | 57 | 47.1 | 121 | 43.4 | 83 | 28.4 | 29 | 30.9 | |
| ASA | | | | | | | | | | | | | <.001 |
| 1/2 | 122 | 42.7 | 271 | 56.3 | 70 | 57.9 | 163 | 58.4 | 203 | 69.5 | 72 | 76.6 | |
| 3/4 | 164 | 57.3 | 210 | 43.7 | 51 | 42.2 | 116 | 41.6 | 89 | 30.5 | 22 | 23.4 | |

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| KL | | | | | | | | | | | | | 0.16 |
| <4 | 147 | 51.4 | 219 | 45.6 | 69 | 57.0 | 142 | 51.3 | 138 | 47.4 | 41 | 43.6 | |
| 4 | 139 | 48.6 | 261 | 54.4 | 52 | 43.0 | 135 | 48.7 | 153 | 52.6 | 53 | 56.4 | |
| SEIFA deciles | | | | | | | | | | | | | 0.37 |
| 1-5 | 93 | 32.5 | 174 | 36.2 | 38 | 31.4 | 110 | 39.4 | 108 | 37.0 | 39 | 41.5 | |
| 6-10 | 193 | 67.5 | 307 | 63.8 | 83 | 68.6 | 169 | 60.6 | 184 | 63.0 | 55 | 58.5 | |
| Rural residence | 27 | 9.4 | 64 | 13.3 | 20 | 16.5 | 62 | 22.2 | 66 | 22.6 | 24 | 25.5 | <.001 |
| **Patient-reported outcomes** | | | | | | | | | | | | | |
| KSS pain [c] | | | | | | | | | | | | | |
| Mild | 9 | 3.2 | 24 | 5.0 | 8 | 6.6 | 23 | 8.2 | 8 | 2.7 | 16 | 17 | <.001 |
| Moderate | 73 | 25.5 | 188 | 39.1 | 42 | 34.7 | 124 | 44.4 | 118 | 40.4 | 51 | 54.3 | |
| Severe | 204 | 71.3 | 269 | 55.9 | 71 | 58.7 | 132 | 47.3 | 166 | 56.9 | 27 | 28.7 | |
| KSS function [c], mean (SD) | 26.7 | 19.8 | 32.9 | 19.7 | 38.0 | 20.2 | 40.1 | 20.1 | 40.2 | 18.4 | 52.2 | 17.3 | P<.001 |
| SF-12, mean (SD) | | | | | | | | | | | | | |
| PCS | 21.8 | 7.2 | 22.8 | 7.5 | 23.5 | 7.4 | 22.9 | 8.3 | 22.1 | 7.6 | 31.4 | 9.3 | P<.001 |
| MCS | 36.7 | 14.8 | 43.2 | 15.2 | 45.2 | 15.3 | 50.0 | 15.3 | 48.7 | 15.3 | 63.3 | 5.6 | P<.001 |
| Utility | 0.49 | 0.08 | 0.55 | 0.09 | 0.56 | 0.10 | 0.59 | 0.09 | 0.56 | 0.08 | 0.81 | 0.07 | P<.001 |

[a] Comparisons across trajectory groups using chi2 test for categorical variables and one-way ANOVA for continuous variables

[b] Other aetiology includes rheumatoid arthritis and avascular osteonecrosis.

[c] KSS pain scores were categorised as follows; none (50), mild occasional (45) mild on stairs (40), mild on walking (30), moderate occasional (20), moderate continual (10) and severe pain as (0) points. KSS function score assesses walking, stair ability and use of walking aids and ranges for 0 to 100 with a higher score indicating better function.

Abbreviations: ASA, American Society of Anesthesiologist; BMI, body mass index; CCI, Charlson Co-morbidity Index; KL, Kellgren-Lawrence scale; MCS, mental component score; PCS, physical component score; REF, reference; RRR, relative risk ratio; SEIFA, Socio-Economic Index for Areas; KSS, Knee Society Score; Traj, trajectory.

Table S4.4: Univariable multinomial logistic regression showing relative risk (RRR) of belonging in each of the trajectory groups compared to Trajectory 5 (highest incremental QALYs)

| | **Trajectory 1** | | | **Trajectory 2** | | | **Trajectory 3** | | | **Trajectory 4** | | | **Trajectory 6** | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Variable** | **RRR** | **95% CI** | **P Value** | **RRR** | **95% CI** | **P Value** | **RRR** | **95% CI** | **P Value** | **RRR** | **95% CI** | **P Value** | **RRR** | **95% CI** | **P Value** |
| Age | 1.03 | 1.01-1.05 | 0.004 | 1.04 | 1.03-1.06 | 0.000 | 1.01 | 0.98-1.03 | 0.519 | 1.04 | 1.02-1.05 | 0.000 | 1.03 | 1.01-1.06 | 0.018 |
| Female | 1.53 | 1.07-2.19 | 0.019 | 1.50 | 1.10-2.06 | 0.011 | 1.14 | 0.72-1.80 | 0.569 | 1.17 | 0.82-1.66 | 0.390 | 0.49 | 0.30-0.79 | 0.003 |
| BMI | 1.04 | 1.01-1.07 | 0.004 | 1.02 | 1.00-1.05 | 0.083 | 1.02 | 0.99-1.06 | 0.206 | 1.02 | 1.00-1.05 | 0.098 | 0.95 | 0.91-0.99 | 0.007 |
| Aetiology | | | | | | | | | | | | | | | |
| OA | 1 [Reference] [a] | | | 1 [Reference] [a] | | | 1 [Reference] [a] | | | 1 [Reference] [a] | | | 1 [Reference] [a] | | |
| Other [f] | 1.50 | 0.75-3.04 | 0.254 | 1.36 | 0.71-2.62 | 0.358 | 1.42 | 0.59-3.43 | 0.433 | 1.13 | 0.54-2.37 | 0.753 | 0.59 | 0.16-2.15 | 0.421 |
| Bilateral surg | 0.84 | 0.56-1.25 | 0.387 | 1.14 | 0.80-1.61 | 0.463 | 1.06 | 0.63-1.77 | 0.825 | 1.42 | 0.97-2.08 | 0.073 | 1.34 | 0.79-2.28 | 0.280 |
| Smoking status | | | | | | | | | | | | | | | |
| No | 1 [Reference] [b] | | | 1 [Reference] [b] | | | 1 [Reference] [b] | | | 1 [Reference] [b] | | | 1 [Reference] [b] | | |
| Ex | 0.92 | 0.62-1.37 | 0.689 | 0.81 | 0.57-1.15 | 0.231 | 0.76 | 0.45-1.29 | 0.308 | 1.16 | 0.80-1.70 | 0.437 | 1.00 | 0.58-1.72 | 0.988 |
| Yes | 1.87 | 0.95-3.67 | 0.069 | 1.38 | 0.73-2.62 | 0.325 | 1.63 | 0.69-3.83 | 0.262 | 0.84 | 0.39-1.85 | 0.674 | 1.14 | 0.42-3.10 | 0.795 |
| Interpr. | 3.84 | 2.25-6.54 | 0.000 | 3.00 | 1.80-4.99 | 0.000 | 1.94 | 0.96-3.92 | 0.064 | 1.67 | 0.93-3.01 | 0.088 | 0.70 | 0.25-1.95 | 0.497 |
| CCI | | | | | | | | | | | | | | | |

| | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 0 | 1 [Reference] [c] | | | 1 [Reference] [c] | | | 1 [Reference] [c] | | | 1 [Reference] [c] | | | 1 [Reference] [c] | | |
| ≥1 | 3.32 | 2.33-4.72 | 0.000 | 2.33 | 1.69-3.19 | 0.000 | 2.12 | 1.35-3.32 | 0.001 | 2.01 | 1.41-2.87 | 0.000 | 1.15 | 0.69-1.93 | 0.585 |
| ASA score | | | | | | | | | | | | | | | |
| 1/2 | 1 [Reference] [c] | | | 1 [Reference] [c] | | | 1 [Reference] [c] | | | 1 [Reference] [c] | | | 1 [Reference] [c] | | |
| 3/4 | 3.13 | 2.21-4.43 | 0.000 | 1.75 | 1.28-2.40 | 0.000 | 1.66 | 1.06-2.61 | 0.026 | 1.69 | 1.19-2.41 | 0.003 | 0.68 | 0.40-1.19 | 0.178 |
| KL | | | | | | | | | | | | | | | |
| <4 | 1 [Reference] [d] | | | 1 [Reference] [d] | | | 1 [Reference] [d] | | | 1 [Reference] [d] | | | 1 [Reference] [d] | | |
| 4 | 0.86 | 0.62-1.20 | 0.373 | 1.08 | 0.80-1.45 | 0.630 | 0.74 | 0.48-1.14 | 0.175 | 0.84 | 0.60-1.18 | 0.322 | 1.19 | 0.74-1.92 | 0.470 |
| SEIFA deciles | | | | | | | | | | | | | | | |
| 1 to 5 | 1 [Reference] [d] | | | 1 [Reference] [d] | | | 1 [Reference] [d] | | | 1 [Reference] [d] | | | 1 [Reference] [d] | | |
| 6 to 10 | 1.25 | 0.88-1.77 | 0.219 | 1.00 | 0.73-1.36 | 0.983 | 1.39 | 0.87-2.21 | 0.166 | 0.91 | 0.64-1.28 | 0.573 | 0.84 | 0.52-1.36 | 0.479 |
| Rural residence | 0.35 | 0.21-0.56 | 0.000 | 0.51 | 0.34-0.74 | 0.001 | 0.60 | 0.34-1.03 | 0.076 | 0.90 | 0.60-1.35 | 0.618 | 1.10 | 0.64-1.91 | 0.725 |
| KSS pain | | | | | | | | | | | | | | | |
| Mild | 1 [Reference] [e] | | | 1 [Reference] [e] | | | 1 [Reference] [e] | | | 1 [Reference] [e] | | | 1 [Reference] [e] | | |
| Moderate | 0.46 | 0.17-1.26 | 0.131 | 0.46 | 0.20-1.08 | 0.076 | 0.29 | 0.10-0.84 | 0.023 | 0.30 | 0.13-0.72 | 0.007 | 0.17 | 0.07-0.43 | 0.000 |
| Severe | 0.95 | 0.35-2.55 | 0.912 | 0.46 | 0.20-1.07 | 0.071 | 0.36 | 0.13-1.01 | 0.052 | 0.23 | 0.10-0.55 | 0.001 | 0.07 | 0.03-0.18 | 0.000 |
| KSS function [g] | 0.997 | 0.996-0.997 | 0.000 | 0.998 | 0.997-0.999 | 0.000 | 0.999 | 0.998-1.000 | 0.219 | 1.000 | 0.999-1.001 | 0.934 | 1.004 | 1.002-1.005 | 0.000 |

[a] Overall P Value = 0.64

[b] Overall P Value = 0.20

[c] Overall P Value < 0.001

[d] Overall P Value = 0.26

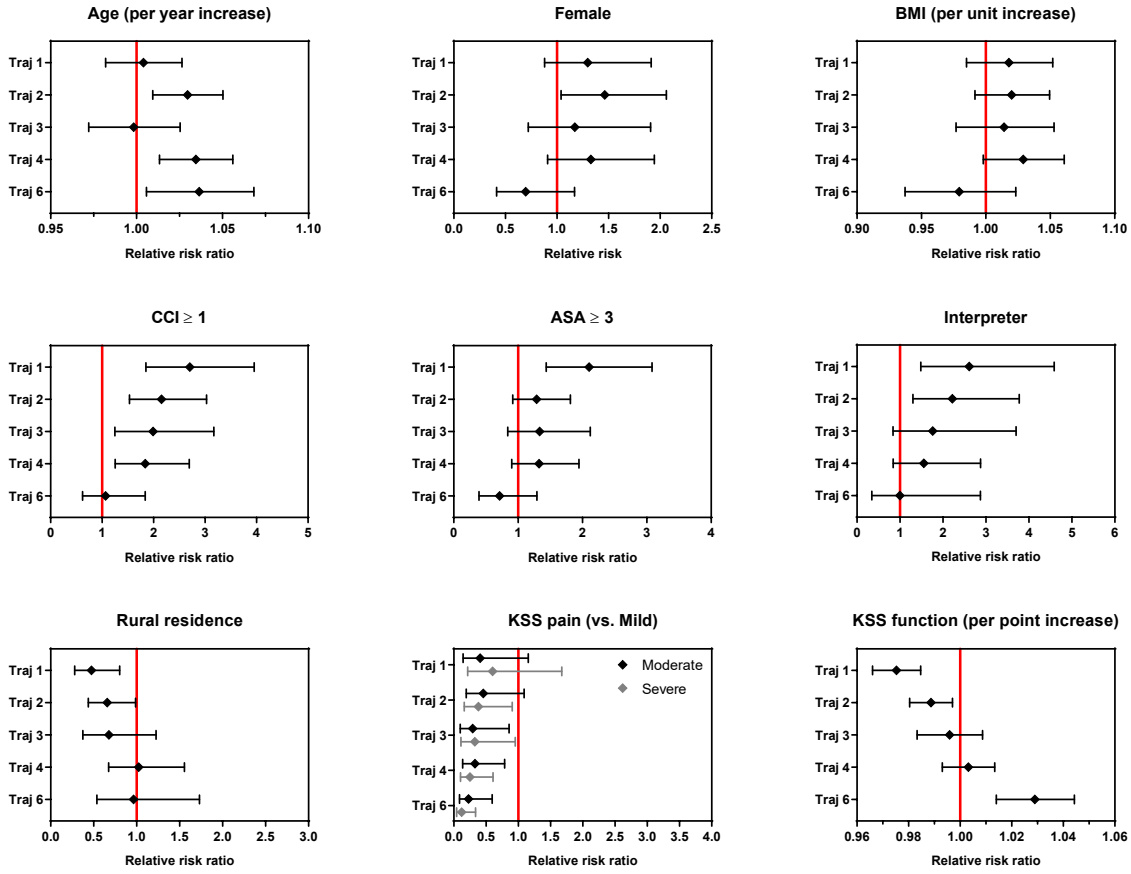
[e] Overall P Value = 0.005

[f] Other aetiology includes rheumatoid arthritis.

[g] Per point increase in KSS function score. The score assesses walking, stair ability and use of walking aids and ranges for 0 to 100 with a higher score indicating better function.

Abbreviations: ASA, American Society of Anesthesiologist; BMI, body mass index; CCI, Charlson Co-morbidity Index; Interpr., Interpreter; KL, Kellgren-Lawrence scale; RRR, relative risk ratio; SEIFA, Socio-Economic Index for Areas; KSS, Knee Society Score; Traj, trajectory.

Figure S4.1: Relative risk ratio with 95% confidence intervals (multivariable multinomial logistic regression) of being in each trajectory vs. reference trajectory (Trajectory 5) for each covariate in the model.



# Chapter 5 : Co-morbidities and sex differences in long-term quality-of-life outcomes among patients with and without diabetes after total knee replacement: Five-year data from registry study

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## 5.1. Abstract

Improved understanding of quality-of-life (QoL) outcomes can provide valuable information on intervention effectiveness and guide better patient care. The aim of this study was to examine whether QoL trajectories differ between patients with and without diabetes and identify to what extent patient characteristics are related to poor QoL outcomes after total joint replacement (TKR). Multilevel modelling was used to analyse long-term QoL patterns of patients undergoing TKR between 2006 and 2011. Patient-reported QoL at baseline and up to 5 years post-surgery were included. Of the 1553 TKR patients, one-fifth ($n$ = 319) had diabetes. Despite there being no significant differences in QoL at baseline, patients with diabetes consistently reported lower QoL (on average by 0.028, $p < 0.001$) and did not improve to the same level as patients without the disease following surgery. Compared to males, females had significantly lower QoL (by 0.03, $p < 0.001$). Other baseline patient characteristics associated with important differences in QoL included presence of respiratory disease and mental health disorder. Patients with diabetes exhibit significantly poorer QoL compared to patients without diabetes, particularly among females. Knowledge of risk factors that impact on QoL can be useful for clinicians in identifying characteristics related to poor QoL outcomes and be used to guide patient-centered care.

## 5.2. Introduction

The global prevalence of diabetes has almost tripled in the last two decades and is the highest among those over the age of 65 years [1]. Among those with diabetes, 50% also suffer from arthritis [2], for which many will require surgery for relief of symptoms. Total knee replacement (TKR) is now one of the most common surgical procedures [3] and the rate of surgeries performed each year continues to grow [4,5]. TKR is proven to be an effective intervention for severe osteoarthritis by improving patients' pain, mobility, well-being and quality-of-life (QoL) [6–8].

Patient-reported outcome measures (PROMs) are important measures of clinical care as they provide valuable information on the effectiveness of the surgical intervention from the patient's perspective. The most prominent use of PROM data is in estimating quality-adjusted life years for informing the value of an intervention, through economic evaluations such as cost-effective analyses. As practices shift towards patient-centred

care and QoL, PROMs facilitate shared decision making with patients to tailor care based on individual needs. These measures can be used to track patient progress and the disease impact on patients' overall QoL.

Impairment in health, functional capacity and pain are some of the mains reasons patients seek surgical care. PROMs in the form of generic QoL instruments, such as the Short Form 12 Health Survey (SF-12), are valuable tools to assess patients' response to treatment. While significant improvement to patients' QoL is commonly observed after TKR, patients with diabetes frequently report lower QoL than the general population [9–12]. Evidence regarding surgical complications and outcomes in relation to TKR in the presence of diabetes remains controversial [13–18]. Some studies have shown the risk of infections, revisions and surgical complications to be greater in patients with diabetes [13–16], while others have demonstrated otherwise, showing no significant differences in revision, surgical complication rates and functional outcomes of TKR between patients with and without diabetes [17,18].

The majority of these studies assess the quality of surgical care through traditional clinical outcome measures. It is unclear whether patient-reported QoL trajectories differ between patients with and without diabetes after TKR. The average summary scores reported in the literature provide limited information about individual change and are usually over a short period post-surgery. A better understanding of longer-term QoL trajectories can be useful in guiding diabetes care and can help patient and physician understand the impact of surgery on patient well-being [19]. Using annual QoL measures collected from a large registry cohort of TKR patients over a 5-year period, we examined if and to what extent QoL trajectories differ between patients with and without diabetes and what patient characteristics or subgroups were related to poor QoL outcomes.

## 5.3. Methods

### 5.3.1. Data source and study population

The St. Vincent's Melbourne Arthroplasty Outcomes (SMART) Registry is a repository of clinical and patient reported outcomes for all patients who undergo elective hip and knee replacement at the study institution. Prospectively collected baseline data on patients who underwent TKR between 1 January 2006 and 31 December 2011 were available and

this included age, sex, body mass index (BMI), smoking status and American Society of Anesthesiologist (ASA) Physical Status Classification and self-reported co-morbidities including diabetes. Socioeconomic status was collected according to the Socio-Economic Index for Areas (SEIFA) [20] and geographical accessibility index (ARIA+) [21] reflecting rurality. Other clinical variables included contralateral knee surgery and radiographic osteoarthritis severity using the Kellgren–Lawrence grading system.

Patients were required to have baseline QoL and at least one follow-up post-surgery to be included in the analysis. Individuals were excluded if they underwent early revision or died within 2 years of surgery. For individuals that underwent staged bilateral knee surgery during the study period, only the most recent TKR was included in the analysis. All patients were followed-up for up to 5 years.

### 5.3.2. Quality-of-life measurements

Patients completed SF-12 surveys within 12 weeks prior to surgery and annually post-operatively. Baseline and annual QoL scores up to 5 years post-surgery were analysed. SF-12 responses were transformed into utility values between 0 and 1, where 0 is equivalent to being 'dead' and 1 is equivalent to 'full health', using the published Brazier algorithm [22]. The algorithm is widely used to score SF-12 responses in clinical trials, outcomes assessments and economic evaluations.

### 5.3.3. Diabetes classification

Patients were classified as diabetes or no diabetes based on self-reported information collected at baseline prior to surgery. Patients identified to have diabetes were further verified through checks of their patient medical records for information on anti-diabetic medication use (none, oral or subcutaneous) and glycated haemoglobin A1c (HbA1c) collected within 6 months of the date of surgery. Patients with diabetes were then further classified as having adequate glycaemic control (HbA1c < 7.0% (53 mmol/mol)) and poor control (HBA1c ≥ 7.0% (53 mmol/mol)).

### 5.3.4. Statistical analysis

Differences in proportions between patients with diabetes and no diabetes were compared using the Pearson's chi-squared test and paired *t*-tests for continuously distributed

variables. Multilevel modelling was used to determine whether changes in QoL differed depending on diabetes status. This approach was used in this study as it can account for the longitudinal nature of the data, assess patterns of change of repeated measures over time, both within and between patients, and account for missing values [23,24]. This modelling approach can produce more robust coefficients compared to standard cross-sectional techniques as it allows for a flexible method of modelling within-cluster correlation; i.e., account for the correlation between QoL measures of individuals over time [23]. Time was modelled as a categorical predictor to allow for the flexibility in capturing QoL patterns over time and to facilitate comparisons across time points [25].

Diabetes status was included in the model as a main effect, and an interaction term with time was included if interaction terms were significant. The analysis was conducted for both males and females separately and combined, with and without controlling for possible confounders including age at surgery, sex, BMI, smoking status, radiographic osteoarthritis severity, existing co-morbidities, rurality and socio-economic status. Variables included in the final model were those variables that demonstrated evidence of significant association with QoL utility values ($p < 0.05$) identified using backwards stepwise elimination and cross validated using forwards stepwise selection. Separate models were also fitted to assess if QoL trends differed between patients on different types of antidiabetic medications and by glycaemic control. All analyses were conducted using Stata SE14 (StataCorp, College Station, TX, USA), employing Stata command MIXED for multilevel mixed-effects linear regression.

## 5.4. Results

A total of 1892 patients were identified from the registry. Patients were excluded if they had missing baseline utility score ($n = 3$), no follow-up utility scores ($n = 36$), underwent early revision ($n = 32$) or died within 2 years of surgery ($n = 14$). For individuals that underwent bilateral knee surgery during the study period ($n = 254$), only the most recent TKR was included in the analysis. After excluding 339 cases, 1553 TKR patients were included in the analysis (Figure 5.1). At five-year follow-up, 1218 (78.43%) patients had complete SF-12 responses at all six time points (including baseline).

Of the 1553 TKR patients, approximately one-fifth ($n = 319$) were identified to have diabetes. Table 5.1 summarizes the baseline characteristics of all patients according to

diabetes status. Patients with diabetes were observed to be more likely to have higher BMI, report co-existing cardiovascular disease and scored higher on the ASA scale. Apart from these characteristics, there were no significant differences between other characteristics. Of note, both groups had similar mean baseline QoL utility values.

Among patient with diabetes, 203 patients (63.64%) and 31 (9.72%) were on oral and subcutaneous medications, respectively, while the remaining 85 (26.65%) were not on any medication. Information on HbA1c was available for 159 patients (49.84%). Among these patients, 99 (62.26%) had adequate glycaemic control (mean HbA1c was 6.34% (46 mmol/mol) (SD, 0.43)) and the remaining were classified as having poor control with mean HbA1c of 8.21% (66 mmol/mol) (SD, 1.21).

Figure 5.2 shows the patterns of quality-of-life over 5 years from pre-surgery to 5-years post-surgery of patients by diabetes status and sex. In general, QoL improved markedly by 1-year post-surgery and plateaued in subsequent years. Despite both groups starting out with the same level of QoL at baseline, results from the multilevel model indicated that patients with diabetes consistently report lower QoL (on average by 0.028, $p < 0.001$) and did not improve to the same level as patients without the disease (Table 5.2). There were also evident differences between males and females (Figure 5.2). Females were found to have significantly lower QoL (by 0.030, $p < 0.001$) compared to males and the impact of diabetes on QoL was much more pronounced in females than in males. There were observable differences between the patterns of recovery between females and males. Females with and without diabetes have the same level of improvement up to 1 year post-surgery, however, their QoL trajectories diverge in subsequent years, resulting in a significant difference in QoL between those with and without diabetes. Contrarily, among males, those with diabetes achieve less improvement at 1-year post-surgery than those without diabetes but this difference reduces in subsequent years. Other risk factors associated with important differences in QoL included pre-existing respiratory or mental health conditions, ASA score, rurality and aetiology of disease (see Table 5.2).

Subgrouping by glycaemic control (HbA1c) and medication types did not reveal any statistically significant differences in QoL trends among patients with diabetes (Figures S5.1 and S5.2 in Appendix A).

## 5.5. Discussion

While studies examining QoL in patients with diabetes frequently report lower QoL than those without diabetes [10–12], there is much less literature reporting the long-term differences in QoL outcomes following a major surgical procedure such as TKR. In this longitudinal analysis of QoL outcomes after TKR, we found that despite there being no significant difference in QoL at surgery and achieving substantial improvement in QoL following TKR surgery, patients with diabetes do not achieve the same gains in health outcomes as patients without diabetes. This difference was most pronounced among females, with this patient subgroup persistently reporting lower QoL across the 5-year post-surgery period. These findings are useful in helping guide care among patients with diabetes and in facilitating discussions of expected outcomes and impact of surgery on their QoL. An important finding was the sex difference in outcomes highlighting the need to consider if females with diabetes should be managed differently in order to maximise their outcomes.

Studies examining functional outcomes after knee replacement found that patients with diabetes have lower ranges of motion and are at higher risk of limitations on daily activities and living post-surgery compared to patients without diabetes [16,26,27]. This may, in part, explain the poorer QoL observed in our study, and, if so, there may be a role for diabetes specific rehabilitation programs to maximise their outcomes. These could include lifestyle interventions to improve physical function [28] or exercise programs structured together with supervision to improve QoL [29]. Currently prescribed regimens tend not to discriminate between patient types, therefore, tailoring post-operative rehabilitation programs according to patients' needs and relevant risk factors such as diabetes, other co-morbidities and by gender may be important. Because QoL utility values follow a rise and plateau pattern over time, the period after surgery (first year post-surgery) appears to be an important window to maximise patient outcomes from which the effects will plateau.

Although there are differences in patient-reported QoL across patient subgroups, it is also important to know if this translates into a meaningful difference. The minimal clinically important difference is commonly used to capture the smallest amount of change that would be considered beneficial to the patient [30]. The findings from this study indicate that improvements in QoL attained from TKR was substantial and significant, and that

the differences observed between diabetes and no diabetes (on average 0.028, $p < 0.001$), and between female and male are important as they are within the range considered clinically important [31].

The sex differences reported in this study concur with existing literature which found females experiencing worse outcomes compared to males. This is not unique to knee surgery, as similar observations have been made in patients with stroke [32,33], rheumatoid arthritis [34] and in bipolar disorders [35]. The specific reasons for this are unclear but pain can have substantial impact on patient's QoL outcomes and women with osteoarthritis may experience more pain and greater pain sensitivity which can translate into poorer QoL [36,37]. It may also be possible that women may be exposed to greater socioeconomic disadvantage than men which may have an impact on their recovery and QoL following surgery [38]. It would be important for future research to examine this to aid our understanding of differences in outcomes after TKR and to identify contributors to sex differences. Particular attention should also be paid to modifiable risk factors to poor response. Comorbidities in diabetes patients have been found to be associated with lower QoL and its negative impact on QoL increases with the number of comorbidities or a comorbidity index/score [39,40]. In this study, we found that patients reporting conditions that are treatable such as respiratory and mental health disorders are at significant risk of reporting poorer QoL (Table 5.2). This provides important information for clinicians to identify patients reporting these conditions as strategies to mitigate these factors may show outcome benefits.

Patients with diabetes are often 'optimized' pre-operatively, starting in primary care, which includes attaining good glycaemic control, sufficiently managing other diabetes-related co-morbidities and ensuring careful planning of care at all stages of the patient pathway [41,42]. Given that a patient's baseline QoL is likely to be strongly correlated with their subsequent QoL over the follow-up period [43], there is scope to leverage the use of PROMs to optimize patients' well-being pre-operatively to improve post-surgical outcomes. A recent randomised controlled study investigating the efficacy of a mental health enhancement program prior to joint surgery found the program an effective strategy in improving pain and physical function among those at risk of poor response to surgery [44]. This therefore suggests that optimizing other aspects of patient's well-being

beyond medication management and glycaemic control could also be an important consideration in ensuring better QoL outcomes post-surgery.

In general, TKR is widely regarded as a cost-effective procedure. However, studies have shown that patients with diabetes are associated with longer length of hospitalization and increased costs [45,46]. Given that QoL utility values are a key component in health economic analyses for assessing the value of the intervention, our findings indicate that patients with diabetes, particularly females and those with poor glycaemic control are less likely to achieve the same value compared to patients without diabetes. This aligns with a recent study identifying diabetes and females to be predictors of low-value care from the patients and payers' perspectives, respectively [47]. Therefore, cost-effectiveness results based on population averages may not adequately reflect the true value of the intervention and more needs to be done to identify vulnerable populations that require better care and quantify the value of intervening. This can be important as healthcare systems are transitioning from volume- to value-based health care and emphasis has been placed on optimizing patient outcomes and experience [48]. The regression coefficients presented in this paper can be used to derive QoL utility values to assess the cost-effectiveness of specific subgroup populations.

Our study has several limitations. Patients included in this analysis were from a single institution which can limit the generalisability of the findings. However, the demographics of patients in this study closely reflect those reported in our National Joint Replacement Registry [5]. It was difficult to distinguish between type 1 and type 2 among diabetes patients based on the information captured in the registry; thus, it is unclear if QoL trajectories between these subgroups would be different, which warrants further research. A substantial amount of HbA1c information was missing as these were not documented in patients' medical records which limited the interpretation of our results by HbA1c subgroups. While we do not know the reason for this missing information and it is uncertain if the missingness is related to an acknowledgement of good glycaemic control, this highlights the need for protocolised screening of diabetes and hyperglycaemia (with or without diagnosis of diabetes) as both are known risk factors for poor outcomes post-surgery [49,50].

## 5.6. Conclusions

Patients with diabetes exhibit significantly poorer QoL compared to patients without diabetes following TKR and this is emphasized in females. These findings highlight the need for a better understanding of patient and physiologic differences and for tailoring management to optimise patient outcomes. Knowledge of risk factors that impact on QoL after TKR may be used to guide patient-centered care.

## 5.7. Tables and figures

Table 5.1: Demographic and clinical characteristics according to diabetes status

| | No diabetes | | Diabetes | | p-value for |
|---|---|---|---|---|---|
| | n | % | n | % | difference |
| Demographics | 1234 | 79.46 | 319 | 20.54 | |
| Age (SD) | 69.90 | 8.73 | 70.67 | 7.74 | 0.149 |
| Female | 838 | 67.96 | 209 | 65.31 | 0.416 |
| Smoking status | | | | | 0.321 |
| No | 840 | 68.05 | 225 | 70.53 | |
| Ex | 303 | 24.57 | 78 | 24.45 | |
| Yes | 91 | 7.38 | 16 | 5.02 | |
| SEIFA | | | | | 0.400 |
| 1-5 | 453 | 36.71 | 109 | 34.17 | |
| 6-10 | 781 | 63.29 | 210 | 65.83 | |
| Rurality | | | | | 0.093 |
| Metropolitan | 1015 | 82.24 | 275 | 86.21 | |
| Regional | 219 | 17.76 | 44 | 13.79 | |
| Clinical characteristics | | | | | |
| BMI | | | | | <0.001 |
| <30 | 449 | 36.39 | 64 | 20.06 | |
| 30-35 | 406 | 32.9 | 104 | 32.6 | |
| 35-40 | 238 | 19.29 | 104 | 32.6 | |
| 40+ | 141 | 11.43 | 47 | 14.73 | |
| Aetiology | | | | | 0.067 |
| Osteoarthritis | 1148 | 93.03 | 308 | 96.55 | |
| Other | 86 | 7.97 | 11 | 3.44 | |
| Kellgren and Lawrence score † | | | | | 0.677 |
| ≤3 | 597 | 48.54 | 159 | 49.84 | |
| 4 | 633 | 51.46 | 160 | 50.16 | |
| Bilateral surgery | 196 | 15.88 | 52 | 16.3 | 0.856 |
| Reported co-morbid conditions | | | | | |
| Cancer | 108 | 8.75 | 20 | 6.27 | 0.151 |
| Cardiovascular | 984 | 79.74 | 297 | 93.1 | <0.001 |
| Respiratory | 225 | 18.23 | 57 | 17.87 | 0.88 |
| Mental health disorder | 223 | 18.07 | 71 | 22.26 | 0.089 |
| Pre-operative status | | | | | |
| ASA | | | | | <0.001 |
| 1/2 | 773 | 62.64 | 128 | 40.13 | |
| 3/4 | 461 | 37.36 | 191 | 59.87 | |
| Patient-reported QoL (SD) | 0.57 | 0.11 | 0.56 | 0.11 | 0.138 |

* Other combines rheumatoid arthritis and avascular necrosis

† KL score missing for 4 patients

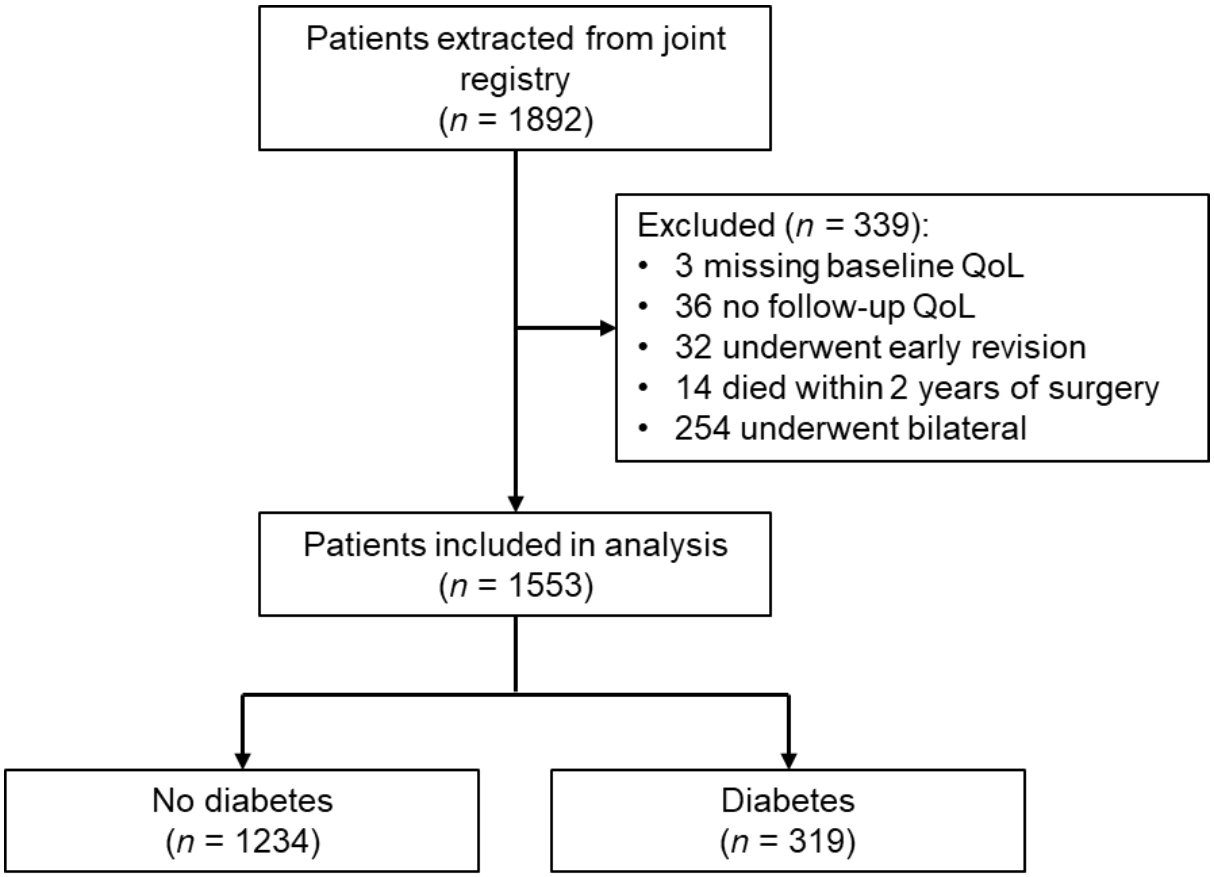
Table 5.2: Effect of patient characteristics on changes in QoL over time: coefficients estimated from multilevel regression model

| Description | All | | | | Female | | | | Male | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Coef. | 95%CI | | p-value | Coef. | 95%CI | | p-value | Coef. | 95%CI | | p-value |
| Year since surgery | | | | | | | | | | | | |
| 1 | 0.164 | 0.155 | 0.172 | 0.000 | 0.161 | 0.151 | 0.172 | 0.000 | 0.168 | 0.153 | 0.184 | 0.000 |
| 2 | 0.161 | 0.152 | 0.170 | 0.000 | 0.159 | 0.148 | 0.170 | 0.000 | 0.164 | 0.147 | 0.180 | 0.000 |
| 3 | 0.152 | 0.143 | 0.161 | 0.000 | 0.152 | 0.141 | 0.162 | 0.000 | 0.152 | 0.136 | 0.169 | 0.000 |
| 4 | 0.139 | 0.129 | 0.148 | 0.000 | 0.140 | 0.129 | 0.151 | 0.000 | 0.136 | 0.119 | 0.153 | 0.000 |
| 5 | 0.132 | 0.123 | 0.142 | 0.000 | 0.134 | 0.123 | 0.146 | 0.000 | 0.127 | 0.109 | 0.145 | 0.000 |
| Diabetes | -0.003 | -0.017 | 0.010 | 0.655 | -0.002 | -0.018 | 0.014 | 0.792 | -0.004 | -0.029 | 0.020 | 0.719 |
| Diabetes x year interaction | | | | | | | | | | | | |
| 1#Diabetes | -0.024 | -0.043 | -0.005 | 0.015 | -0.017 | -0.041 | 0.007 | 0.159 | -0.037 | -0.071 | -0.003 | 0.031 |
| 2#Diabetes | -0.036 | -0.056 | -0.017 | 0.000 | -0.044 | -0.068 | -0.020 | 0.000 | -0.024 | -0.059 | 0.011 | 0.186 |
| 3#Diabetes | -0.028 | -0.048 | -0.008 | 0.006 | -0.033 | -0.058 | -0.009 | 0.007 | -0.018 | -0.053 | 0.018 | 0.321 |
| 4#Diabetes | -0.034 | -0.055 | -0.013 | 0.001 | -0.041 | -0.066 | -0.016 | 0.001 | -0.021 | -0.057 | 0.016 | 0.262 |
| 5#Diabetes | -0.026 | -0.047 | -0.005 | 0.016 | -0.038 | -0.063 | -0.013 | 0.003 | -0.003 | -0.041 | 0.035 | 0.892 |
| Female | -0.030 | -0.040 | -0.020 | 0.000 | - | - | - | - | - | - | - | - |
| Respiratory | -0.020 | -0.032 | -0.008 | 0.001 | -0.018 | -0.032 | -0.004 | 0.014 | -0.026 | -0.049 | -0.002 | 0.031 |
| Mental health disorder | -0.040 | -0.052 | -0.028 | 0.000 | -0.034 | -0.048 | -0.020 | 0.000 | -0.053 | -0.076 | -0.030 | 0.000 |
| ASA | | | | | | | | | | | | |
| 1/2 | Ref | | | | Ref | | | | Ref | | | |
| 3/4 | -0.028 | -0.037 | -0.018 | 0.000 | -0.028 | -0.039 | -0.016 | 0.000 | -0.026 | -0.044 | -0.009 | 0.004 |
| Rurality | | | | | | | | | | | | |
| Metropolitan | Ref | | | | Ref | | | | Ref | | | |
| Rural | 0.031 | 0.018 | 0.043 | 0.000 | 0.030 | 0.014 | 0.046 | 0.000 | 0.032 | 0.012 | 0.053 | 0.002 |
| Aetiology | | | | | | | | | | | | |
| Osteoarthritis | Ref | | | | Ref | | | | Ref | | | |
| Other | -0.030 | -0.049 | -0.011 | 0.002 | -0.020 | -0.042 | 0.003 | 0.083 | -0.055 | -0.093 | -0.017 | 0.005 |
| Constant | 0.601 | 0.578 | 0.623 | 0.000 | 0.571 | 0.562 | 0.581 | 0.000 | 0.607 | 0.592 | 0.621 | 0.000 |
| Random effect | | | | | | | | | | | | |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Residual standard deviation at each time point (SE) | | | | | | | | | | | | |
| 0 | 0.108 | 0.002 | - | - | 0.105 | 0.002 | - | - | 0.115 | 0.004 | - | - |
| 1 | 0.148 | 0.003 | - | - | 0.147 | 0.003 | - | - | 0.150 | 0.005 | - | - |
| 2 | 0.152 | 0.003 | - | - | 0.150 | 0.003 | - | - | 0.156 | 0.005 | - | - |
| 3 | 0.153 | 0.003 | - | - | 0.152 | 0.003 | - | - | 0.155 | 0.005 | - | - |
| 4 | 0.151 | 0.003 | - | - | 0.150 | 0.003 | - | - | 0.154 | 0.005 | - | - |
| 5 | 0.152 | 0.003 | - | - | 0.150 | 0.003 | - | - | 0.156 | 0.005 | - | - |

* Other combines rheumatoid arthritis and avascular necrosis. ASA: American Society of Anaesthesiologist (ASA) Physical Status Classification, CI: confidence interval, Coef: coefficient

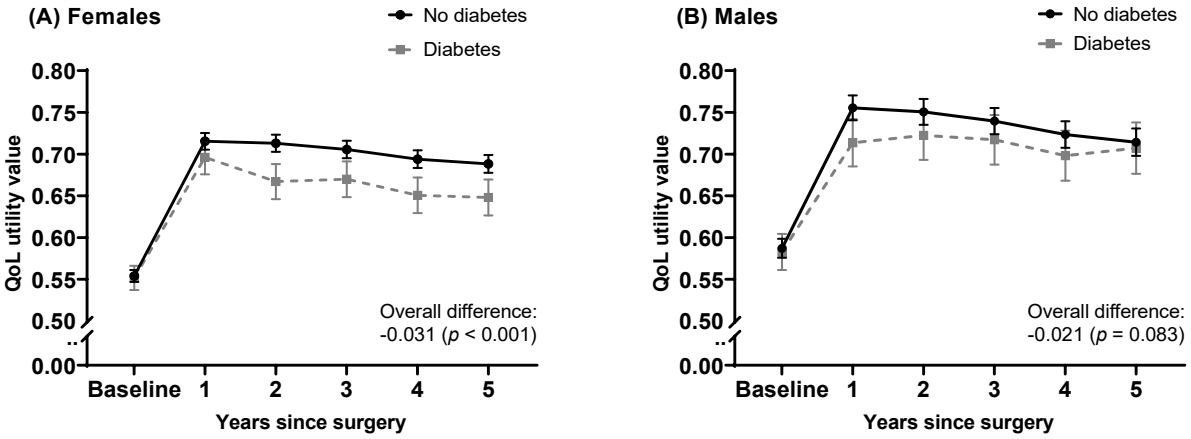
Figure 5.1: Flow diagram of patients included in the longitudinal analysis




QoL: quality-of-life.

Figure 5.2: Long-term patterns of QoL utility value changes in total joint replacement (TKR) patients in (A) females and (B) males.

The solid black lines represent no diabetes group; the grey dotted lines represent the diabetes group. Data points represent the time coefficients for each group predicted by the multilevel model adjusted for covariates. The error bars represent the 95% confidence intervals.




QoL: quality-of-life.

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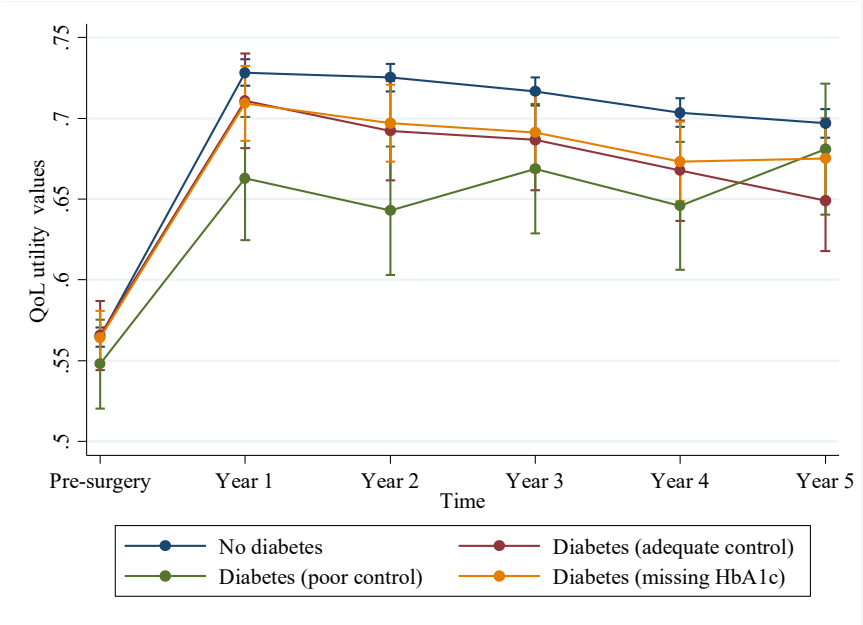
## 5.9. Supplementary materials

### Appendix A

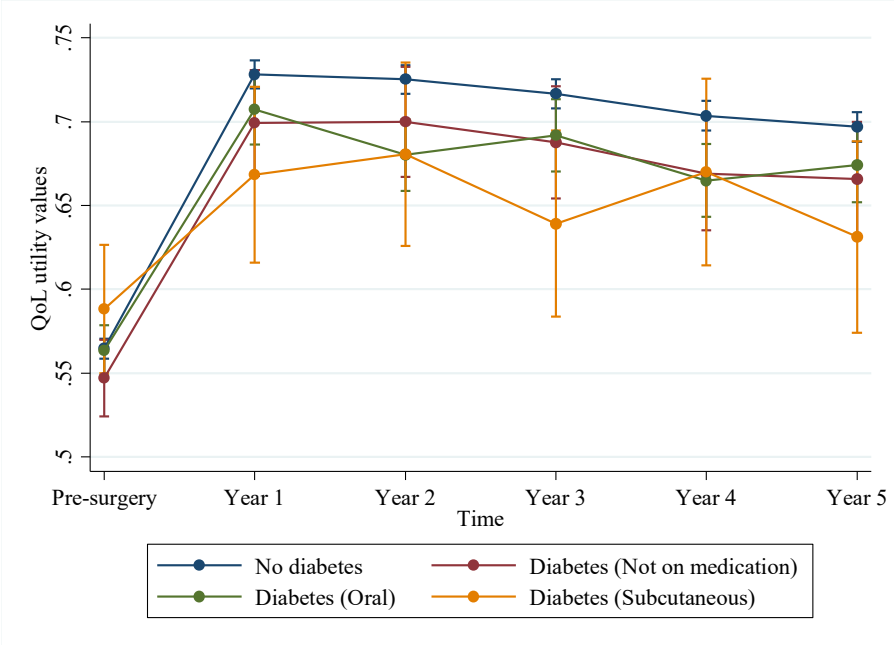
Figure S5.1: QoL utility value changes among TKR patients by HbA1c control




Those in the diabetes group were further sub-grouped into patients with poor (HbA1c ≥ 7%) and adequate glycaemic control (HbA1c < 7%), and those with missing HbA1c values. Data points represent the time coefficients for each group predicted by the multilevel model adjusted for covariates. The error bars represent the 95% confidence intervals.

HbA1c: glycated haemoglobin, QoL: quality-of-life, TKR: total knee replacement

Figure S5.2: QoL utility value changes among TKR patients by medication use




Those in the diabetes group was further categorised by the types of anti-diabetic medication use. The data points represent the time coefficients for each group predicted by the multilevel model adjusted for covariates. The error bars represent the 95% confidence intervals.

# Chapter 6 : Exploring the impact of quality-of-life on survival: A case study in total knee replacement surgery

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*Authors: Michelle Tew, Kim Dalziel, Michelle Dowsey, Peter Choong and Philip Clarke.*

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## 6.1. Abstract


### Background

There is growing evidence that quality-of-life (QoL) has a strong association with mortality. However, incorporation of QoL is uncommon in standard survival modelling.

### Methods

Using data extracted from a registry of patients undergoing total knee replacement (TKR), the impact of incorporating QoL in survival modelling was explored using four parametric survival models. QoL was incorporated and tested in two forms which are baseline and change in QoL due to intervention. Life expectancy and quality-adjusted life years (QALYs) were calculated and comparisons made to a reference model (no QoL) to translate the findings in the context of modelled economic evaluations.

### Results

A total of 2,858 TKR cases (2,309 patients) who had TKR between 2006 and 2015 were included in this analysis. Increases in baseline and change in QoL were associated with a reduction in mortality. Compared to the reference model, differences of up to 0.32 life years and 0.53 QALYs were observed and these translated into a 9.5% change in incremental effectiveness. These differences were much larger as the strength of the association between QoL and mortality increased.

### Conclusions

This work has demonstrated that the inclusion of QoL measures (at baseline and change from baseline) when extrapolating survival does matter. It can influence health outcomes such as life expectancy and QALYs, which are relevant in cost-effectiveness analysis. This is important because neglecting the correlation between QoL and mortality can lead to imprecise extrapolations thus risk misleading results affecting subsequent decisions made by policy makers.

## 6.2. Introduction

Extrapolation of survival beyond the study period is often required to capture outcomes over a longer time frame, such as lifetime horizon, to adequately inform policy makers on funding decisions. A variety of extrapolation approaches can be employed in health economic analysis; for instance, directly derived from life tables [1-3] or by modelling survival to extrapolate observed trends in the hazard for death [4, 5]. The increasing availability of individual-level data has allowed analysts to more accurately model survival to the population of interest [6-8]. Survival modelling approaches can vary from standard (semi-)parametric methods to complex flexible models and there have been much guidance on model selection to avoid inconsistent and biased analyses [9-15]. Underpinning most economic models is a variant of a survival model used to generate hazard functions required for estimating survival. These survivor functions can be used to inform transition probabilities in a Markov model [16] and have helped inform a range of health economic disease progression models [17-19], which simulate both individuals' life expectancy and health states that impact on patients' quality-of-life (QoL).

The relationship between self-reported health and mortality is well-documented and numerous studies have demonstrated the predictive significance of such measures on health outcomes [20-22]. Patient-reported outcomes such as QoL have consistently been demonstrated to be an important predictor of mortality in patients with chronic diseases such as diabetes, pulmonary arterial hypertension, cancer and also in the general population [23-27]. These studies have shown that patients reporting poorer QoL generally have poorer survival even after controlling for standard risk factors such as demographic and clinical characteristics [28, 29]. Similarly, change in QoL has also been reported to be associated with mortality [25, 30]. Considering the growing evidence for this, it can be important for health economic models to account for the relationship between varying levels of QoL and mortality to capture survival estimates for a complete economic analysis. This is important because imprecise extrapolations could misinform policy decisions.

The purpose of this paper is to examine the importance of the relationship between QoL and mortality and how this could influence survival estimates. We illustrate this using a cohort of registry patients who have undergone total knee replacement (TKR) extracted from the St. Vincent's Melbourne Arthroplasty Outcomes (SMART) Registry as our case-

study. We consider the aspects of QoL measurement (baseline and change due to intervention) that are relevant to economic evaluations and correlations that could have implications for estimating survival. Changes in QoL can be important particularly in the context of surgery because changes after surgery can be large [31, 32] therefore the degree to which this can influence survival estimates may be important.

The structure of the paper is as follows. First, we explain the significance of the correlation between QoL and survival and where this can be of importance in health economic models. We then empirically explore the effects of QoL on survival and develop survival models to quantify this. In health economic analyses, gains in health outcomes such as life expectancy (LE) and quality-adjusted life year (QALY) are most relevant. Therefore, survival estimates are used to calculate LE and QALYs to translate our findings and its implications in the context of modelled economic evaluations. The discussion draws together the potential implications on current practices of extrapolating survival, highlight areas for further research directions and limitations of the current study.

*Current survival extrapolation approaches and their underlying QoL assumptions on mortality*

A common approach of extrapolating survival in economic evaluations that typically do not have access to individual-level data is to apply population derived mortality estimates from publicly available life tables. For example, data based on age and sex from national life tables were applied to estimate QALYs gained until the end of the patient's life [1-3, 33]. Although a reasonable approach, it does not take into account the influence of specific patient characteristics of the underlying population on survival estimates [4]. Importantly, it also assumes no correlation between QoL and mortality.

In cases where individual data is available, survival can be estimated through survival analysis if information on death is also collected. These approaches commonly include baseline demographic and patient characteristics such as age, gender and co-morbidity measures to generate survival estimates relevant to the patient population of interest. However, such an approach also neglects any potential correlation between QoL and mortality.

Irrespective of the extrapolation technique employed, current health economic models rarely capture the correlation between QoL and survival. We postulate that if QoL is correlated with mortality, it could influence survival and consequently, LE and QALYs which are relevant to economic evaluations.

*Significance of correlation between QoL and survival in modelled economic evaluations*

In the following section, it is assumed that preference-based health-related QoL can be measured at an individual level which we denote as $U^i$ and similarly the time the individual experience that health state is denoted by $LE^i$ where $i$ denotes the individual. We assume that $0 < U^i < 1$ and for simplicity, impose time invariance on $U^i$ over the period used in the evaluation which for many studies is remaining life expectancy.

While the QALY is ultimately a product of both utility (U) reflecting health status and LE, the assessment of these outcomes has been considered largely independently with little recognition that health status and survival should be jointly modelled as they could be highly correlated. We illustrate the significance of the correlation between QoL and survival using the following well-known identity [34]

$$QALY = E(U \cdot LE) = E(U) \cdot E(LE) + cov(U, LE)$$

where E indicates the expected value and $cov(U, LE)$ denotes the covariance of $U$ and $LE$. If U and LE are uncorrelated (i.e. statistically independent), then $E(U \cdot LE) = E(U) \cdot E(LE)$ and the product of two expected values is likely to be the more efficient estimator. However, if those within the cohort with higher levels of $U$ also have longer survival, indicating a positive correlation, then $cov(U, LE) > 0$ and this approach would result in downward biased estimates. Therefore, calculating QALYs on the assumption that quality and quantity of life is independent can bias QALY estimates. Further illustration is provided in Appendix 1 and for detailed explanations, see [34].

While it is likely that the incorporation of standard baseline characteristics will provide valid survival estimates and will at least partially capture $cov(U, LE)$, there is growing evidence indicating QoL is an important independent predictor of mortality in addition to these standard risk factors [23, 28, 35-37]. Therefore, current extrapolation approaches that do not capture the full correlation between QoL and survival could give rise to the potential for systematic bias in QALY outcomes.

Health economic evaluations involves comparisons between alternative interventions, therefore are primarily concerned with the incremental outcomes associated with health care interventions. Additionally, one must also consider the effect a treatment may have on baseline utility ($U_0^i$), which is denoted as $\Delta U^i$ to represent the change in quality-of-life after the intervention. Importantly, $\Delta U^i$ may vary across patients; for example, some patients experience a great improvement in their QoL which should be reflected in them having a higher $\Delta U^i$, while for a proportion of patients $\Delta U^i < 0$ indicating that the intervention has not had any positive impact.

As far as we are aware the statistical relationship between $\Delta U^i$ and survival has not been widely studied. It is plausible that it is likely to be positively correlated with survival for most interventions (i.e. patients have greatest improvement in quality of life are expected to live longer). Given the bounded nature of health outcomes, lower values of $U_0^i$ will provide greater scope for improvement as $U_0^i + \Delta U^i < 1$ and if this is true, then the correlation is likely to be negative. However, it is also plausible that for some diseases and treatments there is a positive correlation if those with better initial quality of life respond more to treatment. In the next section we will explore this issue empirically for the case of TKR.

## 6.3. Methods

*Data source and study population*

Data on all patients, aged 55 and above, who had TKR between January 1, 2006 and December 31, 2015 were extracted from the SMART Registry. It captures clinical and patient-reported outcomes in all patients who undergo elective hip and knee replacement at the study institution. Baseline data were prospectively collected and included patient socio-demographic variables and self-reported co-morbidities. Patients complete a general health questionnaire (SF-12) within 12 weeks prior to surgery and annually post-operatively. Mortality data was recorded and verified with information from the Registrars of Births, Deaths and Marriages via the Australian Orthopaedic Association National Joint Replacement Registry [38]. Individuals were excluded from analysis if they had missing baseline utility value, underwent revision or died in the first year of follow-up.

A total of 2,858 TKR cases (2,309 patients) contributed to this analysis. All patients were followed up until December 31, 2016, the latest date with complete death records at time of data extraction. The mean duration of follow-up was 5.71 years (SD, 2.75) with the longest duration being 10.99 years. Within this period, 295 (12.78%[*]) of patients died. Baseline (pre-surgery) and 12 month post-surgery utilities were calculated from SF-12 responses using the published SF-6D algorithm [39]. Among those patients who have been followed-up for at least 5 years, 92.4% of patients had completed the SF-12 surveys at all 5 time points. Therefore, using this as a proxy to indicate that patients have not been loss to follow-up, the follow-up rate is 92.4%. Change (improvement or deterioration) in utility ($\Delta U$) was calculated as the difference between baseline and 12-month utilities. To facilitate comparisons, the cohort was grouped into tertiles by baseline utility with the first tertile representing one-third of the cohort with the lowest baseline utility and the third tertile representing those with the highest baseline utility. Further details of the patient population used in this case study can be found in Appendix 2.

*Exploring the empirical relationship between QoL and survival*

To visually examine the impact of different baseline and change in QoL utility values on survival, Kaplan-Meier survival curves were plotted. Comparisons were made between the lowest and highest tertiles by baseline utility and also between those who improved or deteriorated following surgery. Log-rank test was performed to test for differences between groups.

*Survival models for all-cause mortality*

To illustrate and quantify both the impact and extent of influence QoL has on mortality risk, four risk equations were developed to estimate the hazard of all-cause mortality for patients undergoing TKR using parametric survival models, where time at risk starts 12 months post-surgery. For simplicity, only sex and relevant utilities were included, and age was used as the time scale of the model thus allowing for more efficient within sample predictions [12]. The four survival models demonstrated the extent of QoL impact on mortality risk. Model 1 served as the reference model with sex as the only covariate, Model 2 contained sex and baseline utility, Model 3 contained sex and change in utility, and lastly Model 4 included sex, baseline utility and change in utility. Model 1 represents

[*] Corrected post-publication

a simplification of the most common method of estimating survival where mortality risk is defined by non-modifiable patient characteristics such as sex and does not include patient-reported outcomes such as QoL. As individual patients were allowed to contribute multiple knee surgeries (maximum of 2) to the analysis, this was taken into account by clustering the analysis at the level of the individual patient [40].

Various parametric distributions (exponential, Weibull, Gompterz, log-logistic and log-normal) were considered. The Gompertz distribution was determined to be the best fit through assessments based on graphical exploration and both Akaike and Bayesian Information Criterion (AIC/BIC) [15, 41]. Graphical plots, measures of model fit and Stata codes are provided in Appendix 3. These assessed fit to available data (demonstrating internal validity) and external validation included comparing mortality rates and life expectancies by age and gender from life-tables published by the Australian Bureau of Statistics [42]. It is possible that other patient demographic and clinical characteristics (e.g. body mass index (BMI), smoking status, socioeconomic status) could influence survival therefore risk equations including these additional covariates were tested in sensitivity analysis (outlined in Appendix 4). All analyses were conducted using Stata 14.2 SE (Stata Corp, College Station).

*Translating findings in the context of modelled economic evaluations*

Relevant to economic evaluations and health economic disease progression models, survival estimates are commonly translated into life years and/or QALYs to quantify health effects derived from an intervention. As such, survival functions generated were used to estimate the life expectancies for each individual patient using standard life table methods (outlined in Appendix 5). QALYs were calculated using the area under the curve method [43] using patient-level utilities and estimated life expectancies, and assuming linearity between the two utility scores, which is a common approach in cost-effectiveness studies [44, 45]. Incremental QALYs (gained from TKR) was calculated as the difference in QALYs observed and QALYs expected assuming a control group where the patient did not undergo surgery and experienced no change from baseline utility, as is standard in literature [45-49]. LEs and QALYs from each of the models were compared to the reference model (Model 1) to demonstrate the impact of incorporating QoL when estimating survival. To further illustrate the possible impact across different subgroups within the cohort, a simulation exercise was conducted to show how LE and QALY might

vary across ages at different levels of baseline utility. Inputs for change in utility were the mean change at each level of baseline utility as observed in the cohort.

*Assessing the strength of association between QoL and mortality on incremental outcomes*

The relative size of the impact on estimated LEs and QALYs is likely to be larger with stronger associations between QoL and mortality. This will in turn have an impact on incremental outcomes such as incremental QALYs that are of interest in economic evaluations. We tested the impact of the strength of association by imposing a range of 5% increments and decrements on the hazard ratios of QoL predictors generated from each of the survival models on the same cohort. LEs, QALYs and incremental QALYs were calculated as per methods described above and compared to the base case to examine the magnitude of change in incremental outcomes as the association increases or decreases. We present the results to show the effects of varying strengths of association on incremental QALYs for each of the models.

## 6.4. Results

The average utility of the cohort was 0.56 (SD, 0.11) at baseline and improved by 0.16 (SD, 0.19) 12 months after surgery. Figure 6.1A shows the patterns of QoL following TKR for an average TKR patient and for each tertile group. Patients in the second tertile were observed to have a very similar pattern to the cohort average. The pattern of QoL varied depending on baseline utility. Patients with a lower baseline utility exhibited a greater magnitude of improvement post-surgery than those with higher utility thus showing a negative correlation between baseline and change in utility at 12 months ($\Delta U$) (Figure 6.1B). This is likely to be due to ceiling effects where there is less room to improve beyond a maximum utility value of 1, particularly for those with high baseline utility.

*Observed relationship between QoL and survival*

Figure 6.2 shows the Kaplan-Meier survival plots of (A) patients with low baseline utility (first tertile) compared to high baseline utility (third tertile) and (B) patients who deteriorated ($\Delta U \leq 0$) compared to those who improved ($\Delta U > 0$) after surgery. Patients with low baseline utility were observed to have higher mortality risk compared to high baseline

utility patients (P=0.019) and patients who did not improve ($\Delta U \leq 0$) after surgery were also observed to be at a greater risk of death (P<0.001). This highlights the higher rate of mortality among those with lower utility values.

*Coefficients and hazard ratios from survival models*

The coefficients and hazard ratios for each of the models for all-cause mortality are presented in Table 6.1. Results from all models indicated that being female was associated with a significant reduction in all-cause mortality hazard by up to 45.6%. Results from Model 2 indicate a 9% reduction in hazard of death for every 0.1 unit increase in baseline utility, although not statistically significant (P=0.115). Incorporating change in utility (Model 3) produced a statistically significant coefficient, indicating a 15% (95%CI, 7.8-21.6%) reduction in hazard of death for each 0.1 unit increase in utility change. Results from Model 4 showed a statistically significant relationship with mortality indicating that a 0.1 unit increase in baseline utility is associated with a 18.8% reduction in hazard of death (95% CI, 8.02-28.3%), while a 0.1 unit greater improvement in utility 12 months following surgery was associated with a 20.0% (95% CI, 12.4-27.0%) reduction in hazard of death. These results point to evidence of a relationship between QoL and overall survival; particularly for change in utility. Similar results were produced from our sensitivity analysis with models including additional covariates (patient demographic and clinical characteristics). These results can be found in Appendix 4. The inclusion of QoL variables improved model fit as Models 2, 3 and 4 have lower AIC/BIC values (Table 6.1) compared to Model 1.

*Life expectancy and QALY estimates*

The results (Table 6.2) show that compared to the reference model, incorporating baseline utility into the survival model had a very small impact (less than a 0.2% change) on the average LE and QALY of the cohort. Change in utility had a larger impact as observed by Models 3 and 4, with differences of up to 0.32 years of life expectancy and 0.53 QALYs. Although small in absolute numbers, the relative differences in incremental QALYs were up to 9.5% compared to the reference model and these may not be insignificant to incremental cost-effectiveness results. Similar results were obtained using models that included patient demographic and clinical characteristics (see Appendix 4 for sensitivity analysis results).

Results from the simulation exercise are presented as contour plots (Figure S6.4 in Appendix 6) for each of the models showing the differences in estimated LE across ages 55 to 90 at varying baseline utility. LEs generated from Model 1 for each year in age were the same irrespective of baseline utility while Models 2, 3 and 4 showed variations in LE at different utility levels. Generally, patients with higher baseline QoL were observed to have longer LEs compared to those with lower QoL. While variations in health outcomes were small when the cohort was considered collectively (Table 6.2), these differences were much larger at different levels of baseline utility. For example, the LE of a 65-year old female estimated using Model 1 was 24.9 years regardless of baseline utility. Using Model 4, the estimated LE for 65-year old female patients with baseline utility in the first tertile (low baseline) is 24.6 years and 26.5 years for those in the third tertile (high baseline).

*Impact of strength of association on incremental QALYs*

Figure 6.3 shows how incremental QALYs change (compared to base case incremental QALYs presented in Table 6.2) for Models 2, 3 and 4 as the strength of association between QoL and mortality varies. Across all models, it is observed that as the strength of the association increases, the change in incremental QALYs increases. Using Model 4 as an example, reducing the QoL hazard ratios by 20% (representing an increase in strength of association), resulted in a 30.3% increase in incremental QALYs. This was similarly observed using Models 2 and 3 with a 29.6% and 15.6% change from the base case estimates, respectively. The observed curves appear to plateau with further increases and decreases in the % change in QoL HRs (i.e. as HRs become very small and big, respectively), particularly for Model 4 and 2. The impact of strength of association appears much weaker in Model 3 as observed by the flatter curve, thus indicating larger changes in HR of change in QoL are required for the same impact on incremental QALYs.

As Model 4 incorporates the effects of both baseline and change in QoL, this may explain its asymmetrical shape which does not sit between the curves of Models 2 and 3. Within Model 4, the impact of QoL appears to be influenced by baseline QoL based on the similarities in the shape of the curve with Model 2. This may likely be due to the larger scale of baseline QoL compared to the change in QoL, which is on a smaller scale; i.e. the mean baseline QoL utility of the cohort is 0.56 while the mean change in QoL of the cohort is 0.16. As baseline QoL is much larger than the change in QoL, the same relative

change on either of these variables will have very different impacts and expected to be larger for baseline QoL.

## 6.5. Discussion

Using an example of TKR, survival models were developed to investigate the relationship between QoL and survival, and its implications on outcomes relevant to economic evaluations. In this case study, it was postulated that QoL (utility value) could affect mortality risk; via the baseline utility and the change in utility 12-months post-surgery. The results from this study suggest that the inclusion of QoL measures when extrapolating survival can influence outcomes such as LEs and QALYs. The main implication this has for economic evaluations is that while there has been much research pointing towards a positive relationship between the two [23-26, 50, 51], it is uncommon to quantitatively consider QoL when extrapolating survival. This therefore overlooks the possible correlation between the two. If a positive correlation is present, patients with higher QoL are expected to exhibit longer LE compared to those with lower QoL. This will translate to more QALYs thus impacting cost-effectiveness results.

Although the absolute impact on LE and QALYs on the overall cohort was small (0.32 years and 0.53 QALYs respectively), these translated into a 9.5% change in incremental effectiveness, noting that even small differences in the denominator can lead to quite different cost-effectiveness results and can have an impact on decision making. TKR is generally considered a cost-effective procedure [1, 45], therefore in this case, inclusion of QoL is less likely to have a substantial impact on decision-making if based on cost-effectiveness thresholds. However, the impact on decisions based on ranking of interventions could be more pronounced although dependent on the competing alternatives compared. The differences in incremental effectiveness were much larger when examined at different levels of QoL and can provide valuable information on the value of intervening within a cohort. Further, the inclusion of QoL into survival models enables important patient-level heterogeneity to be incorporated and allows for subgroup analyses which can have important economic and clinical implications; for instance, targeting a subgroup of younger patients with poorer QoL.

In most modelling approaches, utilities are often incorporated as a fixed uniform utility for a health state that is applied to all patients in the health state [52] therefore not taking

into account the potential influence of QoL on survival and potentially neglecting the underlying heterogeneity in patient-reported outcomes. Approaches that consider QoL when estimating outcomes such as survival are not new as techniques such as quality-adjusted survival analysis [53] have been used; for instance, Hayes et al. [28] developed a diabetes simulation model which considers the significance of QoL as a predictor of future events and incorporates dynamically changing utilities when extrapolating long-term outcomes. Simulated results showed patients reporting full health (utility=1) had 4.7 years longer life expectancy and enjoy 10.9 QALYs more compared to a patient with a baseline utility of 0.6. This large difference in QALYs suggests a potential for bias if the effect of QoL was omitted.

The integration of QoL in health economic models will require estimation of risk equations for transition probabilities that explicitly include measure of health status such as utilities as demonstrated in this case study. While it is acknowledged that such analyses would require access to individual-patient level data, such information is becoming increasingly available particularly as health status instruments are routinely used in many clinical studies. Further, as a new generation of risk equations are published, these can further inform future health economic models. The survivor functions estimated in this study can potentially be applied as an external data source to extrapolate survival in cases where patient-level data is not available using the framework and methods described by Jackson et al. [12]. For example, these survival functions can be used to extrapolate longer term mortality of the treatment and/or control group of patients that have common characteristics to those in this study, such as patients with osteoarthritis. Mortality can be adjusted to the baseline utility and change in utility captured in trials of such populations using the hazard ratios presented in this study.

The associations between QoL and mortality could differ depending on the disease or intervention which may be due to the underlying pathophysiology of the disease. As health economic models are increasingly used in cost-effectiveness analysis to evaluate new drugs and treatment strategies and there is a need to test this correlation in working economic models in different disease areas as evidence suggests that health-related QoL indicators exhibit important predictive value for survival over clinical and demographic baseline characteristics. This has been demonstrated across various chronic diseases such as diabetes [23, 54], end-stage renal disease [35, 55], cardiovascular diseases [51, 56] and

in cancer [57, 58]. In such cases, the exclusion of an important predictor such as QoL can result in omitted variable bias when estimating survival [59]. The results presented in this study also indicate that the relative impact on incremental outcomes is likely to be dependent on the strength of the association between QoL and mortality (Figure 6.3). Therefore, approaches to estimate survival for economic evaluations should examine potential correlations and consider the inclusion of QoL.

Incorporating the effects of change in utility is rarely considered when extrapolating survival. The results from this study have shown that it is important to measure change (pre and post) and consider the possible effects of correlations for interventions such as surgery where large improvements in QoL are observed. This analysis has highlighted the importance of having pre- and post-measures which can be used in clinical settings to not just measure patient's baseline QoL but also to include post-intervention assessment which can reveal important information on disease progression and outcomes; for example, would patients who respond favourably to an expensive cancer treatment also have better survival?

The clear relationship between baseline and change in utility (Figure 6.1B) appears to be important. It shows that individuals with the lowest QoL have the greatest potential to gain which will have a significant impact on incremental QALYs. It is acknowledged that the observed correlation is an artefact (mathematical coupling) resulting from the calculation of two variables commonly noted in pre- and post-measurements [60-62]. Specific methods for resolution are beyond the scope of this paper and have been widely discussed in the literature [62, 63]. Regardless, results from this case study have demonstrated that the correlation between baseline and change in QoL is relevant when considering extrapolating survival and effectiveness. It is difficult to ascertain to what extent this correlation is accounted for in most economic evaluations. Generally cost-effectiveness analyses apply an average change that is similar across all subgroups [64] and do not consider this potential correlation. However, in doing so, it is likely one would underestimate the improvements of those with low baseline and overestimate for those with high baseline. Therefore, this needs to be carefully considered as this could have implications for economic evaluations, particularly in subgroup analyses.

There are several limitations to the current analysis. Linear assumptions were made regarding the interpolation and extrapolation of utility. These assumptions are commonly

employed in most modelling approaches [45-49] however it is noted that potential regression to the mean effects may result in an overestimation of QoL and therefore QALYs [65]. Although there are a number of survival analysis techniques such a time-dependent survival analysis and frailty models that can model correlated data and were considered for this analysis, these models impose a large number of assumptions and results can be difficult to interpret. Therefore, to clearly demonstrate our aims, we opted for survival analysis methods that are most commonly used to estimate survival in economic evaluations [4, 5, 9, 41].

Preference-based measures such as EQ-5D are more commonly used to derive utility values for economic evaluations. This analysis uses utility values derived from SF-12. Although differences in utility values from different instruments are well-documented [66-68] and are likely due to the constructs of these instruments [69], utility values derived from instruments such as EQ-5D and HUI3 have similarly been shown to be strong predictors of mortality [23, 26]. The advantage of using SF-12 is that it is less prone to ceiling effects compared to EQ-5D [70] and therefore is better able to discriminate between patients with different levels of improvement following surgery. Conversely, it suffers from floor effects which makes it less useful in describing severe health states [66]. It remains unclear if utility values from different instruments would provide the same level of discrimination by baseline and change in utility values as observed in this study and if the association between QoL and mortality would differ depending on the instruments used. Further research is required to examine if survival extrapolation using other instruments would give different results that could influence decision-making and compromise comparability of cost-effectiveness analyses.

## 6.6. Conclusion

This research aimed to investigate the effect of accounting for the relationship between QoL (baseline and change) and mortality when extrapolating outcomes to a lifetime horizon illustrated with a case study in total knee replacement surgery. The results showed that correlations between QoL and mortality can influence health outcomes such as life expectancies and QALYs and consequently incremental QALYs. Although observable differences in LE and QALYs were small, this could translate into an important difference in incremental QALYs and can be relevant in cost-effectiveness calculations. Therefore,

future approaches to estimate survival for economic evaluations should consider the inclusion of QoL because overlooking this correlation can result in imprecise extrapolations and risk misleading results affecting subsequent decisions made by policy makers.

## 6.7. Tables and figures

Table 6.1: Coefficients and hazard ratios from Gompertz proportional hazards survival model for all-cause mortality

| | Model 1 | | | | Model 2 | | | |
|---|---|---|---|---|---|---|---|---|
| **Parameter** | **Coef.** | **(95%CI)** | **HR** | **(95%CI)** | **Coef.** | **(95%CI)** | **HR** | **(95%CI)** |
| **Gamma** | 0.12 | (0.11,0.14) | | | 0.13 | (0.11,0.14) | | |
| **Constant** | -13.25 | (-14.78,-11.71) | 0.00 | (0.00,0.00) | -12.74 | (-14.43,-11.05) | 0.00 | (0.00,0.00) |
| **Female** | -0.52 | (-0.77,-0.28) | 0.59 | (0.46,0.76) | -0.56 | (-0.81,-0.31) | 0.57 | (0.45,0.73) |
| **Baseline utility [a]** | - | - | - | - | -0.09 | (-0.21,0.02) | 0.91 | (0.81,1.02) |
| **Change in utility [a]** | - | - | - | - | - | - | - | - |
| **AIC/BIC** | | -10.49 | 7.39 | | | -11.55 | 12.28 | |

| | Model 3 | | | | Model 4 | | | |
|---|---|---|---|---|---|---|---|---|
| **Parameter** | **Coef.** | **(95%CI)** | **HR** | **(95%CI)** | **Coef.** | **(95%CI)** | **HR** | **(95%CI)** |
| **Gamma** | 0.12 | (0.10,0.14) | | | 0.12 | (0.10,0.14) | | |
| **Constant** | -12.80 | (-14.37,-11.23) | 0.00 | (0.00,0.00) | -11.52 | (-13.30,-9.74) | 0.00 | (0.00,0.00) |
| **Female** | -0.52 | (-0.77,-0.27) | 0.59 | (0.46,0.76) | -0.61 | (-0.86,0.36) | 0.54 | (0.42,0.70) |
| **Baseline utility [a]** | - | - | - | - | -0.21 | (-0.33,-0.08) | 0.81 | (0.72,0.92) |
| **Change in utility [a]** | -0.16 | (-0.24,-0.08) | 0.85 | (0.78,0.92) | -0.22 | (-0.31,0.13) | 0.8 | (0.73,0.88) |
| **AIC/BIC** | | -26.78 | -2.94 | | | -38.42 | -8.64 | |

[a] Increase in utility per 0.1 unit

Note: Model 1 (reference model) with sex as the only covariate, Model 2 contained sex and baseline utility, Model 3 contained sex and change in utility, and lastly Model 4 included sex, baseline utility and change in utility

Coef.: Coefficient; HR: Hazard ratio; 95%CI; 95% Confidence interval

Table 6.2: Estimated life expectancies and QALYs of the cohort from each of the models

| | Model 1 | | Model 2 | | | | Model 3 | | | | Model 4 | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Mean** | **SD** | **Mean** | **SD** | **Diff [a]** | **% change** | **Mean** | **SD** | **Diff [a]** | **% change** | **Mean** | **SD** | **Diff [a]** | **% change** |
| **Life expectancy** | 18.39 | 6.46 | 18.37 | 6.47 | -0.03 | -0.16% | 18.67 | 6.69 | 0.28 | 1.52% | 18.71 | 6.80 | 0.32 | 1.74% |
| **QALY (TKR)** | 13.84 | 5.6 | 13.85 | 5.68 | 0.01 | 0.07% | 14.21 | 6.20 | 0.37 | 2.67% | 14.37 | 6.56 | 0.53 | 3.83% |
| **QALY (no surgery) [b]** | 10.78 | 4.08 | 10.82 | 4.29 | 0.05 | 0.46% | 10.87 | 4.03 | 0.10 | 0.93% | 11.02 | 4.46 | 0.24 | 2.23% |
| **Incremental QALY** | 3.06 | 3.37 | 3.03 | 3.33 | -0.04 | -1.31% | 3.34 | 3.65 | 0.27 | 8.82% | 3.35 | 3.70 | 0.29 | 9.48% |

[a] Difference in comparison to Model 1 (reference).

[b] Assuming the patient's baseline quality of life is carried forward for life and QALY calculated using area under the curve method.

Note: Model 1 (reference model) with sex as the only covariate, Model 2 contained sex and baseline utility, Model 3 contained sex and change in utility, and lastly Model 4 included sex, baseline utility and change in utility

Diff: Difference; QALY: Quality-adjusted life years; TKR: Total knee replacement

Figure 6.1: (A) Variation in the pattern of QoL following TKR across groups (tertiles) categorised by baseline utility (B) Mean change in utility at 12 months across tertile groups.

Error bars represent the 95% confidence intervals.

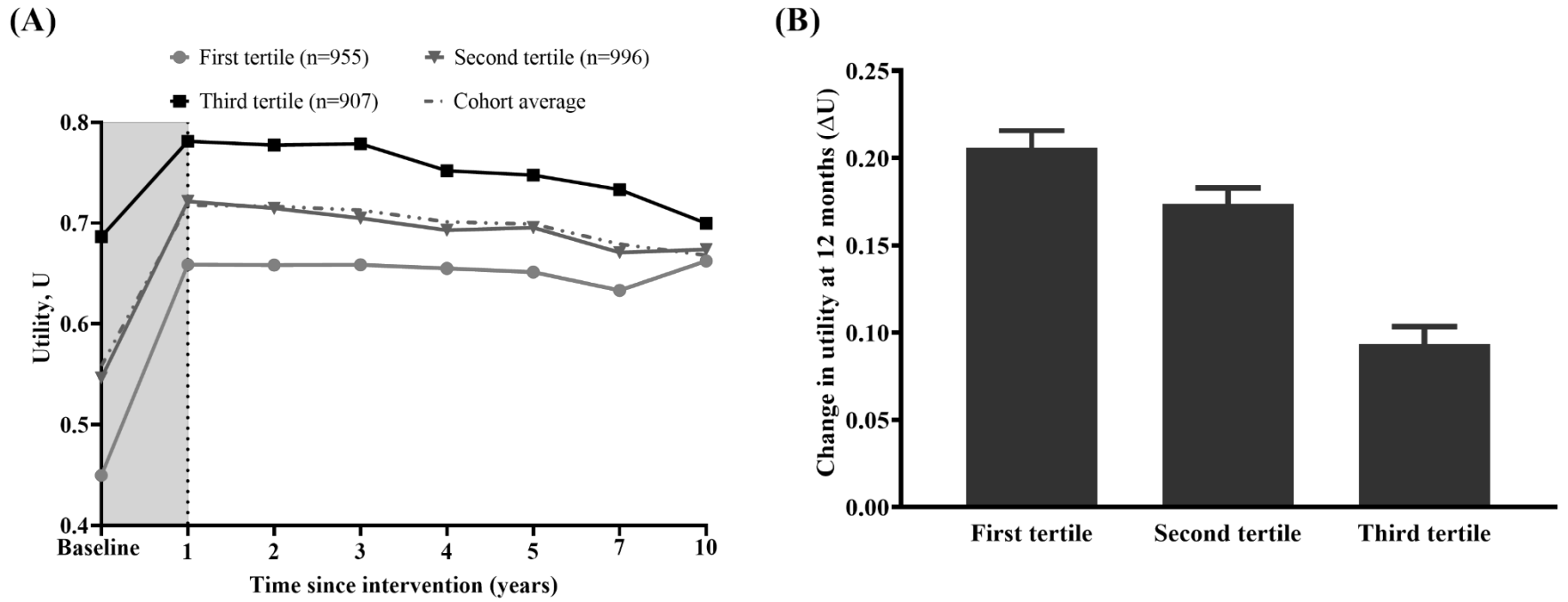
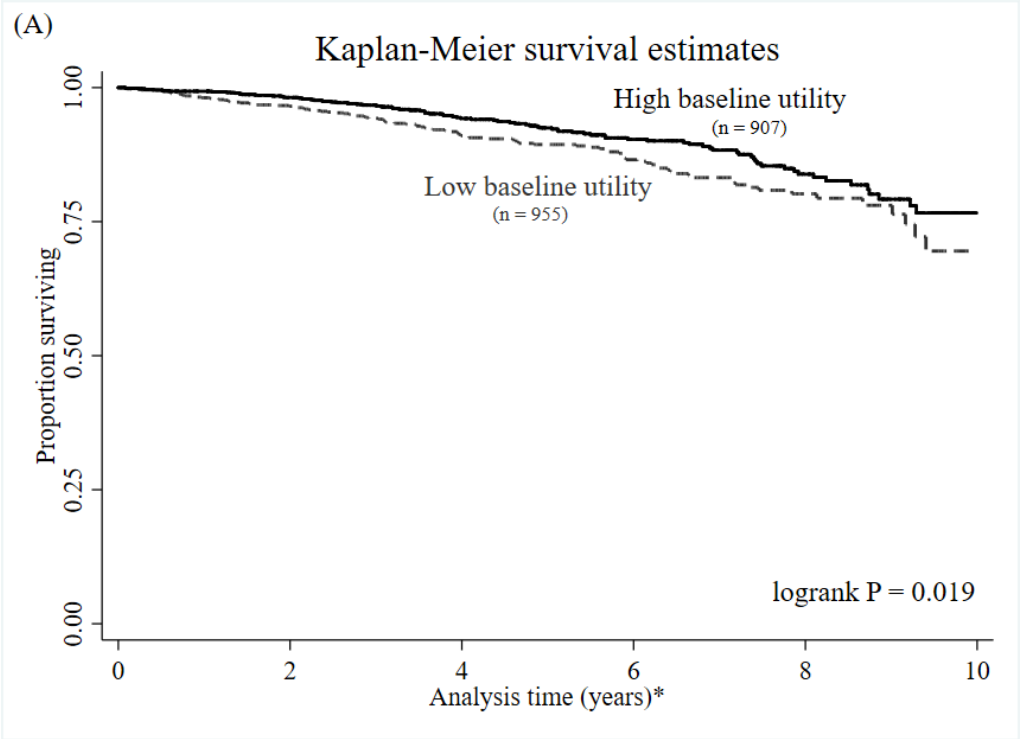


Figure 6.2: Kaplan-Meier survival curves (A) Survival differences by baseline utility (B) Survival differences by change in utility

*Note: Analysis time begins 12 months after surgery



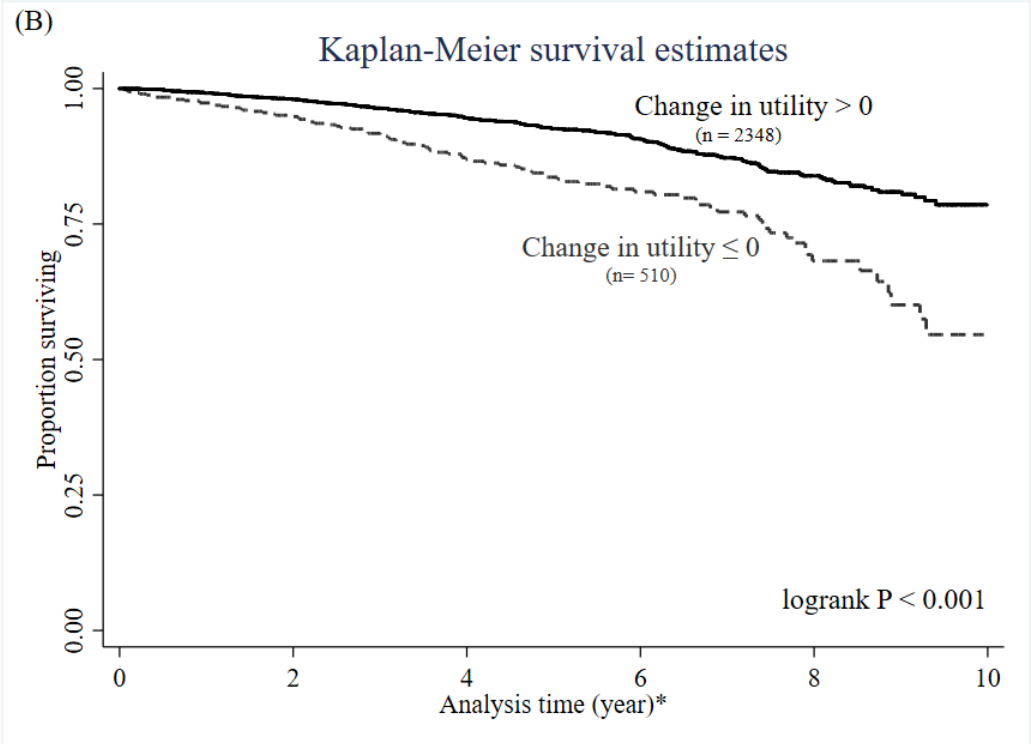
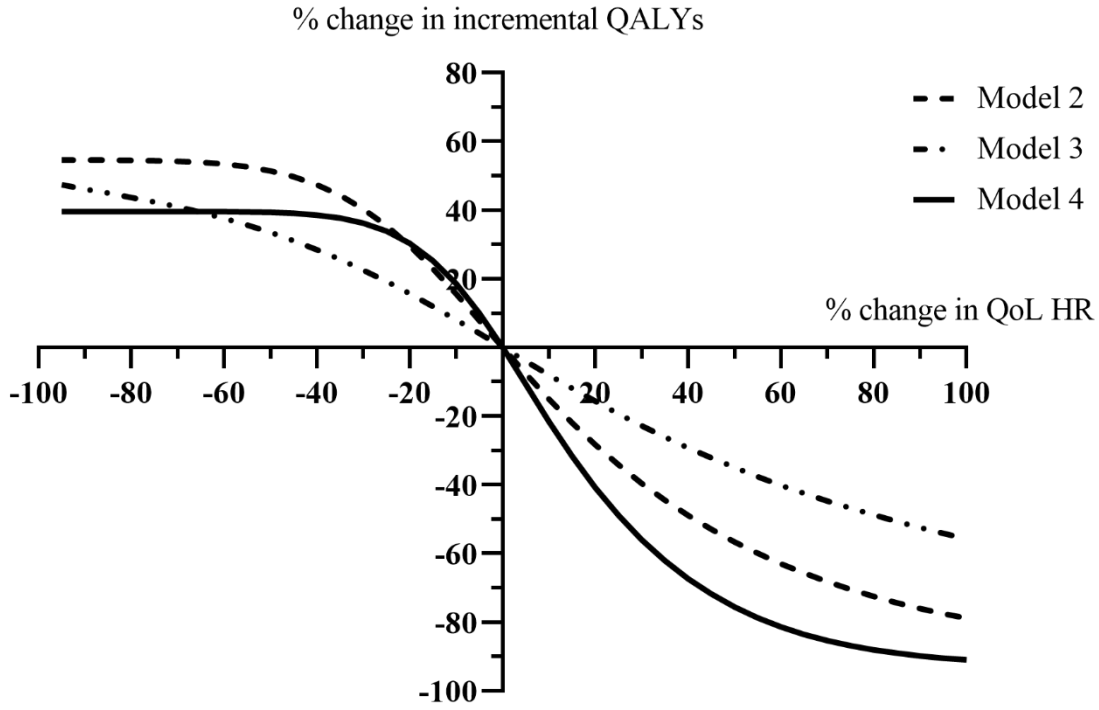



Figure 6.3: Change in incremental QALYs against change in QoL HR across models



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## 6.9. Supplementary materials

### Appendix 1

**Illustrating the impact of the correlation between U and LE on QALYs.**

QALY is ultimately a product of both utility (U) reflecting health status and life expectancy (LE). A common approach employed to calculate lifetime QALYs in economic evaluations (for example, [1-3]) that typically do not have access to individual-level data is to assume that remaining QALYs for the population by simply multiplying $E(U)$ by $E(LE)$ (method 1) where E indicates the expected (mean) value and LE derived from publicly available life tables. For example, in reference to the table below across two hypothetical scenarios A and B, the mean of utility is 0.46 and the mean of estimated life expectancy is 16.52. The calculated QALY using method 1 is 7.61 which is the same across both scenarios. Such an approach will only hold when $U$ and $LE$ are statistically independent and more generally the relationship can be described using the following well known identity [4]

$$QALY = E(U \cdot LE) = E(U) \cdot E(LE) + cov(U, LE)$$

| | | **Estimated life expectancies (LE)** | |
|---|---|---|---|
| | Utility (U) | A | B |
| | 0.50 | 20.24 | 20.24 |
| | 0.46 | 14.46 | 25.81 |
| | 0.41 | 9.77 | 9.77 |
| | 0.52 | 23.42 | 17.42 |
| | 0.52 | 25.81 | 7.21 |
| | 0.35 | 7.21 | 15.50 |
| | 0.46 | 16.88 | 16.88 |
| | 0.48 | 17.42 | 14.46 |
| | 0.35 | 7.21 | 15.50 |
| Expected value, E | 0.46 | 16.52 | 16.52 |
| **Correlation between U and LE** | | **0.95** | **0.03** |
| Calculated QALYs | | | |
| *Method 1: E(U)E(LE)* | | 7.61 | 7.61 |
| *Method 2: E(U*LE)* | | 7.86 | 7.62 |
| Covariance | | 0.26 | 0.01 |

However, if this assumption of independence between utility and LE does not hold, based on the above mathematical entity, there is an additional covariance term that needs to be

accounted for. For example, if there is a correlation between utility and LE, meaning that we assume higher levels of baseline utility have longer survival as in scenario A below (i.e. quality of life is positively correlated with survival which has been demonstrated in diabetes [5] and cancer [6]), then there is some degree of covariance that is not captured, and so this would bias QALY estimates downwards (7.86 vs. 7.61). Where the assumption of independence between utility and LE holds, this is less likely to matter.

## Appendix 2

### Data Source

Data on all patients, aged 55 and above, who had TKR between January 1, 2006 and December 31, 2015 were extracted from the St. Vincent's Melbourne Arthroplasty Outcomes (SMART) Registry which captures clinical and patient reported outcomes in all patients who undergo elective hip and knee replacement at the study institution. Baseline data were prospectively collected and included patient socio-demographic variables and self-reported co-morbidities. Follow-up data captured an extensive range of outcomes, including surgery and prosthesis-related variables. Patients complete a general health questionnaire (SF-12) within 12 weeks prior to surgery and annually post-operatively. Mortality data is recorded and verified with information from the Registrars of Births, Deaths and Marriages via the Australian Orthopaedic Association National Joint Replacement Registry [7]. Individuals were excluded from analysis if they had missing baseline utility value, underwent revision or died in the first year of follow-up.

Utilities were calculated from SF-12 measures using the published SF-6D algorithm [8]. For a small proportion of patients (n=45, 1.6%), 12-month utilities were missing and these were imputed using linear interpolation between measurement points where available, and for patients where subsequent measurement points were missing, their baseline utilities were carried forward to 12 months [9]. Change (improvement or deterioration) in utility was calculated as the difference between baseline and 12-month utilities.

A total of 2,858 TKR cases (2,309 patients) contributed to the analysis (Table S6.1) after 108 cases were excluded based on: missing baseline utility (n=3), deceased in first year of follow-up (n=23) or revision surgery (n=82). The average age of patients undergoing TKR was 70.66 years (SD, 7.72) and two-thirds (67%) were female. The mean duration of follow-up was 5.71 years (SD, 2.75) with the longest duration being 10.99 years. Within this period, 295 (12.78%[*]) of patients died. A comparison between survivors and those who died showed that those who were deceased were observed to be significantly older (69.99 vs. 76.49 years; p=0.000), significantly fewer females (68.40% vs. 54.92%; p=0.000) and with a significantly smaller change in utility following surgery (0.16 vs.

[*] Corrected post-publication

0.11; p=0.000). The average QoL utility was 0.56 (SD, 0.11) at baseline and on average, patients' utility improved by 0.16 (SD, 0.19) 12 months after surgery.

Table S6.1: Patient characteristics

| | **All cases** | | **Survivors** | | **Deceased** | | **p-value** [a] |
|---|---|---|---|---|---|---|---|
| **Number of cases** | 2858 | | 2563 | | 295 | | |
| **Mean age (SD)** | 70.66 | 7.72 | 69.99 | 7.53 | 76.49 | 6.79 | <0.001 |
| **Female (%)** | 1915 | 67.00 | 1753 | 68.40 | 162 | 54.92 | <0.001 |
| **Deaths (%)** | 295 | 10.32 | | | | | |
| **Follow-up, years (SD)** | 5.71 | 2.75 | 5.77 | 2.78 | 5.19 | 2.47 | |
| **Utility (SD)** | | | | | | | |
| **Baseline** | 0.56 | 0.11 | 0.56 | 0.11 | 0.56 | 0.12 | 0.854 |
| **12 months after surgery** | 0.72 | 0.16 | 0.72 | 0.16 | 0.67 | 0.16 | <0.001 |
| **Difference at 12 months** | 0.16 | 0.19 | 0.16 | 0.16 | 0.11 | 0.16 | <0.001 |

[a] statistical test between survivors and deceased

## Appendix 3

Figure S6.1: Kaplan-Meier survival curve of the observed data

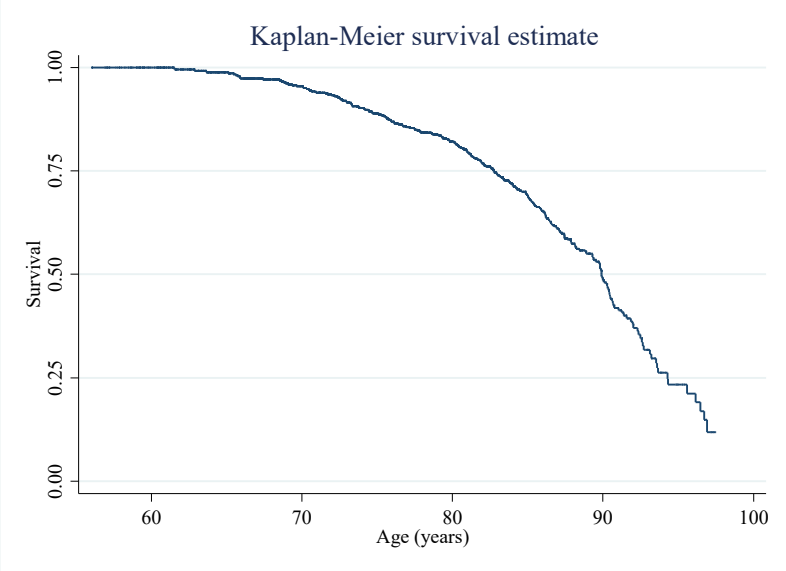
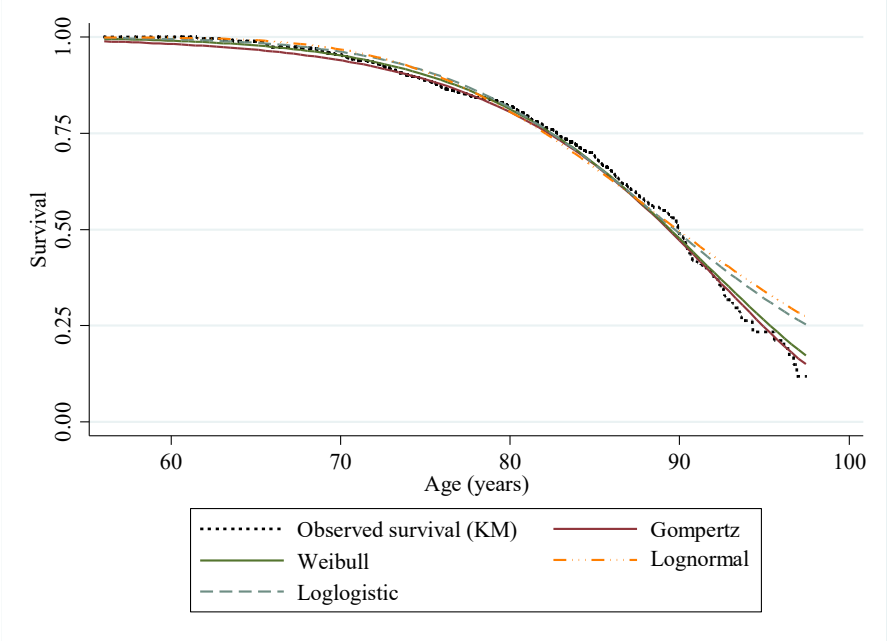



Figure S6.2: Predicted survival curves from various parametric survival models fitted to the observed data




Graphical exploratory analysis (Figure S6.2) showed Gompertz and Weibull distributions to have the most suitable fit. Further determination of the best fit was explored through Akaike and Bayesian Information Criterion (AIC/BIC). Lower AIC/BIC values indicated better fit therefore was used as the criteria to guide final choice. Table S6.2 shows the AIC/BIC values from various distributions for all four models.

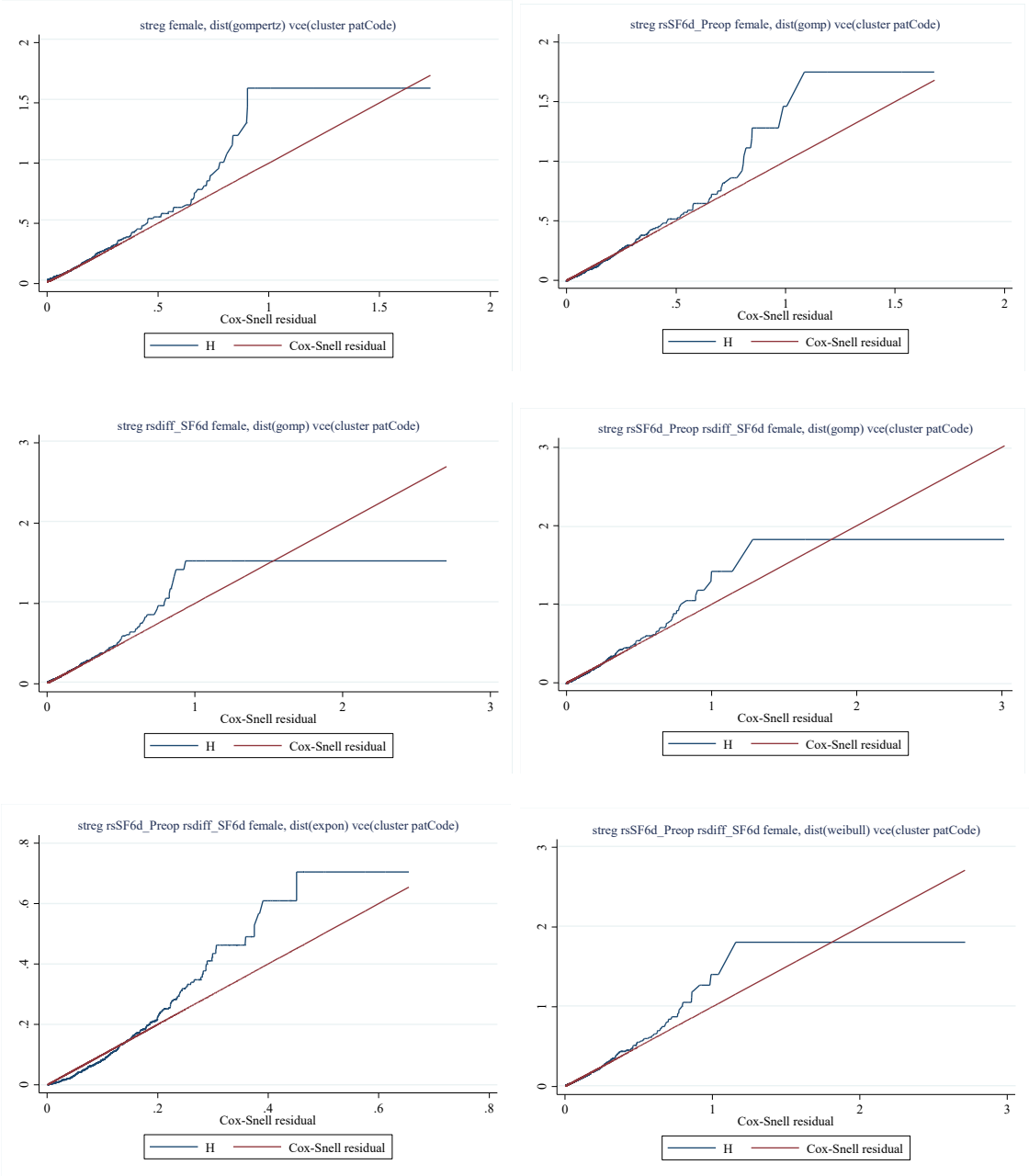
Table S6.2: Measures of model fit for survival models

| **Model diagnostics** | **Model 1** | | **Model 2** | | **Model 3** | | **Model 4** | |
|---|---|---|---|---|---|---|---|---|
| | **AIC** | **BIC** | **AIC** | **BIC** | **AIC** | **BIC** | **AIC** | **BIC** |
| *Gompterz* | -10.49 | 7.39 | -11.55 | 12.28 | -26.78 | -2.94 | -38.42 | -8.64 |
| *Exponential* | 230.15 | 242.06 | 231.26 | 249.13 | 202.56 | 220.44 | 194.34 | 218.17 |
| *Weibull* | -7.45 | 10.43 | -8.56 | 15.28 | -23.91 | -0.08 | -35.75 | -5.96 |
| *Loglogistic* | 9.76 | 27.64 | 8.05 | 31.88 | -9.42 | 14.41 | -22.82 | 6.97 |
| *Lognormal* | 16.54 | 34.41 | 14.84 | 38.67 | -1.04 | 22.79 | -13.45 | 16.34 |

Note: Model 1 (reference model) with sex as the only covariate, Model 2 contained sex and baseline utilities, Model 3 contained sex and change in utility, and lastly Model 4 included sex, baseline utilities and change in utility

AIC: Akaike information criterion; BIC: Bayesian information criterion

Figure S6.3: Cox-Snell residual plots



**Stata codes to fit each of the survival models used in the study are listed below.**

Age was used as the time scale of the model. Time at risk starts 12 months post-surgery and patients are censored at death or end of follow-up period (whichever comes first). Female is the dummy for female sex, rsSF6d_Preop is the baseline utility score, rsdiff_SF6d is the difference in utility (between baseline and 12 months post-surgery). Utility scores are scaled by a factor of 10 to allow ease of interpretation of coefficients. All cases are analysed individually, however patients who have multiple surgery (max 2 on both knees) are clustered for analysis. [Parameterisation] is a place holder for the specification of the survival function: weibull, gompertz, exponential, loglogistic and lognormal.

Models fitted to the SMART Registry data

```
stset censored_date, failure(died) enter (time enter_at12m)
origin (time DOB) id(patid) scale(365.25)
```

Model 1

```
streg female, dist([Parameterisation]) vce(cluster patCode)

estat ic
```

Model 2

```
streg rsSF6d_Preop female dist([Parameterisation])
vce(cluster patCode)

estat ic
```

Model 3

```
streg rsdiff_SF6d female, dist([Parameterisation])
vce(cluster patCode)

estat ic
```

Model 4

```
streg rsSF6d_Preop rsdiff_SF6d female,
dist([Parameterisation]) vce(cluster patCode)

estat ic
```

## Appendix 4

### Sensitivity analysis - Survival models for all-cause mortality including patient socio-demographic and clinical characteristics

Additional covariates that were considered in the models were socio-demographic and clinical characteristics (at baseline) as extracted from the registry. These included sex, body mass index (BMI), smoking status (yes/no), Charlson Comorbidity Index (0/>1), aetiology of disease (osteoarthristis/other), radiographic osteoarthritis severity using the Kellgren-Lawrence grading system, Socio-Economic Index for Areas (SEIFA) [10] to describe socioeconomic status and the need for an interpreter. The final model was determined using backwards stepwise elimination where covariates were dropped from the regressions with an exit criterion of P>0.1. Significant coefficients and hazard ratios in the risk equations for Models 1 to 4 are presented in Table S6.3. Life expectancies and QALYs were estimated for each of these models following methods described in the main manuscript and the results are presented in Table S6.4.

Table S6.3: Coefficients, hazard ratios from Gompertz proportional hazards survival model for all-cause mortality (including patient socio-demographic and clinical characteristics)

| | Model 1 | | | | Model 2 | | | |
|---|---|---|---|---|---|---|---|---|
| **Parameter** | **Coef.** | **(95%CI)** | **HR** | **(95%CI)** | **Coef.** | **(95%CI)** | **HR** | **(95%CI)** |
| **Gamma** | 0.13 | (0.11,0.15) | | | 0.13 | (0.11,0.15) | | |
| **Constant** | -13.72 | (-15.34,-12.10) | 0.00 | (0.00,0.00) | -13.29 | (-15.06,-11.51) | 0.00 | (0.00,0.00) |
| **Female** | -0.44 | (-0.69,-0.18) | 0.65 | (0.50,0.83) | -0.47 | (-0.73,-0.22) | 0.62 | (0.48,0.81) |
| **Smoker (0/1)** | 0.75 | (0.21,1.28) | 2.11 | (1.23,3.61) | 0.74 | (0.20,1.27) | 2.09 | (1.23,3.57) |
| **Co-morbidity (0/1)** | 0.38 | (0.13,0.63) | 1.46 | (1.13,1.87) | 0.37 | (0.12,0.62) | 1.44 | (1.12,1.85) |
| **Baseline utility [a]** | - | - | - | - | -0.08 | (-0.20,0.04) | 0.92 | (0.82,1.04) |
| **Change in utility [a]** | - | - | - | - | - | - | - | - |

| | Model 3 | | | | Model 4 | | | |
|---|---|---|---|---|---|---|---|---|
| **Parameter** | **Coef.** | **(95%CI)** | **HR** | **(95%CI)** | **Coef.** | **(95%CI)** | **HR** | **(95%CI)** |
| **Gamma** | 0.12 | (0.10,0.14) | | | 0.12 | (0.10,0.14) | | |
| **Constant** | -13.25 | (-14.91,-11.59) | 0.00 | (0.00,0.00) | -12.07 | (-13.95,-10.19) | 0.00 | (0.00,0.00) |
| **Female** | -0.44 | (-0.70,-0.19) | 0.64 | (0.50,0.83) | -0.53 | (-0.79,-0.27) | 0.59 | (0.45,0.76) |
| **Smoker (0/1)** | 0.71 | (0.18,1.25) | 2.04 | (1.19,3.47) | 0.66 | (0.13,1.19) | 1.94 | (1.14,3.30) |
| **Co-morbidity (0/1)** | 0.33 | (0.08,0.58) | 1.39 | (1.08,1.79) | 0.29 | (0.03,0.54) | 1.33 | (1.03,1.72) |
| **Baseline utility [a]** | - | - | - | - | -0.19 | (-0.31,-0.06) | 0.83 | (0.73,0.94) |
| **Change in utility [a]** | -0.16 | (-0.24,-0.07) | 0.86 | (0.79,0.93) | -0.21 | (-0.30,-0.12) | 0.81 | (0.74,0.89) |

[a] Increase in utility per 0.1 unit

Note: Model 1 (reference model) with only sociodemographic and clinical characteristics, Model 2 additionally includes baseline utilities, Model 3 additionally includes change in utility, and lastly Model 4 additionally includes baseline utilities and change in utility

Table S6.4: Estimated life expectancies and QALYs of the cohort from each of the models (including patient socio-demographic and clinical characteristics)

| | Model 1 | | Model 2 | | | | Model 3 | | | | Model 4 | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Mean** | **SD** | **Mean** | **SD** | **Diff [a]** | **% change** | **Mean** | **SD** | **Diff [a]** | **% change** | **Mean** | **SD** | **Diff [a]** | **% change** |
| **Life expectancy** | 18.30 | 6.56 | 18.28 | 6.56 | -0.02 | -0.12% | 18.55 | 6.75 | 0.25 | 1.36% | 18.58 | 6.82 | 0.28 | 1.54% |
| **QALY (TKR)** | 13.80 | 5.73 | 13.81 | 5.80 | 0.01 | 0.06% | 14.14 | 6.26 | 0.33 | 2.42% | 14.27 | 6.56 | 0.47 | 3.40% |
| **QALY (no surgery) [b]** | 10.76 | 4.18 | 10.80 | 4.34 | 0.04 | 0.38% | 10.84 | 4.11 | 0.08 | 0.77% | 10.97 | 4.47 | 0.21 | 1.94% |
| **Incremental QALY** | 3.05 | 3.39 | 3.01 | 3.36 | -0.03 | -1.06% | 3.30 | 3.64 | 0.25 | 8.23% | 3.31 | 3.67 | 0.26 | 8.59% |

[a] Difference in comparison to Model 1 (reference).

[b] Assuming the patient's baseline quality of life is carried forward for life and QALY calculated using area under the curve method.

Note: Model 1 (reference model) with only sociodemographic and clinical characteristics, Model 2 additionally includes baseline utilities, Model 3 additionally includes change in utility, and lastly Model 4 additionally includes baseline utilities and change in utility

Diff: Difference; QALY: Quality-adjusted life years; TKR: Total knee replacement

## Appendix 5

### Estimation of life expectancy using standard life table methods

Life expectancies for each individual patient were estimated using standard life table methods (for detailed methodology, please refer to [11]. Using the hazard ratios and standard errors derived from each of the risk equations (Gompertz parametric survival models – Table 1 in publication), survivor function S(t) (i.e. probability of each individual is alive at time t) can be derived using the following:

$$S(t|x_k) = \exp(-\frac{1}{\gamma}\ \exp(\beta_0 + x_k\beta_x)\ (\exp(\gamma t) - 1))$$

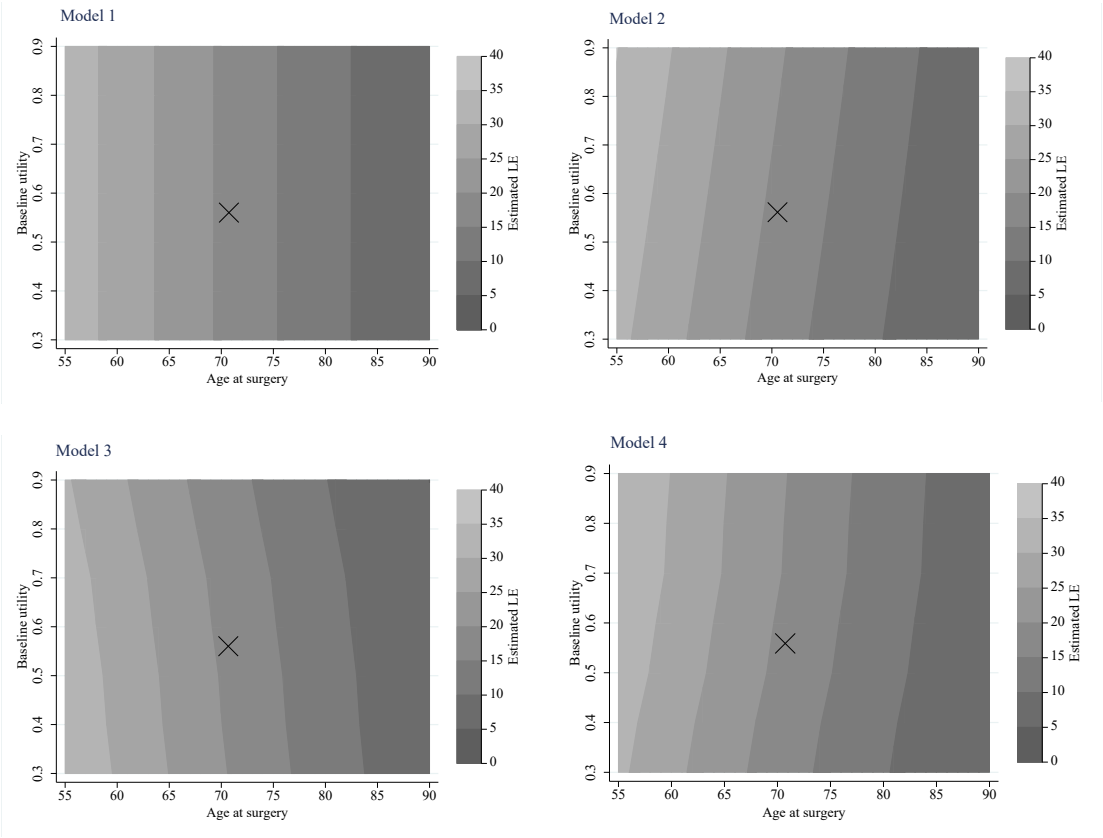
Where $\beta_0$ is the regression constant, $\beta_x$ represent the coefficients for $k$ explanatory variables such as age and $\gamma$ describes the hazard.

From this, the annual probability of mortality, $q_{(v)}$, to age 100 was calculated using $q_{(v)} = 1 - S_{(v+1)}/ S_{(v)}$), where v is the number of years 12 months from age at surgery. $q_{(v)}$ was then used to estimate the number alive $l_v$ from an initial population size ($l_0$) of 10000. The number of years lived was then calculated using $L_{(v)} = [l_{(v)} + l_{(v+1)}] /2$ and total number of years ($T_v$) lived beyond 12 months after surgery up to 100 years = $T_0 = L_v+L_{v+1}+\ldots+L_{100}$. Life expectancy was that calculated by $e_v = T_v/l_v$.

## Appendix 6

Figure S6.4: Variations in estimated life expectancies across ages and different levels of baseline utility simulated using each of the models.

**Note:** Marker `X' represents the cohort mean.



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# SECTION III : Generating Real-World Evidence

| Chapter / Study | | Methods of analysis | Key contributions | |
|---|---|---|---|---|
| | | | Methodology | Clinical and policy |
| **I : EXTRAPOLATION OF COSTS** | | | | |
| 2 | Incorporating future medical costs: Impact on CEA | + Cost-utility analysis<br>+ Decision tree analysis<br>+ Markov model | Demonstrate feasibility of appropriately including future medical costs | Provide evidence of cost-effectiveness of sepsis protocol and highlight potential differences in cost-effectiveness results |
| 3 | National cost savings from an ambulatory program for LR FN patients | + Cost-effectiveness analysis<br>+ GLM regression<br>+ Cost projections | Undertake evaluation beyond cost-effectiveness analysis | Offer strong evidence for national implementation of a cost-effective program |
| **II: MODELLING & TRANSLATING LONG-TERM OUTCOMES** | | | | |
| 4 | Using PROMs to guide patient-centred care and optimise outcomes | + Latent class growth analysis<br>+ Multinomial logistic regression | Employ novel application of technique to uncover heterogeneity | Show important heterogeneity in longer-term outcomes and variations in the value of surgery for different patient groups |
| 5 | Co-morbidities and sex differences in long-term QoL outcomes | + Multi-level modelling | Demonstrate method to assess patterns of change of repeated QoL measures over time and generate utility values for cost-effectiveness analyses | Highlight notable differences in long-term QoL patterns among specific patient subgroups (diabetes, females) and need for tailored post-surgery management |
| 6 | Exploring the impact of QoL on survival | + Survival analysis<br>+ Life table methods for life expectancy | Advance understanding of influence and consequence of correlation between QoL and mortality when extrapolating survival outcomes | Quantify impact of unaccounted correlation and heterogeneity on cost-effectiveness results |
| **III : GENERATING REAL-WORLD EVIDENCE** | | | | |
| 7 | Economic burden of sepsis in cancer patients | + Matching (case-control)<br>+ Panel data manipulation<br>+ Survival-adjusted estimation of costs | Generate short- and long-term cost estimates | Provide key insights on burden of sepsis and useful inputs for future economic evaluations and resource allocation decisions |

# Chapter 7 : Economic burden of sepsis in cancer patients

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## 7.1. Abstract


### Objective

Cancer patients are at significant risk of developing sepsis due to underlying malignancy and necessary treatments. Little is known about the economic burden of sepsis in this high-risk population. We estimate the short- and long-term healthcare costs associated with sepsis in cancer patients using individual-level linked-administrative data.

### Design

Population-based cohort study of costs of care associated with sepsis in cancer patients over 5 years.

### Setting

Health care system (through data sources capturing up to 90% of all healthcare resources provided to the population of Ontario, Canada)

### Patients

Cancer patients aged ≥18, diagnosed between 2010 and 2017. Cases were identified if diagnosed with sepsis during the study period, and were matched 1:1 by age, sex, cancer type and other variables to controls without sepsis.

### Interventions

None

### Measurements and Main Results

We estimated mean costs (2018 Canadian dollars) for patients with and without sepsis up to 5 years. Excess cost associated with sepsis presented as a cost difference between the two cohorts. Haematological and solid cancers were analysed separately. 77,483 cancer patients with sepsis were identified and matched. 64.3% of the cohort were aged ≥65, 46.3% female and 17.8% with haematological malignancies. Among solid tumour patients, the excess cost of care associated with sepsis was $29,081 (95% CI, 28,404-29,757) in the first year, rising to $60,714 (95% CI, 59,729-61,698) over 5 years. This

was higher for haematology patients; $46,154 (95% CI, 45,505-46,804) in year 1, increasing to $75,931 (95% CI, 74,895-76,968).

**Conclusions**

Sepsis imposes substantial economic burden and can result in a doubling of cancer care costs, particularly during the first year of cancer diagnosis. These estimates are helpful in improving our understanding of burden of sepsis along the cancer pathway and to deploy targeted strategies to alleviate this burden.

## 7.2. Introduction

Sepsis is a potentially life-threatening organ dysfunction caused by the body's response to infection [1]. It is a major cause of morbidity and mortality [2-7] contributing up to one-fifth of deaths reported globally in 2017 [8]. Patients with cancer are at high risk of developing sepsis. It is estimated that cancer patients are 10-times more likely to develop sepsis compared to non-cancer patients [9]. Numerous factors contribute to this risk including underlying malignancy, immune dysfunction following life-saving treatments, recurrent hospitalisations, and the need for invasive procedures. The cost of managing sepsis is high. Sepsis is among the most expensive conditions treated in hospitals, amounting to approximately $24 billion in hospital costs in the US in 2013 alone [10, 11]. This tops other high-cost hospitalisations such as acute myocardial infarctions ($12.1 billion). Based on US projections, the burden of cancer is even larger at $158 billion [12]. While much is known about cancer care costs at various phases of patient's cancer journey from initial diagnosis to end-of-life, it is unclear how much of this burden is attributed to sepsis.

Although sepsis incidence and its associated outcomes such as mortality have been well described in the literature [5-9, 13-16], majority of these studies were focused on severe sepsis and were not specific to cancer. Limited attention has focused on the economic burden of sepsis in the high-risk cancer population. Among those that quantified costs, estimates [7, 14-17] have relied solely on hospital admissions data which is likely to capture only the most severe cases and potentially miss sepsis burden incurred outside of the hospital. Robust cost estimates that provide long-term estimates beyond the index hospitalisation are lacking.

In this study, we aim to describe short- and long-term healthcare costs of care of cancer patients with and without sepsis in Ontario, Canada. We use population-linked administrative data to capture health services use including those beyond inpatient hospitalisations. This provides a unique opportunity to study the economic burden of sepsis across the entire health care system and will be useful to align appropriate resources for health workforce capacity, infrastructure including sepsis programs to achieve efficient allocation of public resources across various services and inform on need for further research.

## 7.3. Materials and methods

We conducted a population-based retrospective cohort study using patient-level administrative health data to determine healthcare costs associated with sepsis in patients up to 5 years following cancer diagnosis. This study protocol was approved by research ethics board at the University of Toronto (#37526) and University of Melbourne (#1953663).

### 7.3.1. Patient cohort and data source

Patients were selected from the Ontario Cancer Registry [18] and included in study if aged 18 and above, whose first diagnosis for a primary cancer occurred between January 1, 2010 and December 31, 2017. Patients were followed until death or end of analysis period, March 31, 2018. Patients were excluded if cancer diagnosis was first identified at death, or if there was previous cancer diagnosis prior to the study period. Cancer patients were classified by tumour site according to International Classification of Diseases-Oncology (ICD-O) topography code corresponding to their primary cancer diagnosis and classified into two broad groups - haematological and solid cancers [19].

Individual-level data on all patient healthcare resource use from diagnosis up to study end date were obtained from ICES in Toronto, Ontario. These data describe resource utilisation for residents of Ontario, Canada (population 14.6 million) covered by Ontario Health Insurance Plan (97%). The data sources include inpatient hospitalisations, emergency department, cancer clinic visits, physician services, diagnostic tests, long-term care, prescription drugs, chemotherapy and radiotherapy (Appendix 1 for details). These datasets were linked using unique encoded identifiers and analysed at ICES. These data

sources capture up to 90% of all healthcare resources provided universally and paid for by Ontario Ministry of Health and Long-Term Care [20] and have been used in numerous costing analyses [21-23].

### 7.3.2. Identification of sepsis, cases and controls

Sepsis is defined as life-threatening organ dysfunction caused by dysregulated host response to infection [1] and was identified using ICD-10-CA diagnosis codes captured within the data source. We applied the explicit and implicit definition for case finding recently published by the Global Burden of Disease Group [8] which reflects the most current definition of sepsis, and thus allowed for better case ascertainment (Appendix 2). Cancer patients were classified as cases if identified with sepsis within the 5-year study period and within 1 month prior to cancer diagnosis. The '1 month prior' inclusion period allowed for some flexibility in accuracy of diagnosis dates and also inclusion of patients whose sepsis presentation may have been the result of undiagnosed cancer [24]. Cancer patients were classified as potential controls if no sepsis record was identified throughout the study period. Cases (cancer patients with sepsis) were hard (exact) matched 1:1 by age (+/-2 years), sex, cancer type, year of cancer diagnosis and rurality to cancer patients without sepsis (controls) selected from the same patient cohort [25, 26].

### 7.3.3. Estimating costs

The cost analysis is undertaken from the healthcare payer perspective. Costs for all healthcare services were estimated as described in [20]. Costs for inpatient hospitalisations, emergency department and ambulatory care visits and long-term care were estimated by multiplying resource intensity weight by cost per weighted case or day. Costs for medications, chemotherapy and physician services were available directly in the data. Radiation costs were based on the intensity of resource use captured by National Hospital Productivity Improvement Program (NHPIP) codes and unit cost obtained from Earle et al. [27]. Details of costing methodology are described in Appendix 1. All costs were adjusted to 2018 Canadian dollars using healthcare component of the Statistics Canada Consumer Price Index [28].

As patients were observed over different time periods, not all patients had complete cost information across the entire 5-year period. Therefore, to estimate costs with incomplete

follow-up data (common in longitudinal studies), methods that take into account this form of censoring is required to ensure unbiased cost estimates [29, 30]. This was done by partitioning the study period into monthly intervals and adjusting observed costs at each interval by the survival probability of corresponding interval [31]. This provided estimates for mean monthly cost of care for cancer patients with sepsis (cases) and without sepsis (controls). The average total (cumulative) cost across 5 years was estimated as the sum across 60-monthly intervals. Excess (net) cost due to sepsis were estimated as the difference between the sepsis cases and no sepsis controls [32, 33]. As costs and survival probabilities are likely to be different between haematological and solid cancers, these patients were analysed separately. As cost of care at the end-of-life which is expected to be high [21, 33] and an important contributor to overall costs, costs in the last 6 months of life were segmented into a separate category of 'terminal care costs' to distinguish these. Sub-group analyses by sex and age groups were also conducted. Bootstrapping with 1000 replicates was used to calculate the 95% confidence intervals for all costs. A number of additional analyses were performed to test the robustness of the results. These sensitivity analyses are described and presented in Appendix 3. All tests of significance used two-sided P-values at less than 0.05. Analyses were conducted using Stata version 16.

## 7.4. Results

### 7.4.1. Study cohort and patient characteristics

A total of 485,105 cancer patients met eligibility criteria of the study and 83,028 patients (17.1%) experienced at least one sepsis episode over study period. Of these cases, matches were found for 77,483 (93.3%) patients. 64.3% were aged 65 and above, 46.3% were female and 17.8% had haematological malignancies. Among those with solid tumours, lung (18.2%), colorectal (16.3%), breast (9.8%) and prostate (8.7%) were the most common cancer types. Leukemia (59.4%) formed the largest proportion of patients in the haematology group. Table 7.1 describes baseline characteristics of cancer patients with sepsis by malignancy type.

Across the 5-year period, a large proportion of sepsis episodes occurred in the first year of cancer diagnosis. Among haematology patients, 68.2% of first sepsis episodes were within the first year and this was 53.2% for solid tumour patients. A higher proportion of

haematology patients (41.0%) had >1 episode of sepsis compared to solid tumour patients (26.7%). The difference in five-year overall survival between cancer patients with sepsis and without sepsis was statistically significant (log rank test $p<0.001$) across both cancer types (Appendix 4).

Overall, controls were well matched to cases, except on income quintiles (Appendix 5). Unmatched individuals were observed to be older, more likely to be male, have a haematological malignancy and more likely to have died by the end of the study period (Appendix 6).

### 7.4.2. Cost of care of sepsis

The monthly cost of care by malignancy type across the 5-year period for sepsis cancer patients and matched controls are presented in Figure 7.1. In general, healthcare costs were higher among those with sepsis compared to those without sepsis irrespective of malignancy types. Cost of care of sepsis for haematology patients is at least double that of a non-sepsis patient, and this difference is greatest particularly in the first 12 months of cancer diagnosis. In solid tumour patients, sepsis resulted in at least a 61% increase in overall cost of care. Across the 5-year period, total excess (net) cost of care associated with sepsis is substantial (Table 7.2) and is higher among haematology patients at $75,931 (95% CI, 74,895-76,968) compared to solid tumour patients at $60,714 (95% CI, 59,729-61,698).

A large proportion of excess cost of care associated with sepsis was incurred in the first 12 months of cancer diagnosis and this gradually declined in subsequent months (Figure S7.2 in Appendix 7). Across the 5-year period, approximately 39% of the total excess cost was attributed to terminal care cost (last 6 months of life) in solid tumour patients. In haematology patients, the proportion of terminal care cost increased gradually over the 5-year period, from 36.8% at six months to above 90% by year 5.

Figure 7.2 shows variations in 1-year cumulative excess sepsis cost across different sub-groups by sex and age categories. Similar patterns were observed for costs over a longer time horizon (2- and 5-years). Costs of care and the resulting excess cost associated with sepsis were higher for males and highest among males with a haematological malignancy. Across age groups, costs of care generally rose with increasing age. Among those aged

≤65, 5-year healthcare costs of patients with sepsis were at least twice that compared to patients without sepsis, resulting in higher excess cost among these patients compared to older patients. These results indicate that the burden of sepsis was highest among those in younger age categories (full results in Appendix 8).

## 7.5. Discussion

This study used patient-level administrative data to estimate for the first time whole of system healthcare cost of cancer patients with and without sepsis and has documented the excess cost of care associated with sepsis over a 5-year period. Our results indicate that compared to patients without sepsis, cancer patients with sepsis have significantly higher rates of mortality with less than one-third surviving 5-years post-cancer diagnosis. Cost of care associated with sepsis is substantial in cancer patients, resulting in up to an 85% increase for solid tumour patients and up to a 179% increase for haematology patients. This translated into an excess cost associated with sepsis of $29,081 in the first year, rising to $60,714 over 5 years for solid malignancies. This was higher for haematology; $46,154 in the first year, increasing to $75,931 after 5 years. These findings indicate that sepsis is a high cost, high mortality condition in cancer patients requiring urgent need for interventions and health policies to alleviate this significant burden.

Excess cost associated with sepsis was highest in the first month of cancer diagnosis and remained high through the first year. This coincides with the initial phase of cancer care covering the diagnosis and initial treatment (chemotherapy or surgical intervention or radiotherapy) when patients are at increased risk of sepsis with neutropenic fever and other infections. This highlights the need for increased attention at this critical stage on the cancer pathway. Sepsis has been found to commonly occur within 14 days of cancer treatment [24], therefore strategies to increase vigilance and improve early recognition and timely interventions may be warranted in helping reduce this significant excess burden. There needs to be increased focus on the implementation of clinical pathways in both the emergency and hospital wards, and to strengthen initiatives for prompt sepsis identification and diagnosis particularly in the first year of cancer diagnosis [17]. Clinical pathways for sepsis have demonstrated efficacy in reducing mortality [34] which can also impact future costs of managing sepsis and cancer [35]. Therefore, effective

implementation of sepsis pathways can have a big impact in driving down costs and improving patient outcomes.

The excess cost burden of sepsis was found be highest among haematological malignancies, males and younger (below age 55 years) patients. The higher cost of care among haematology patients compared to solid tumour patients was unsurprising as similar findings have been reported [12, 21, 36] reflecting more intensive chemotherapy regimens that may then progress to allogenic stem cell transplant within the first few months of diagnosis. We had anticipated excess cost of sepsis to remain substantial over the study period due to morbidities related to sepsis [4, 37, 38] and increased risk of sepsis in cancer survivors [39] which necessitates a greater level of care. However, we observed a long tail with much lower excess cost (Figure 7.1) over the 5-year time horizon. This is likely to reflect the acute nature of sepsis which requires intensive and expensive treatments when it occurs, most commonly within first year of diagnosis. It could also be due to a multitude of factors; for instance, episodes of sepsis can lead to changes in the management of these patients including reduced intensity of treatments, cessation of therapy and/or prevention strategies for further episodes [40, 41]. Conversely, it may also be an indication of a lack of support, coordination and availability of post-sepsis care. A large multi-national survey of sepsis survivors (n=1731) reported approximately half of sepsis survivors were dissatisfied with hospital support services [42] and may not be accessing necessary services. Further research to better understand pathways of care of cancer patients with sepsis is warranted. Enhancing our understanding of the role of different healthcare services can help guide policy design and allocation of healthcare sources to alleviate both the cost and illness burden of sepsis on health system as well as patients.

A key strength of this study is the use of population-linked healthcare datasets which captures nearly all publicly funded healthcare services thus providing a whole of system view of the impact of sepsis. It provides a valuable opportunity to gain critical insights on the implications and burden of sepsis across the cancer care continuum which was not possible without access to robust linked-administrative datasets and systems. Data generated from contact with the healthcare system provides important real-world evidence and a more accurate reflection of the economic burden across the healthcare system. They provide a broader and longer view of the impact of sepsis in cancer patients,

going beyond the limited hospital estimates currently available. These cost estimates are helpful in informing resource allocation and health policy prioritisation considerations and can also be used in cost-effectiveness models for decisions on sepsis interventions and are useful in helping inform development of sepsis programs and policies across the cancer care continuum, which can include prevention, screening, treatment and end-of-life care.

With the growing use of novel cancer treatment strategies such as immunotherapies as emerging standards of care, this could change patterns of sepsis currently observed [43, 44]. In light of this, cost estimates presented in this study can be an important input for economic models when evaluating the value of these expensive new therapies and inform policy decisions on the value of cancer care. The large differences in costs of care between haematology and solid tumour patients requires further examination into the impact of sepsis across different tumour types, particularly haematological malignancies. For example, patients with acute myeloid leukemia tend to have poorer outcomes and may be more susceptible to sepsis. Additionally, future research should also aim to better understand how the duration, timing and severity of sepsis will impact costs and this can contribute towards a fuller understanding of the economic burden of sepsis in cancer patients.

There is a lot of heterogeneity in capturing sepsis from administrative datasets which can lead to variations in our understanding and monitoring of sepsis [45]. This can also result in differences in cost estimates produced as demonstrated in our sensitivity analysis (Appendix 3). Applying an alternate sepsis definition (Sepsis-2) resulted in more sepsis cases captured which produced lower cost estimates. This may be due to the high negative predictive value of the approach (i.e. potential of increase in false positives) [46]. In the current analysis, we applied a comprehensive approach reflecting the most recent sepsis definition to ensure better case ascertainment [1, 8]. Further, capturing sepsis cases using the explicit and implicit codes provides a more realistic capture of sepsis and its associated costs than would be reflected through sepsis-specific codes only [47].

It is acknowledged that health care costs can vary across jurisdictions, particularly among those with differently funded health systems; for instance, cancer care costs often higher in the US compared to universal, publicly funded health systems in Canada and New Zealand [12, 21, 22, 33, 36, 48]. However, given the similarity in disease patterns and

cancer care strategies across the developed world, these results may be generalisable and can be valuable to other similar settings that currently lack a clear view of the economic burden of sepsis in cancer patients. Similar studies using large population-based samples for generating real-world estimates will be helpful in enhancing our understanding of the role of different healthcare services. This will further help guide policy design and allocation of healthcare sources to alleviate both the cost and illness burden of sepsis on health system as well as patients.

There are some limitations that should be considered when interpreting these results. The presence of sepsis could be confounded by a number of factors such as cancer stage or grade at diagnosis, treatments and comorbidities. Although we have attempted to match for cancer type, complete information on these potential confounders were not available to allow further matching in the analysis. It is possible that patients with sepsis had a late cancer stage at diagnosis, were on more aggressive treatments and/or had existing comorbidities which may predispose sepsis cases to incur higher costs[48, 49]. This could result in over-estimation of the excess cost of sepsis. Large variations in survival and costs have been observed across different cancer types [21, 36], and an exploration of burden of sepsis to reflect this heterogeneity will also be important. The cost estimates presented in this study should be interpreted as associations rather than a causal impact of sepsis, but do offer a measure of the economic burden of sepsis care in cancer patients across 5 years of diagnosis which has not been previously quantified.

## 7.6. Conclusion

In summary, this study has demonstrated the substantial economic burden of sepsis in cancer patients over a 5-year period from initial cancer diagnosis using real-world population-linked data for a large cohort of cancer patients. Key efforts in improving sepsis prevention, recognition and management needs to be focused in the first year of cancer diagnosis when mortality and costs are highest. Given the increased susceptibility of this high-risk population to sepsis, these cost estimates are helpful in improving our understanding of burden of sepsis along the cancer pathway and to deploy targeted strategies to alleviate this burden. There should also be continued efforts in refining these estimates to reflect the heterogeneity across different cancer types.

## 7.7. Tables and figures

Table 7.1: Characteristics of cancer patients with sepsis by malignancy type

| Characteristic | Haematology (n = 13,762) | Solid tumour (n = 63,721) |
|---|---|---|
| Age, No. (%) | | |
| 18-34 | 496 (3.6) | 964 (1.5) |
| 35-44 | 554 (4.0) | 1,962 (3.1) |
| 45-54 | 1,343 (9.8) | 6,141 (9.6) |
| 55-64 | 2,541 (18.5) | 13,655 (21.4) |
| 65-74 | 3,486 (25.3) | 18,639 (29.3) |
| 75-84 | 3,521 (25.6) | 15,821 (24.8) |
| 85+ | 1,821 (13.2) | 6,539 (10.3) |
| Female, No. (%) | 6,115 (44.4) | 29,765 (46.7) |
| Urban/rural residence, No. (%) | | |
| Urban | 12,236 (88.9) | 56,034 (88.3) |
| Rural | 1,526 (11.1) | 7,473 (11.7) |
| Income quintile, No. (%) | | |
| Low | 2,878 (21.0) | 14,509 (22.8) |
| Medium-low | 2,955 (21.5) | 13,788 (21.7) |
| Medium | 2,679 (19.5) | 12,531 (19.7) |
| Medium-high | 2,628 (19.1) | 11,675 (18.4) |
| High | 2,590 (18.9) | 11,060 (17.4) |
| Type of cancer, No. (%) | | |
| *Haematology* | | |
| Leukaemia | 8,174 (59.4) | - |
| Lymphoma | 3,367 (24.5) | - |
| Myeloma | 2,221 (16.1) | - |
| *Solid tumour* | | |
| Lung | - | 11,601 (18.2) |
| Colorectal | - | 10,415 (16.3) |
| Breast [a] | - | 6,271 (9.8) |
| Prostate | - | 5,565 (8.7) |
| Bladder | - | 2,929 (4.6) |
| Others | - | 26,940 (42.3) |
| Year of cancer diagnosis, No. (%) | | |
| 2010 | 1,767 (12.8) | 7,881 (12.4) |
| 2011 | 1,698 (12.3) | 8,441 (13.3) |
| 2012 | 1,725 (12.5) | 8,670 (13.6) |
| 2013 | 1,772 (12.9) | 8,925 (14.0) |
| 2014 | 1,799 (13.1) | 8,524 (13.4) |
| 2015 | 1,855 (13.5) | 8,145 (12.8) |
| 2016 | 1,694 (12.3) | 7,571 (11.9) |
| 2017 | 1,452 (10.6) | 5,564 (8.7) |

[a] Breast cancer among females

Table 7.2: Cumulative cost of care ($CAD 2018, 95% CI) between sepsis cases and matched controls

| Time since cancer diagnosis (months) | Haematology | | | Solid tumour | | |
|---|---|---|---|---|---|---|
| | Sepsis cases | Matched controls (no sepsis) | Excess cost | Sepsis cases | Matched controls (no sepsis) | Excess cost |
| 1 | 19,520 (19,174-19,867) | 7,026 (6,859-7,193) | 12,494 (12,105-12,883) | 17,403 (17,069-17,737) | 9,765 (9,606-9,925) | 7,638 (7,272-8,004) |
| 3 | 35,270 (34,866-35,675) | 14,255 (14,050-14,459) | 21,016 (20,562-21,470) | 35,592 (35,180-36,005) | 22,008 (21,767-22,249) | 13,585 (13,107-14,062) |
| 6 | 55,155 (54,661-55,650) | 23,731 (23,484-23,977) | 31,425 (30,884-31,966) | 53,064 (52,562-53,566) | 33,038 (32,749-33,326) | 20,026 (19,449-20,603) |
| 12 | 81,316 (80,718-81,915) | 35,162 (34,857-35,467) | 46,154 (45,050-46,804) | 72,817 (72,230-73,405) | 43,736 (43,400-44,073) | 29,081 (28,404-29,757) |
| 24 | 110,328 (109,624-111,032) | 49,773 (49,410-50,136) | 60,555 (59,786-61,323) | 94,456 (93,787-95,124) | 54,174 (53,793-54,554) | 40,282 (39,496-41,068) |
| 60 | 160,109 (159,204-161,014) | 84,178 (83,626-84,730) | 75,931 (74,895-76,968) | 133,683 (132,842-134,524) | 72,969 (72,498-73,440) | 60,714 (59,729-61,698) |

Figure 7.1: Mean monthly cost of care by malignancy type.

Light bars represent sepsis (cases) and dark bars for no sepsis (controls).

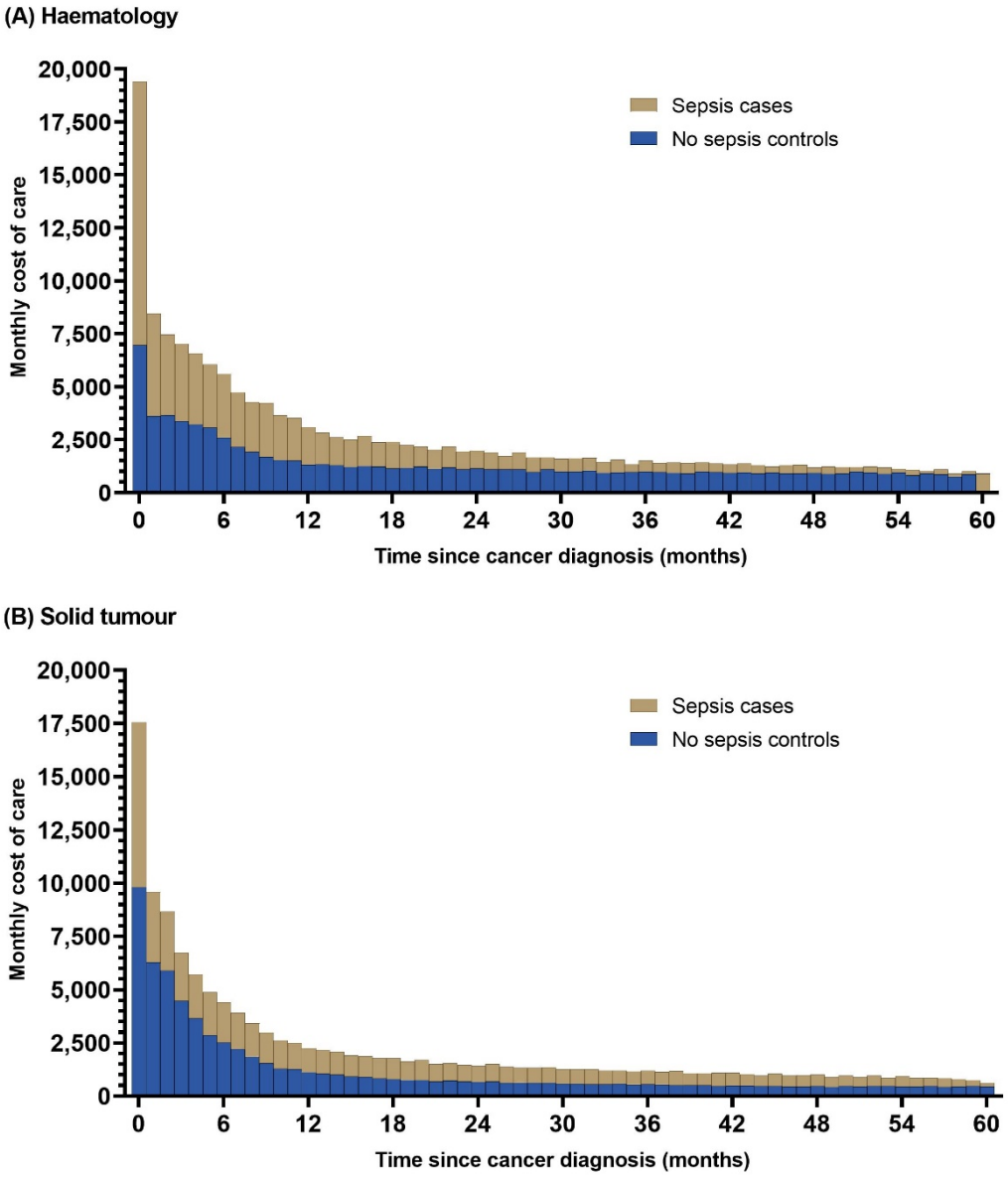
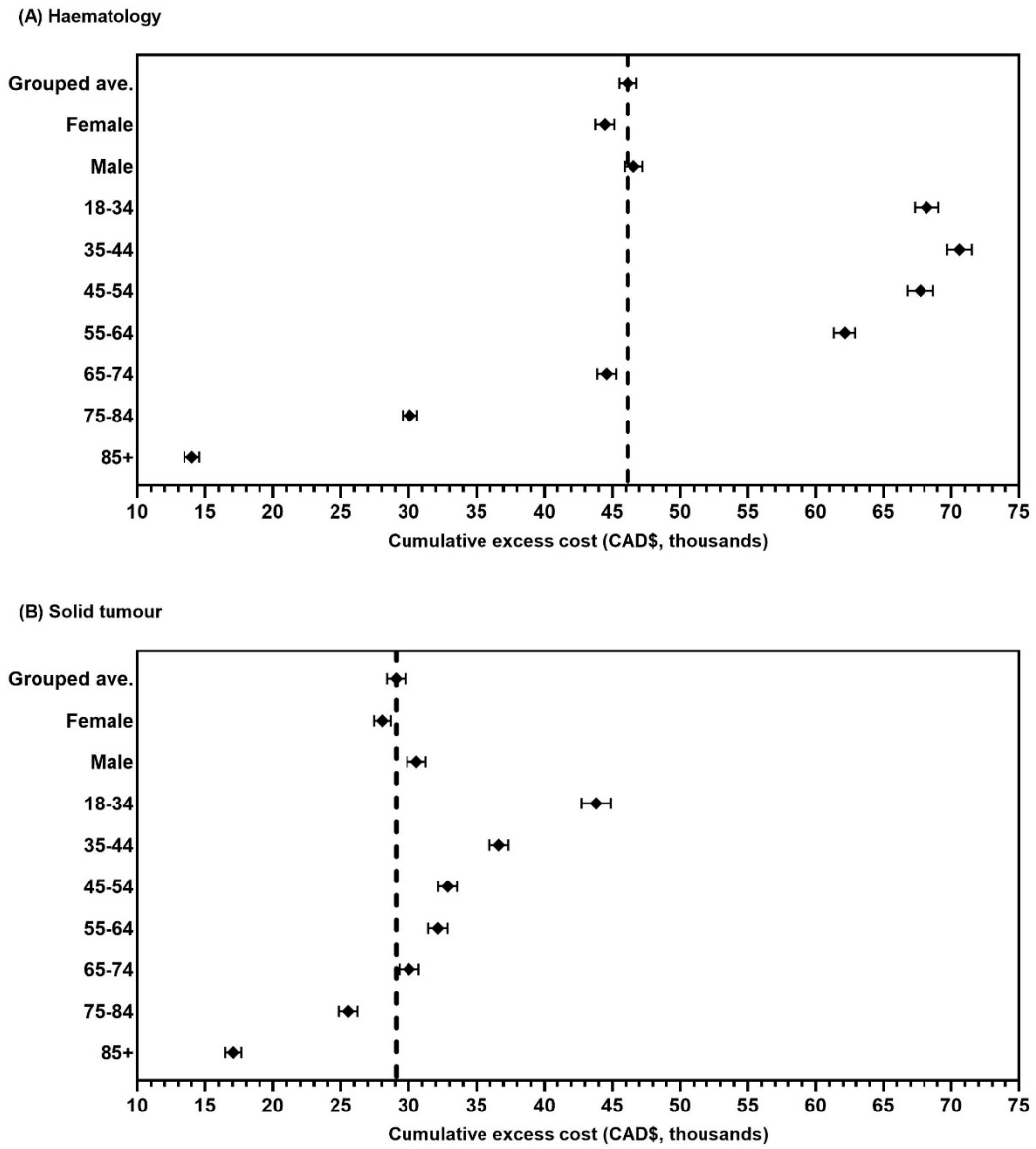


Figure 7.2: Variations in the 1-year cumulative excess cost by sex and age groups.

The dotted vertical line represents the excess cost presented in our main analysis (overall grouped average). Error bars represent the 95% confidence intervals.



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## 7.9. Supplementary materials

### Appendix 1: Data source

Health care administrative databases containing information on all Ontario residents used for this study were held at and accessed through the Institute for Clinical Evaluative Sciences (ICES).

Table S7.1: List of datasets and costing methodology

| Dataset | Information / Type of health care service | Resource use information for costing | Cost estimation methodology |
|---|---|---|---|
| **Ontario Cancer Registry** | Used to identify cancer cohort, type of cancer diagnosed | - | - |
| **Registered Person Database** | Mortality (date of death) and baseline demographics (e.g. age, sex, socioeconomic status) | - | - |
| **Canadian Institute for Health Information-Discharge abstract** | Inpatient hospitalisation & same day surgery | Resource intensity weight (RIW) | RIW * Unit cost per weighted case [1] |
| **Canadian Institute for Health Information-National ambulatory care reporting system** | Ambulatory care – emergency department, cancer clinic and dialysis clinic | Resource intensity weight (RIW) | RIW * Unit cost per weighted case [1] |
| **Ontario Health Insurance Plan claims** | All physician services including primary care consultations, specialist consultations, allied health services, diagnostic tests and laboratory services | Costs reported in dataset | Costs as per provided in dataset. However, for physicians that were shadow-billed (reported cost in dataset = $0), costs were imputed using the mean cost of the fee-for-service records of the same year and fee code [1, 2] |

| | | | |
|---|---|---|---|
| **Continuing Care reporting system** | Other institution-based care; e.g. rehabilitation, complex continuing care and long-term care | Utilisation intensity weight and length of stay (LOS) | Utilisation intensity weight * LOS * per diem cost [1] |
| **Ontario Drug Benefit program** | Outpatient prescriptions | Costs reported in dataset | Costs as per provided in dataset |
| **New Drug Funding Program** | Chemotherapy supplied | Costs reported in dataset | Costs as per provided in dataset |
| **Activity level reporting system** | Radiation therapy | National Hospital Productivity Improvement Program (NHPIP) codes | Intensity of resource use (minutes) from NHPIP codes * cost per min [1, 3] |

Costs for inpatient hospitalisations, emergency department and ambulatory care visits and long-term care were estimated by multiplying resource intensity weight by cost per weighted case or day (relevant to the year the resource was used). Costs for medications, chemotherapy and physician services were available directly in the data. Radiation costs were based on the intensity of resource use captured by National Hospital Productivity Improvement Program (NHPIP) codes and unit cost obtained from Earle et al.[3]. All costs were then adjusted to 2018 dollars using the healthcare component of the Statistics Canada Consumer Price Index.

**Appendix 2: Diagnostic codes used for identification of sepsis**

Sepsis cases were identified using codes from the 10th (ICD-10-CA) Revisions sourced from the Global Burden of Disease Study [4]. Cases were classified within two mutually exclusive groups, "explicit" and "implicit." Explicit sepsis cases were those with an ICD code explicitly referencing sepsis listed as an admission diagnosis. Implicit sepsis cases were those with both an infection code and organ dysfunction code listed as admission diagnoses. Any cases captured through either explicit or implicit codes were considered to be a sepsis case.

Table S7.2: ICD-10-CA codes used in the identification of sepsis

| Explicit | Implicit | |
|---|---|---|
| | Infection codes | Organ dysfunction codes |
| A02.1-A02.9, A20.7-A20.9, A21.7-A21.9, A22.7-A22.9, A24.1-A24.9, A26.7-A26.9, A28.2-A28.9, A32.7-A32.9, A39.0, A39.4-A41.9, A42.7-A42.9, A50-A50.9, A54.86, B00.7-B00.9, B37.7-B37.9, N98.0, O03.0, O03.3, O03.5, O03.8, O04.5, O04.8, O07.3, O08.0, O08.83, O23-O23.9, O41.1-O41.9, O75.3, O85- O86.8, O88.3-O88.3, O91-O91.23, O98, O98.2-O98.9, P00.2, P22-P23.9, P29.1, P29.8, P35-P37, P37.1-P39.9, R65.2-R65.2, R68.1 | A01-A02.0, A03-A09.9, A19-A20.3, A21-A21.3, A22-A22.2, A23-A24.0, A25-A26.0, A27-A28.1, A31-A32.12, A36-A39, A39.1-A39.3, A42-A42.2, A43-A46.0, A48-A49.9, A59-A59.9, A65-A65.0, A69-A69.1, A74, A74.8- A75.9, A77-A81.9, A83-A96.9, A98-B00.59, B01-B10.89, B25-B27.99, B29.4, B33-B34.9, B37-B37.6, B38-B50.9, B54-B55, B55.1-B55.9, B58-B60.8, B64, B67-B67.99, B91, B95-B99.9, G00-G08.0, G14-G14.6, H05.01-H05.039, H60.2-H60.23, H70.0-H70.009, I00, I02, I02.9, I26.01-I26.09, I26.90-I26.99, I33-I33.9, I38-I39.9, I40.0-I40.9, I76, I96-I96.9, I98.1, J01-J06.9, J09-J22.9, J36-J36.0, J39.0-J39.1, J85-J86.9, K35-K37.9, K57-K57.93, K61-K61.4, K63.0-K63.1, K65-K65.9, K67.8, K75.0-K75.1, K75.3, K76.3, K77.0, K81.0, K81.2, K83.0, K95.01, K95.81, L02-L08.9, M00-M02.9, M86-M86.9, M89.6-M89.69, N10-N10.9, N15.1-N15.9, N30-N30.91, N39.0, N41.0, N41.2-N41.3, | D65-D65.9, D69.5-D69.59, E87.2-E87.99, G93.4-G93.49, I46-I46.9, I95.1-I95.9, J80-J80.9, J95.2-J95.3, J96- J96.92, K72-K72.91, N00- N01.9, N17-N17.9, R09.02, R09.2, R40.0-R40.4, R41.82, R55-R55.0, R57-R57.9 |

| | | |
|---|---|---|
| | N45-N45.9, N70-N77.8, R78.81, T80.2-T80.29, T81.4, T82.6-T82.7, T83.5, T83.6, T84.5-T84.7, T85.7, T88.0, U04 | |

Within the Ontario Health Insurance Plan (OHIP) dataset, diagnosis was captured using a separate set of diagnostic codes and sepsis was identified using the diagnosis code “038 – Septicaemia”.

**Appendix 3: Sensitivity analyses**

The following sensitivity analyses were conducted, and their results presented in the tables below.

(i) Including income quintiles and additional socioeconomic scores (dependency, deprivation, ethnic concentration) as matching variables to identify controls (at the expense of identifying suitable controls)

(ii) Excluding the 1-month pre-diagnosis period from our sepsis case definition

(iii) Alternate case definition of sepsis (Sepsis-2) [5] using Jolley's et al. ICD-10-coded case definition [6]

(iv) Duration attributed to end-of-life costs (12 months rather than 6 as in our main analysis)

In summary, the inclusion of additional matching variables and exclusion of the 1-month pre-diagnosis period from our sepsis case definition did not substantially change our cost estimates (variations between -3% and 8%). Cost estimates were sensitive to the sepsis definitions used. Using the Sepsis-2 definition resulted in lower excess cost, 14-33% lower costs for solid tumours and 3-13% lower costs for haematology. Unsurprisingly, the proportion of end-of-life cost increased from 57% to 77% for haematology patients and from 39% to 54% for solid tumour patients as the length of terminal care increased from 6 to 12 months.

Table S7.3: Cumulative cost of care ($CAD 2018) results from sensitivity analysis (i)

| Time since cancer diagnosis (months) | Haematology | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Sepsis cases | | | Matched controls | | | Excess cost | | |
| | Mean | 95% CI | | Mean | 95% CI | | Mean | 95% CI | |
| | | LL | UL | | LL | UL | | LL | UL |
| 1 | 19,472 | 19,163 | 19,782 | 6,603 | 6,446 | 6,761 | 12,869 | 12,528 | 13,210 |
| 3 | 35,130 | 34,751 | 35,508 | 13,485 | 13,286 | 13,685 | 21,644 | 21,221 | 22,068 |
| 6 | 54,173 | 53,713 | 54,633 | 2,568 | 2,319 | 2,817 | 1,605 | 31,094 | 32,116 |
| 12 | 79,978 | 79,391 | 80,564 | 33,759 | 33,454 | 34,064 | 46,218 | 45,577 | 46,860 |
| 24 | 109,342 | 108,662 | 110,022 | 48,391 | 48,030 | 48,752 | 60,951 | 60,193 | 61,708 |
| 60 | 158,901 | 157,970 | 159,833 | 82,589 | 82,044 | 83,134 | 76,312 | 75,239 | 77,386 |

| Time since cancer diagnosis (months) | Solid tumour | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Sepsis cases | | | Matched controls | | | Excess cost | | |
| | Mean | 95% CI | | Mean | 95% CI | | Mean | 95% CI | |
| | | LL | UL | | LL | UL | | LL | UL |
| 1 | 17,194 | 16,879 | 17,510 | 9,388 | 9,223 | 9,552 | 7,807 | 7,448 | 8,166 |
| 3 | 35,001 | 34,557 | 35,445 | 21,197 | 20,960 | 21,433 | 13,804 | 13,310 | 14,298 |
| 6 | 52,024 | 51,495 | 52,553 | 32,140 | 31,851 | 32,429 | 19,884 | 19,295 | 20,473 |
| 12 | 72,206 | 71,605 | 72,808 | 43,309 | 42,977 | 43,641 | 28,898 | 28,225 | 29,570 |
| 24 | 94,157 | 93,477 | 94,838 | 53,846 | 53,482 | 54,210 | 40,311 | 39,547 | 41,076 |
| 60 | 135,036 | 134,177 | 135,896 | 73,738 | 73,270 | 74,206 | 61,298 | 60,340 | 62,257 |

Table S7.4: Cumulative cost of care ($CAD 2018) results from sensitivity analysis (ii)

| Time since cancer diagnosis (months) | Haematology | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Sepsis cases | | | Matched controls | | | Excess cost | | |
| | Mean | 95% CI | | Mean | 95% CI | | Mean | 95% CI | |
| | | LL | UL | | LL | UL | | LL | UL |
| 1 | 20,005 | 19,683 | 20,327 | 7,064 | 6,907 | 7,220 | 12,941 | 12,581 | 13,301 |
| 3 | 36,292 | 35,883 | 36,701 | 14,442 | 14,243 | 14,641 | 21,850 | 21,387 | 22,312 |
| 6 | 56,110 | 55,614 | 56,606 | 24,067 | 23,827 | 24,307 | 32,043 | 31,493 | 32,593 |
| 12 | 82,887 | 82,285 | 83,489 | 35,557 | 35,252 | 35,861 | 47,330 | 46,654 | 48,006 |
| 24 | 112,841 | 112,143 | 113,538 | 49,950 | 49,583 | 50,317 | 62,890 | 62,104 | 63,676 |
| 60 | 164,526 | 163,611 | 165,442 | 83,061 | 82,518 | 83,605 | 81,465 | 80,389 | 82,541 |

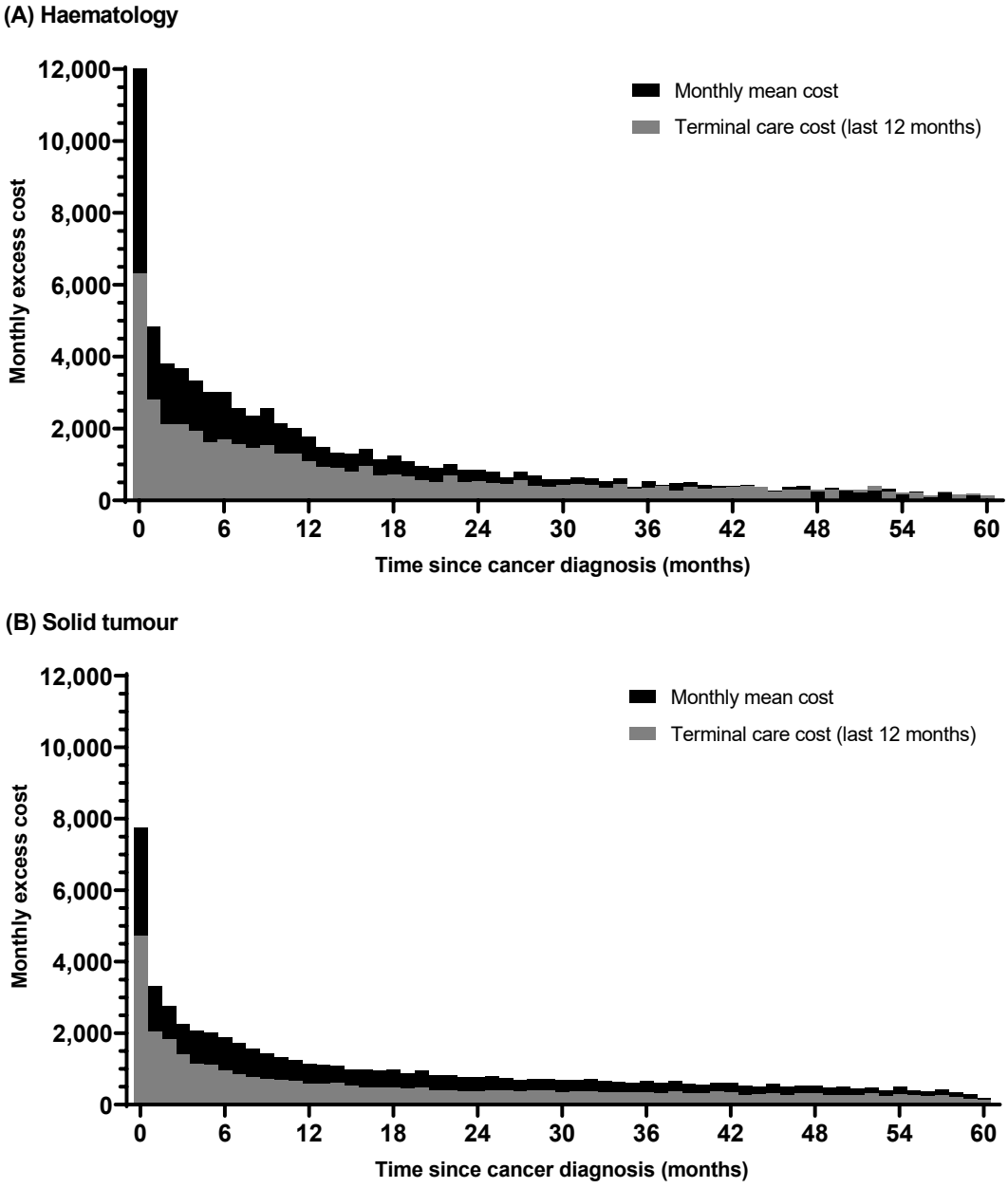
| Time since cancer diagnosis (months) | Solid tumour | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Sepsis cases | | | Matched controls | | | Excess cost | | |
| | Mean | 95% CI | | Mean | 95% CI | | Mean | 95% CI | |
| | | LL | UL | | LL | UL | | LL | UL |
| 1 | 17,819 | 17,474 | 18,164 | 9,873 | 9,699 | 10,047 | 7,946 | 7,563 | 8,330 |
| 3 | 36,262 | 35,794 | 36,730 | 22,225 | 21,974 | 22,476 | 14,037 | 13,509 | 14,565 |
| 6 | 53,806 | 53,259 | 54,353 | 33,119 | 32,823 | 33,414 | 20,688 | 20,073 | 21,302 |
| 12 | 73,758 | 73,130 | 74,386 | 43,745 | 43,406 | 44,083 | 30,013 | 29,302 | 30,725 |
| 24 | 95,619 | 94,911 | 96,326 | 53,697 | 53,318 | 54,075 | 41,922 | 41,128 | 42,716 |
| 60 | 134,361 | 133,514 | 135,208 | 72,498 | 72,032 | 72,964 | 61,863 | 60,881 | 62,844 |

Table S7.5: Cumulative cost of care ($CAD 2018) results from sensitivity analysis (iii)

| Time since cancer diagnosis (months) | Haematology | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Sepsis cases | | | Matched controls | | | Excess cost | | |
| | Mean | 95% CI | | Mean | 95% CI | | Mean | 95% CI | |
| | | LL | UL | | LL | UL | | LL | UL |
| 1 | 17,353 | 17,025 | 17,681 | 6,530 | 6,385 | 6,676 | 10,822 | 10,458 | 11,186 |
| 3 | 32,795 | 32,386 | 33,205 | 13,289 | 13,100 | 13,479 | 19,506 | 19,050 | 19,962 |
| 6 | 51,693 | 51,196 | 52,189 | 22,127 | 21,897 | 22,358 | 29,566 | 29,009 | 30,122 |
| 12 | 76,441 | 75,834 | 77,049 | 32,507 | 32,215 | 42,798 | 43,935 | 43,244 | 44,625 |
| 24 | 103,912 | 103,215 | 104,608 | 45,373 | 45,023 | 45,722 | 58,539 | 57,736 | 59,342 |
| 60 | 153,690 | 152,784 | 154,596 | 73,602 | 73,093 | 74,110 | 80,088 | 79,038 | 81,138 |

| Time since cancer diagnosis (months) | Solid tumour | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Sepsis cases | | | Matched controls | | | Excess cost | | |
| | Mean | 95% CI | | Mean | 95% CI | | Mean | 95% CI | |
| | | LL | UL | | LL | UL | | LL | UL |
| 1 | 14,284 | 14,010 | 14,559 | 9,097 | 8,932 | 9,263 | 5,187 | 4,861 | 5,513 |
| 3 | 30,789 | 30,416 | 31,163 | 20,385 | 20,142 | 20,628 | 10,404 | 9,960 | 10,848 |
| 6 | 46,505 | 46,082 | 46,929 | 30,953 | 30,664 | 31,242 | 15,553 | 15,041 | 16,064 |
| 12 | 64,746 | 64,234 | 65,257 | 41,424 | 41,088 | 41,759 | 23,322 | 22,707 | 23,937 |
| 24 | 84,259 | 83,668 | 84,851 | 50,343 | 49,969 | 50,717 | 33,916 | 33,218 | 34,614 |
| 60 | 119,377 | 118,632 | 120,121 | 66,613 | 66,171 | 67,056 | 52,763 | 51,898 | 53,628 |

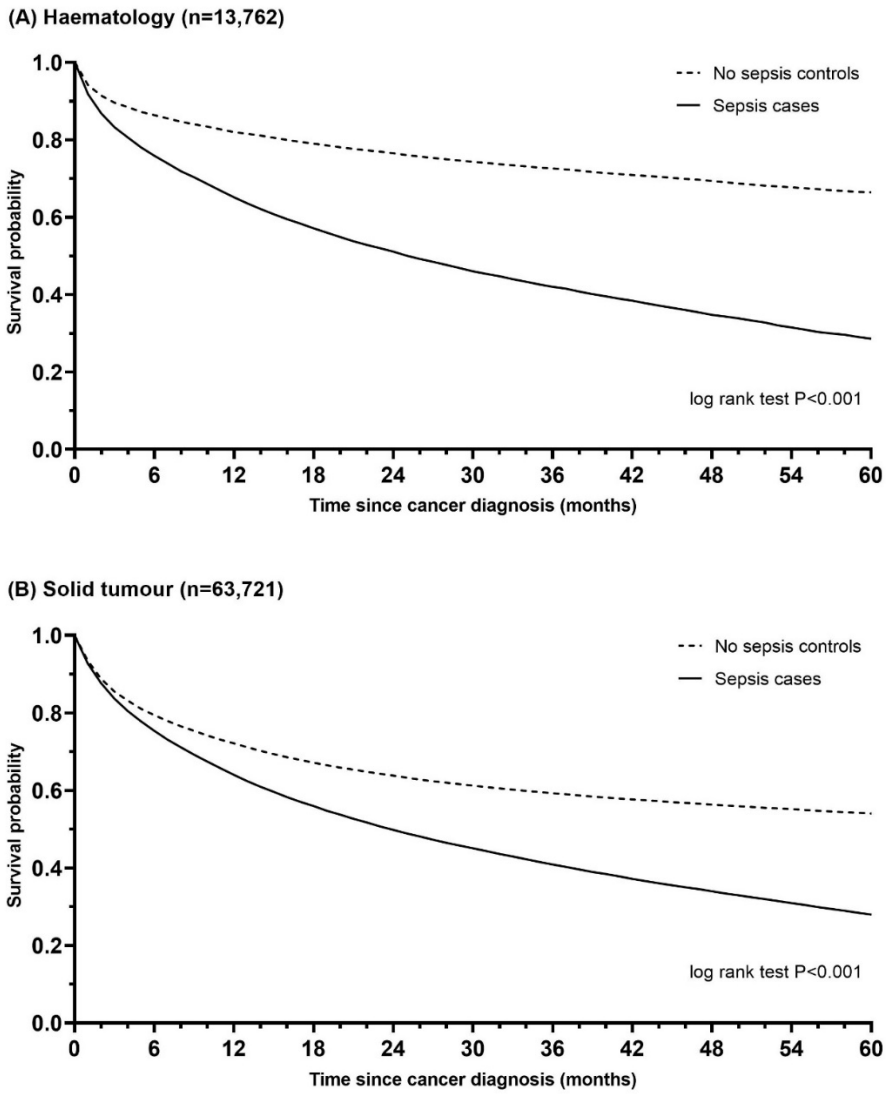
Figure S7.1: Excess cost of care ($CAD 2018) results from sensitivity analysis (iv)



**Appendix 4: Kaplan-Meier survival curves comparing sepsis cases to no sepsis controls.**

Figure S7.2 shows Kaplan-Meier survival curves comparing sepsis cases to no sepsis controls. Mortality was high among sepsis cases, particularly in the first year of cancer diagnosis. The 5-year overall survival rate for haematology patients with sepsis was 29.1% (95% CI, 28.2-30.0) and 66.5% (95% CI, 65.6-67.4) for those without sepsis. In the solid tumour cancer group, the 5-year overall survival for patients with and without sepsis was 28.4% (95% CI, 28.0-28.8) and 54.2% (95% CI, 53.8-54.6), respectively. The difference in five-year overall survival between cancer patients with sepsis and without sepsis was statistically significant (log rank test p<0.001) across both cancer types.

Figure S7.2: Kaplan-Meier survival curves comparing sepsis cases and matched no sepsis controls for (A) haematological and (B) solid tumour cancer.



## Appendix 5: Descriptive statistics of sepsis cases vs. matched controls by malignancy types

Table S7.6: Characteristics of sepsis cases vs. matched controls for haematology patients

| Characteristic | Haematology | | | | |
|---|---|---|---|---|---|
| | Sepsis cases | | Matched controls (no sepsis) | | |
| | Number (N = 13,762) | Percent | Number (N = 13,762) | Percent | P-value |
| Age | | | | | P=0.996 |
| 18-34 | 496 | 3.6 | 497 | 3.61 | |
| 35-44 | 554 | 4.03 | 575 | 4.18 | |
| 45-54 | 1,343 | 9.76 | 1,334 | 9.69 | |
| 55-64 | 2,541 | 18.46 | 2,563 | 18.62 | |
| 65-74 | 3,486 | 25.33 | 3,458 | 25.13 | |
| 75-84 | 3,521 | 25.58 | 3,514 | 25.53 | |
| 85+ | 1,821 | 13.23 | 1,821 | 13.23 | |
| Female | 6,115 | 44.43 | 6,115 | 44.43 | P=1.000 |
| Urban/rural residence | | | | | P=1.000 |
| Urban | 12,236 | 88.91 | 12,236 | 88.91 | |
| Rural | 1,526 | 11.09 | 1,526 | 11.09 | |
| Income quintile | | | | | P<0.001 |
| Low | 2,878 | 20.96 | 2,636 | 19.21 | |
| Medium-low | 2,955 | 21.52 | 2,815 | 20.52 | |
| Medium | 2,679 | 19.51 | 2,666 | 19.43 | |
| Medium-high | 2,628 | 19.14 | 2,678 | 19.52 | |
| High | 2,590 | 18.86 | 2,926 | 21.32 | |
| Type of cancer | | | | | |
| Leukaemia | 8,174 | 59.40 | 8,174 | 59.40 | |
| Lymphoma | 3,367 | 24.47 | 3,367 | 24.47 | |
| Myeloma | 2,221 | 16.14 | 2,221 | 16.14 | |
| Year of cancer diagnosis | | | | | P=1.000 |
| 2010 | 1,767 | 12.84 | 1,767 | 12.84 | |
| 2011 | 1,698 | 12.34 | 1,698 | 12.34 | |
| 2012 | 1,725 | 12.53 | 1,725 | 12.53 | |
| 2013 | 1,772 | 12.88 | 1,772 | 12.88 | |
| 2014 | 1,799 | 13.07 | 1,799 | 13.07 | |
| 2015 | 1,855 | 13.48 | 1,855 | 13.48 | |
| 2016 | 1,694 | 12.31 | 1,694 | 12.31 | |
| 2017 | 1,452 | 10.55 | 1,452 | 10.55 | |

Table S7.7: Characteristics of sepsis cases vs. matched controls for solid tumour patients

| Characteristic | Solid tumour | | | | |
|---|---|---|---|---|---|
| | Sepsis cases | | Matched controls (no sepsis) | | |
| | Number (N = 63,721) | Percent | Number (N = 63,721) | Percent | P-value |
| Age | | | | | P=0.728 |
| 18-34 | 964 | 1.51 | 973 | 1.53 | |
| 35-44 | 1,962 | 3.08 | 1,953 | 3.06 | |
| 45-54 | 6,141 | 9.64 | 6,338 | 9.95 | |
| 55-64 | 13,655 | 21.43 | 13,627 | 21.39 | |
| 65-74 | 18,639 | 29.25 | 18,551 | 29.11 | |
| 75-84 | 15,821 | 24.83 | 15,740 | 24.7 | |
| 85+ | 6,539 | 10.26 | 6,539 | 10.26 | |
| Female | 29,765 | 46.71 | 29,765 | 46.71 | P=1.000 |
| Urban/rural residence | | | | | P=1.000 |
| Urban | 56,034 | 88.29 | 56,034 | 88.29 | |
| Rural | 7,473 | 11.73 | 7,473 | 11.73 | |
| Income quintile | | | | | P<0.001 |
| Low | 14,509 | 22.83 | 12,780 | 20.1 | |
| Medium-low | 13,788 | 21.69 | 13,164 | 20.71 | |
| Medium | 12,531 | 19.71 | 12,701 | 19.98 | |
| Medium-high | 11,675 | 18.37 | 12,492 | 19.65 | |
| High | 11,060 | 17.4 | 12,432 | 19.56 | |
| Type of cancer | | | | | P=1.000 |
| Lung | 11,601 | 18.21 | 11,601 | 18.21 | |
| Colorectal | 10,415 | 16.34 | 10,415 | 16.34 | |
| Breast [b] | 6,271 | 9.84 | 6,271 | 9.84 | |
| Prostate | 5,565 | 8.73 | 5,565 | 8.73 | |
| Bladder | 2,929 | 4.6 | 2,929 | 4.6 | |
| Pancreatic | 2,627 | 4.12 | 2,627 | 4.12 | |
| Stomach | 2,224 | 3.49 | 2,224 | 3.49 | |
| Head and neck | 2,220 | 3.48 | 2,220 | 3.48 | |
| Kidney | 1,960 | 3.08 | 1,960 | 3.08 | |
| Liver | 1,916 | 3.01 | 1,916 | 3.01 | |
| Melanoma | 1,812 | 2.84 | 1,812 | 2.84 | |
| Uterus | 1,705 | 2.68 | 1,705 | 2.68 | |
| Ovary | 1,395 | 2.19 | 1,395 | 2.19 | |
| Brain | 1,066 | 1.67 | 1,066 | 1.67 | |
| Oesophagus | 1,044 | 1.64 | 1,044 | 1.64 | |
| Thyroid | 666 | 1.05 | 666 | 1.05 | |
| Cervical | 506 | 0.79 | 506 | 0.79 | |
| Testis | 181 | 0.28 | 181 | 0.28 | |
| Others | 7,618 | 11.96 | 7,618 | 11.96 | |
| Year of cancer diagnosis | | | | | P=1.000 |
| 2010 | 7,881 | 12.37 | 7,881 | 12.37 | |
| 2011 | 8,441 | 13.25 | 8,441 | 13.25 | |
| 2012 | 8,670 | 13.61 | 8,670 | 13.61 | |
| 2013 | 8,925 | 14.01 | 8,925 | 14.01 | |

| | | | | | |
|---|---|---|---|---|---|
| 2014 | 8,524 | 13.38 | 8,524 | 13.38 | |
| 2015 | 8,145 | 12.78 | 8,145 | 12.78 | |
| 2016 | 7,571 | 11.88 | 7,571 | 11.88 | |
| 2017 | 5,564 | 8.73 | 5,564 | 8.73 | |

## Appendix 6: Descriptive statistics of sepsis cases vs. unmatched cases by malignancy types

Table S7.8: Characteristics of sepsis cases vs. unmatched cases for haematology patients

| Characteristic | Haematology | | | | |
|---|---|---|---|---|---|
| | Sepsis cases | | Unmatched cases | | |
| | Number (N = 13,762) | Percent | Number (N = 2,763) | Percent | P-value |
| Age | | | | | P<0.001 |
| 18-34 | 496 | 3.6 | 116 | 4.2 | |
| 35-44 | 554 | 4.03 | 70 | 2.53 | |
| 45-54 | 1,343 | 9.76 | 173 | 6.26 | |
| 55-64 | 2,541 | 18.46 | 433 | 15.67 | |
| 65-74 | 3,486 | 25.33 | 671 | 24.29 | |
| 75-84 | 3,521 | 25.58 | 810 | 29.32 | |
| 85+ | 1,821 | 13.23 | 490 | 17.73 | |
| Female | 6,115 | 44.43 | 1,139 | 41.22 | |
| Urban/rural residence | | | | | P<0.001 |
| Urban | 12,236 | 88.91 | 2,522 | 91.22 | |
| Rural | 1,526 | 11.09 | 241 | 8.78 | |
| Income quintile | | | | | P=0.309 |
| Low | 2,878 | 20.96 | 567 | 20.7 | |
| Medium-low | 2,955 | 21.52 | 553 | 20.19 | |
| Medium | 2,679 | 19.51 | 551 | 20.12 | |
| Medium-high | 2,628 | 19.14 | 514 | 18.77 | |
| High | 2,590 | 18.86 | 554 | 20.23 | |
| Type of cancer | | | | | P<0.001 |
| Leukaemia | 8,174 | 59.40 | 1,575 | 57 | |
| Lymphoma | 3,367 | 24.47 | 356 | 12.88 | |
| Myeloma | 2,221 | 16.14 | 832 | 30.11 | |
| Year of cancer diagnosis | | | | | P<0.001 |
| 2010 | 1,767 | 12.84 | 418 | 15.13 | |
| 2011 | 1,698 | 12.34 | 416 | 15.06 | |
| 2012 | 1,725 | 12.53 | 478 | 17.3 | |
| 2013 | 1,772 | 12.88 | 482 | 17.44 | |
| 2014 | 1,799 | 13.07 | 385 | 13.93 | |
| 2015 | 1,855 | 13.48 | 329 | 11.91 | |
| 2016 | 1,694 | 12.31 | 180 | 6.51 | |
| 2017 | 1,452 | 10.55 | 75 | 2.71 | |
| Outcome at end of study period | | | | | |
| Died | 8,831 | 64.17 | 1,910 | 69.13 | P<0.001 |

Table S7.9: Characteristics of sepsis cases vs. unmatched cases for solid tumour patients

| Characteristic | Solid tumour | | | | |
|---|---|---|---|---|---|
| | Sepsis cases | | Unmatched cases | | |
| | Number (N = 63,721) | Percent | Number (N = 2,782) | Percent | P-value |
| Age | | | | | P<0.001 |
| 18-34 | 964 | 1.51 | 88 | 3.16 | |
| 35-44 | 1,962 | 3.08 | 74 | 2.66 | |
| 45-54 | 6,141 | 9.64 | 148 | 5.32 | |
| 55-64 | 13,655 | 21.43 | 359 | 12.9 | |
| 65-74 | 18,639 | 29.25 | 721 | 25.92 | |
| 75-84 | 15,821 | 24.83 | 907 | 32.6 | |
| 85+ | 6,539 | 10.26 | 485 | 17.43 | |
| Female | 29,765 | 46.71 | 1,044 | 37.53 | P<0.001 |
| Urban/rural residence | | | | | P=0.240 |
| Urban | 56,034 | 88.29 | 2,408 | 87.53 | |
| Rural | 7,473 | 11.73 | 343 | 12.47 | |
| Income quintile | | | | | P=0.058 |
| Low | 14,509 | 22.83 | 589 | 21.47 | |
| Medium-low | 13,788 | 21.69 | 566 | 20.63 | |
| Medium | 12,531 | 19.71 | 593 | 21.62 | |
| Medium-high | 11,675 | 18.37 | 498 | 18.16 | |
| High | 11,060 | 17.4 | 497 | 18.12 | |
| Type of cancer | | | | | P<0.001 |
| Lung | 11,601 | 18.21 | 357 | 12.83 | |
| Colorectal | 10,415 | 16.34 | 486 | 17.47 | |
| Breast [a] | 6,271 | 9.84 | 32 | 1.15 | |
| Prostate | 5,565 | 8.73 | 110 | 3.95 | |
| Bladder | 2,929 | 4.6 | 358 | 12.87 | |
| Pancreatic | 2,627 | 4.12 | 228 | 8.2 | |
| Stomach | 2,224 | 3.49 | 173 | 6.22 | |
| Head and neck | 2,220 | 3.48 | 50 | 1.8 | |
| Kidney | 1,960 | 3.08 | 66 | 2.37 | |
| Liver | 1,916 | 3.01 | 257 | 9.24 | |
| Melanoma | 1,812 | 2.84 | 33 | 1.19 | |
| Uterus | 1,705 | 2.68 | 18 | 0.65 | |
| Ovary | 1,395 | 2.19 | 38 | 1.37 | |
| Brain | 1,066 | 1.67 | 40 | 1.44 | |
| Oesophagus | 1,044 | 1.64 | 93 | 3.34 | |
| Thyroid | 666 | 1.05 | 13 | 0.47 | |
| Cervical | 506 | 0.79 | 20 | 0.72 | |
| Testis | 181 | 0.28 | 18 | 0.65 | |
| Others | 7,618 | 11.96 | 392 | 14.09 | |
| Year of cancer diagnosis | | | | | P<0.001 |
| 2010 | 7,881 | 12.37 | 326 | 11.72 | |
| 2011 | 8,441 | 13.25 | 356 | 12.8 | |
| 2012 | 8,670 | 13.61 | 459 | 16.5 | |
| 2013 | 8,925 | 14.01 | 520 | 18.69 | |
| 2014 | 8,524 | 13.38 | 421 | 15.13 | |

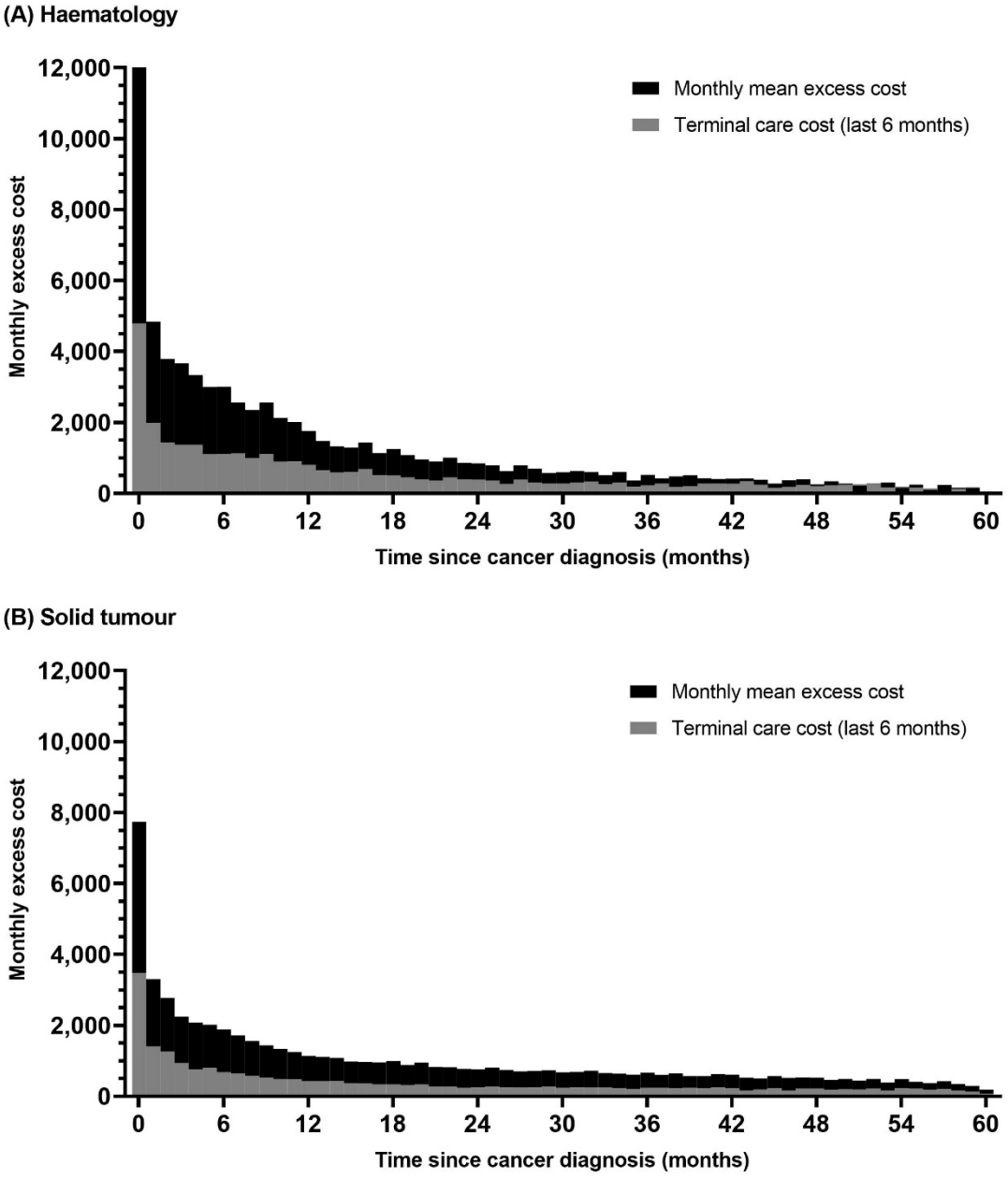
| | | | | | |
|---|---|---|---|---|---|
| 2015 | 8,145 | 12.78 | 366 | 13.16 | |
| 2016 | 7,571 | 11.88 | 239 | 8.59 | |
| 2017 | 5,564 | 8.73 | 95 | 3.41 | |
| Outcome at end of study period | | | | | |
| Died | 42,357 | 66.47 | 2,145 | 77.1 | P<0.001 |

[a] Breast cancer among females

## Appendix 7: Breakdown of excess cost of care due to sepsis

Figure S7.3: Mean monthly excess cost of care due to sepsis by malignancy type.

Black bars represent monthly mean excess costs and the grey bars represent terminal care cost (last 6 months).



**Appendix 8: Sub-group analyses results**

Table S7.10: Cumulative cost of care ($CAD 2018) between sepsis cases and matched controls among females

| Time since cancer diagnosis (months) | Haematology (Female) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Sepsis cases | | | Matched controls | | | Excess cost | | |
| | Mean | 95% CI | | Mean | 95% CI | | Mean | 95% CI | |
| | | LL | UL | | LL | UL | | LL | UL |
| 1 | 18,881 | 18,586 | 19,177 | 7,116 | 6,942 | 7,290 | 11,765 | 11,416 | 12,114 |
| 3 | 34,262 | 33,883 | 34,641 | 13,810 | 13,597 | 14,022 | 20,452 | 20,016 | 20,888 |
| 6 | 53,478 | 52,986 | 53,970 | 23,080 | 22,816 | 23,344 | 30,398 | 29,835 | 30,961 |
| 12 | 78,626 | 78,027 | 79,224 | 34,165 | 33,846 | 34,484 | 44,461 | 43,774 | 45,148 |
| 24 | 107,489 | 106,807 | 108,172 | 48,503 | 48,136 | 48,871 | 58,986 | 58,201 | 59,771 |
| 60 | 157,059 | 156,184 | 157,933 | 82,892 | 82,338 | 83,446 | 74,166 | 73,146 | 75,187 |

| Time since cancer diagnosis (months) | Solid tumour (Female) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Sepsis cases | | | Matched controls | | | Excess cost | | |
| | Mean | 95% CI | | Mean | 95% CI | | Mean | 95% CI | |
| | | LL | UL | | LL | UL | | LL | UL |
| 1 | 17,069 | 16,770 | 17,369 | 9,501 | 9,351 | 9,652 | 7,568 | 7,233 | 7,904 |
| 3 | 34,362 | 33,973 | 34,751 | 21,145 | 20,925 | 21,366 | 13,217 | 12,774 | 13,660 |
| 6 | 51,286 | 50,835 | 51,736 | 32,629 | 32,349 | 32,910 | 18,656 | 18,134 | 19,178 |
| 12 | 72,642 | 72,129 | 73,154 | 44,588 | 44,246 | 44,931 | 28,053 | 27,446 | 28,660 |
| 24 | 93,571 | 92,982 | 94,160 | 54,918 | 54,531 | 55,305 | 38,653 | 37,957 | 39,349 |
| 60 | 131,394 | 130,657 | 132,131 | 73,543 | 73,064 | 74,022 | 57,851 | 56,989 | 58,713 |

Table S7.11: Cumulative cost of care ($CAD 2018) between sepsis cases and matched controls among males

| Time since cancer diagnosis (months) | Haematology (Male) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Sepsis cases | | | Matched controls (no sepsis) | | | Excess cost | | |
| | Mean | 95% CI | | Mean | 95% CI | | Mean | 95% CI | |
| | | LL | UL | | LL | UL | | LL | UL |
| 1 | 19,463 | 19,141 | 19,786 | 6,939 | 6,786 | 7,092 | 12,524 | 12,170 | 12,879 |
| 3 | 35,922 | 35,528 | 36,315 | 14,625 | 14,425 | 14,825 | 21,297 | 20,854 | 21,740 |
| 6 | 56,239 | 55,740 | 56,738 | 24,483 | 24,242 | 24,725 | 31,756 | 31,204 | 32,309 |
| 12 | 82,709 | 82,112 | 83,306 | 36,127 | 35,825 | 36,428 | 46,583 | 45,918 | 47,248 |
| 24 | 112,218 | 111,537 | 112,899 | 51,067 | 50,708 | 51,426 | 61,151 | 60,391 | 61,912 |
| 60 | 162,082 | 161,234 | 162,930 | 85,493 | 84,951 | 86,035 | 76,589 | 75,588 | 77,589 |

| Time since cancer diagnosis (months) | Solid tumour (Male) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Sepsis cases | | | Matched controls (no sepsis) | | | Excess cost | | |
| | Mean | 95% CI | | Mean | 95% CI | | Mean | 95% CI | |
| | | LL | UL | | LL | UL | | LL | UL |
| 1 | 18,015 | 17,682 | 18,348 | 10,058 | 9,894 | 10,221 | 7,957 | 7,587 | 8,328 |
| 3 | 37,309 | 36,858 | 37,760 | 22,697 | 22,457 | 22,937 | 14,611 | 14,089 | 15,134 |
| 6 | 54,874 | 54,338 | 55,409 | 33,354 | 33,065 | 33,642 | 21,520 | 20,894 | 22,145 |
| 12 | 73,562 | 72,962 | 74,163 | 42,991 | 42,670 | 43,313 | 30,571 | 29,880 | 31,262 |
| 24 | 95,732 | 95,054 | 96,411 | 53,457 | 53,099 | 53,816 | 42,275 | 41,493 | 43,057 |
| 60 | 135,851 | 135,006 | 136,697 | 71,915 | 71,472 | 72,358 | 63,936 | 62,970 | 64,903 |

Table S7.12: Cumulative cost of care ($CAD 2018) between haematology sepsis cases and matched controls by age categories

| Time since cancer diagnosis (months) | Haematology (Age 18-34) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Sepsis cases | | | Matched controls (no sepsis) | | | Excess cost | | |
| | Mean | 95% CI | | Mean | 95% CI | | Mean | 95% CI | |
| | | LL | UL | | LL | UL | | LL | UL |
| 1 | 26,543 | 26,038 | 27,047 | 7,331 | 7,139 | 7,523 | 19,212 | 18,681 | 19,742 |
| 3 | 46,633 | 46,047 | 47,219 | 13,633 | 13,413 | 13,853 | 33,000 | 32,392 | 33,609 |
| 6 | 71,611 | 70,892 | 72,330 | 23,201 | 22,912 | 23,490 | 48,410 | 47,643 | 49,177 |
| 12 | 100,093 | 99,281 | 100,905 | 31,899 | 31,559 | 32,238 | 68,194 | 67,321 | 69,068 |
| 24 | 122,815 | 121,894 | 123,735 | 37,218 | 36,855 | 37,582 | 85,596 | 84,614 | 86,579 |
| 60 | 146,932 | 145,816 | 148,047 | 43,974 | 43,596 | 44,351 | 102,958 | 101,781 | 104,134 |
| | Haematology (Age 35-44) | | | | | | | | |
| 1 | 27,644 | 27,109 | 28,178 | 5,721 | 5,560 | 5,883 | 21,922 | 21,359 | 22,486 |
| 3 | 46,253 | 45,669 | 46,837 | 12,598 | 12,386 | 12,810 | 33,655 | 33,025 | 34,286 |
| 6 | 70,313 | 69,614 | 71,012 | 21,150 | 20,895 | 21,406 | 49,163 | 48,412 | 49,914 |
| 12 | 99,545 | 98,707 | 100,383 | 28,936 | 28,624 | 29,249 | 70,609 | 69,709 | 71,509 |
| 24 | 123,203 | 22,254 | 124,152 | 34,915 | 34,581 | 35,250 | 88,287 | 87,280 | 89,294 |
| 60 | 150,125 | 149,082 | 151,169 | 44,165 | 43,797 | 44,534 | 105,960 | 104,851 | 107,069 |
| | Haematology (Age 45-54) | | | | | | | | |
| 1 | 24,943 | 24,448 | 25,438 | 5,474 | 5,324 | 5,625 | 19,469 | 18,947 | 19,990 |
| 3 | 43,392 | 42,818 | 43,966 | 12,373 | 12,180 | 12,567 | 31,019 | 30,407 | 31,630 |
| 6 | 68,321 | 67,585 | 69,058 | 21,204 | 20,962 | 21,447 | 47,117 | 46,343 | 47,891 |
| 12 | 97,304 | 96,394 | 98,213 | 29,578 | 29,275 | 29,881 | 67,726 | 66,765 | 68,686 |
| 24 | 123,026 | 122,013 | 124,039 | 36,665 | 36,338 | 36,992 | 86,361 | 85,295 | 87,426 |
| 60 | 156,246 | 155,112 | 157,380 | 52,025 | 51,626 | 52,424 | 104,221 | 103,010 | 105,431 |
| | Haematology (Age 55-64) | | | | | | | | |
| 1 | 21,522 | 21,120 | 21,923 | 5,913 | 5,732 | 6,094 | 15,608 | 15,167 | 16,049 |
| 3 | 40,664 | 40,145 | 41,183 | 12,830 | 12,623 | 13,036 | 27,834 | 27,279 | 28,389 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| 6 | 64,255 | 63,640 | 64,870 | 22,101 | 21,856 | 22,346 | 42,154 | 41,494 | 42,815 |
| 12 | 93,558 | 92,798 | 94,319 | 31,427 | 31,127 | 31,727 | 62,132 | 61,317 | 62,946 |
| 24 | 121,625 | 120,727 | 122,523 | 41,986 | 41,627 | 42,346 | 79,639 | 78,662 | 80,615 |
| 60 | 166,346 | 165,334 | 167,359 | 65,631 | 65,159 | 66,102 | 100,715 | 99,577 | 101,854 |
| | **Haematology (Age 65-74)** | | | | | | | | |
| 1 | 18,387 | 18,058 | 18,716 | 6,200 | 6,044 | 6,357 | 12,187 | 11,828 | 12,546 |
| 3 | 35,181 | 34,762 | 35,600 | 13,996 | 13,796 | 14,196 | 21,185 | 20,713 | 21,657 |
| 6 | 54,685 | 54,198 | 55,173 | 24,562 | 24,309 | 24,814 | 30,124 | 29,559 | 30,688 |
| 12 | 81,656 | 81,058 | 82,253 | 37,067 | 36,759 | 37,375 | 44,589 | 43,895 | 45,283 |
| 24 | 14,394 | 113,702 | 115,086 | 53,933 | 53,568 | 54,298 | 60,461 | 59,661 | 61,262 |
| 60 | 172,429 | 171,562 | 173,296 | 97,012 | 96,435 | 97,589 | 75,417 | 74,361 | 76,474 |
| | **Haematology (Age 75-84)** | | | | | | | | |
| 1 | 16,153 | 15,879 | 16,428 | 7,369 | 7,218 | 7,520 | 8,785 | 8,468 | 9,101 |
| 3 | 29,494 | 29,172 | 29,816 | 14,885 | 14,684 | 15,086 | 14,609 | 14,232 | 14,986 |
| 6 | 45,127 | 44,754 | 45,499 | 24,245 | 24,007 | 24,482 | 20,882 | 20,443 | 21,322 |
| 12 | 67,166 | 66,712 | 67,620 | 37,073 | 36,792 | 37,353 | 30,093 | 29,559 | 30,628 |
| 24 | 95,795 | 95,253 | 96,337 | 56,118 | 55,741 | 56,494 | 39,678 | 39,008 | 40,348 |
| 60 | 159,212 | 158,354 | 160,070 | 106,427 | 105,746 | 107,108 | 52,785 | 51,691 | 53,879 |
| | **Haematology (Age 85+)** | | | | | | | | |
| 1 | 15,516 | 15,322 | 15,709 | 10,686 | 10,525 | 10,847 | 4,830 | 4,582 | 5,077 |
| 3 | 25,162 | 24,924 | 25,399 | 17,609 | 17,412 | 17,807 | 7,552 | 7,243 | 7,862 |
| 6 | 37,738 | 37,437 | 38,039 | 27,731 | 27,469 | 27,994 | 10,007 | 9,605 | 10,408 |
| 12 | 57,390 | 56,963 | 57,816 | 43,365 | 43,014 | 43,716 | 11,782 | 10,084 | 13,479 |
| 24 | 90,308 | 89,751 | 90,865 | 71,445 | 70,953 | 71,937 | 14,024 | 13,475 | 14,574 |
| 60 | 160,594 | 159,410 | 161,779 | 148,812 | 147,618 | 150,006 | 18,863 | 18,121 | 19,606 |

Table S7.13: Cumulative cost of care ($CAD 2018) between solid tumour sepsis cases and matched controls by age categories

| Time since cancer diagnosis (months) | Solid tumour (Age 18-34) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Sepsis cases | | | Matched controls (no sepsis) | | | Excess cost | | |
| | Mean | 95% CI | | Mean | 95% CI | | Mean | 95% CI | |
| | | LL | UL | | LL | UL | | LL | UL |
| 1 | 20,342 | 19,636 | 21,049 | 7,540 | 7,382 | 7,698 | 12,803 | 12,069 | 13,536 |
| 3 | 39,657 | 38,844 | 40,470 | 17,266 | 17,034 | 17,499 | 22,391 | 21,539 | 23,242 |
| 6 | 58,618 | 57,663 | 59,573 | 26,554 | 26,236 | 26,871 | 32,064 | 31,068 | 33,061 |
| 12 | 81,086 | 80,094 | 82,079 | 37,268 | 36,887 | 37,648 | 43,819 | 42,757 | 44,880 |
| 24 | 100,188 | 99,141 | 101,234 | 43,622 | 43,219 | 44,025 | 56,566 | 55,441 | 57,691 |
| 60 | 126,715 | 125,552 | 127,878 | 54,177 | 53,719 | 54,634 | 72,539 | 71,293 | 73,785 |
| | Solid tumour (Age 35-44) | | | | | | | | |
| 1 | 16,672 | 16,360 | 16,985 | 7,999 | 7,845 | 8,153 | 8,673 | 8,324 | 9,023 |
| 3 | 35,677 | 35,243 | 36,111 | 19,591 | 19,338 | 19,843 | 16,086 | 15,596 | 16,577 |
| 6 | 53,634 | 53,126 | 54,142 | 30,911 | 30,606 | 31,216 | 22,723 | 22,143 | 23,302 |
| 12 | 81,789 | 81,181 | 82,396 | 45,132 | 44,754 | 45,509 | 36,657 | 35,972 | 37,342 |
| 24 | 102,269 | 101,606 | 102,931 | 52,682 | 52,277 | 53,087 | 49,587 | 48,834 | 50,339 |
| 60 | 132,553 | 131,787 | 133,319 | 62,949 | 62,514 | 63,384 | 69,604 | 68,745 | 70,464 |
| | Solid tumour (Age 45-54) | | | | | | | | |
| 1 | 16,761 | 16,439 | 17,083 | 9,113 | 8,917 | 9,310 | 7,647 | 7,274 | 8,020 |
| 3 | 36,964 | 36,526 | 37,403 | 22,674 | 22,382 | 22,967 | 14,290 | 13,761 | 14,819 |
| 6 | 55,091 | 54,588 | 55,593 | 34,073 | 33,739 | 34,408 | 21,017 | 20,396 | 21,638 |
| 12 | 79,098 | 78,526 | 79,669 | 46,224 | 45,846 | 46,602 | 32,874 | 32,171 | 33,577 |
| 24 | 99,798 | 99,166 | 100,429 | 53,772 | 53,365 | 54,180 | 46,025 | 45,264 | 6,786 |
| 60 | 131,390 | 130,643 | 132,138 | 64,980 | 64,519 | 65,441 | 66,410 | 65,511 | 67,309 |
| | Solid tumour (Age 55-64) | | | | | | | | |
| 1 | 17,140 | 16,818 | 17,462 | 9,429 | 9,257 | 9,602 | 7,711 | 7,348 | 8,073 |
| 3 | 36,982 | 36,551 | 37,413 | 22,797 | 22,539 | 23,055 | 14,185 | 13,681 | 14,689 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| 6 | 55,963 | 55,433 | 56,492 | 34,147 | 33,834 | 34,459 | 21,816 | 21,196 | 22,436 |
| 12 | 77,051 | 76,444 | 77,658 | 44,896 | 44,539 | 45,253 | 32,155 | 31,442 | 32,868 |
| 24 | 98,557 | 97,876 | 99,238 | 53,899 | 53,516 | 54,283 | 44,657 | 43,857 | 45,457 |
| 60 | 133,984 | 133,159 | 134,809 | 68,481 | 68,035 | 68,927 | 65,503 | 64,554 | 66,451 |
| | **Solid tumour (Age 65-74)** | | | | | | | | |
| 1 | 17,675 | 17,330 | 18,020 | 9,690 | 9,520 | 9,860 | 7,985 | 7,597 | 8,372 |
| 3 | 36,550 | 36,113 | 36,988 | 22,581 | 22,321 | 22,840 | 13,970 | 13,451 | 14,488 |
| 6 | 54,886 | 54,362 | 55,409 | 34,473 | 34,158 | 34,788 | 20,413 | 19,795 | 21,031 |
| 12 | 74,595 | 73,979 | 75,211 | 44,569 | 44,214 | 44,925 | 30,026 | 29,310 | 30,742 |
| 24 | 95,856 | 95,161 | 96,550 | 54,596 | 54,199 | 54,992 | 41,260 | 40,452 | 42,069 |
| 60 | 135,891 | 135,026 | 136,755 | 72,383 | 71,923 | 72,843 | 63,507 | 62,531 | 64,484 |
| | **Solid tumour (Age 75-84)** | | | | | | | | |
| 1 | 17,897 | 17,568 | 18,226 | 10,369 | 10,179 | 10,559 | 7,528 | 7,139 | 7,918 |
| 3 | 34,847 | 34,375 | 35,318 | 21,635 | 21,384 | 21,886 | 13,212 | 12,679 | 13,745 |
| 6 | 50,144 | 49,628 | 50,660 | 31,796 | 31,506 | 32,086 | 18,348 | 17,752 | 18,944 |
| 12 | 66,996 | 66,416 | 67,577 | 41,436 | 41,106 | 41,765 | 25,561 | 24,885 | 26,237 |
| 24 | 88,887 | 88,236 | 89,537 | 52,768 | 52,391 | 53,146 | 36,118 | 35,354 | 36,882 |
| 60 | 134,325 | 133,440 | 135,210 | 77,195 | 76,690 | 77,700 | 57,130 | 56,112 | 58,148 |
| | **Solid tumour (Age 85+)** | | | | | | | | |
| 1 | 18,136 | 17,832 | 18,440 | 11,373 | 11,232 | 11,514 | 6,763 | 6,428 | 7,099 |
| 3 | 30,487 | 30,102 | 30,873 | 20,360 | 20,161 | 20,558 | 10,127 | 9,689 | 10,565 |
| 6 | 42,248 | 41,805 | 42,691 | 29,075 | 28,824 | 29,326 | 13,173 | 12,665 | 13,680 |
| 12 | 57,902 | 57,407 | 58,397 | 40,844 | 40,522 | 41,166 | 27,781 | 26,655 | 28,906 |
| 24 | 81,831 | 81,237 | 82,424 | 59,043 | 58,609 | 59,476 | 17,058 | 16,471 | 17,646 |
| 60 | 133,159 | 132,322 | 133,996 | 105,378 | 104,616 | 106,140 | 22,788 | 22,051 | 23,526 |

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# Chapter 8: Discussion & Conclusion

## 8.1. Chapter summary

This thesis includes six individual health economics studies. They collectively contribute towards advancing economic evaluation methodologies and applications to support better decision making. In addition to these contributions, the work presented in this thesis also demonstrates the value of using longitudinal administrative data to supplement and test current evaluation limitations and assumptions, and to help bridge the translation gap between research and clinical practice with real-world evidence.

Across this body of work, a diverse range of data sources (Table 8.1), locally and internationally, were used to answer specific research questions in two unique treatment populations of prevalent chronic diseases – medical (cancer) and surgical (severe osteoarthritis). As each data source was distinct and captured different types of data, a variety of data manipulation techniques, health economics and longitudinal modelling methods were employed to complete each of the six studies presented in this thesis.

Table 8.1: Real-world data sources used in this thesis

| **Chapter(s)** | **2** | **3** | **4 – 6** | **7** |
|---|---|---|---|---|
| **Data source** | Published resources by Blakely et al. | Independent Hospital Pricing Authority | SMART Registry | ICES Data Repository |
| **Coverage** | National (New Zealand) | National (Australia) | Single institution (Australia) | Provincial (Ontario, Canada) |
| *Patient demographics* | | | X | X |
| *Clinical characteristics* | | | X | X |
| *Patient-reported outcomes* | | | X | |
| *Health care cost estimates* | X | X | | X |
| *Health service utilisation* | | X | | X |

The first two chapters were focused on the extrapolation of costs. In Chapter 2, I investigated the implications of incorporating future medical costs in economic

evaluations through an applied example – evaluating the cost-effectiveness of a sepsis clinical pathway in cancer patients. To examine this, I made use of published regression equations to generate future costs inputs for cancer patients and structured the economic model to reflect changes in costs over time. I found that the inclusion of lifetime health care costs can result in markedly different cost-effectiveness results, leading to higher ICERs (up to a 290% increase). I concluded that there was potential for bias in cost-effectiveness results if future medical costs of surviving patients are not included in the evaluation and this can potentially result in different policy decisions depending on willingness-to-pay thresholds. Through this study, I provided a methodological contribution by demonstrating the practicability and value of appropriately including future medical costs in economic evaluations to support decision-makers' considerations relating to future healthcare budgets. I also show the feasibility of maximising the opportunity to incorporate methodological research alongside an economic evaluation.

In Chapter 3, I used nationally reported hospital data to extrapolate the cost benefits of an ambulatory program for low-risk febrile neutropenia patients to show the economic impact of introducing the program as standard of care across Australia. Beyond establishing cost-effectiveness of the program, I provided evidence of benefits of changing practice by demonstrating the significant return-on-investment to the healthcare system by eliminating avoidable costs and freeing up hospital beds to meet other medical demands. This can be important and necessary to help facilitate efficient uptake of interventions that are clinically effective. This presented a strong case for institutions and decision makers to consider allocating resources for implementation and to support the continuity of the program. This study highlighted the need to also consider providing additional supportive evidence to help translate research findings into real-world implementation.

In Chapters 4, 5 and 6, I turned my focus to the modelling and translation of long-term health outcomes, where I used patient-reported outcomes collected from total knee replacement patients over a 10-year period from the SMART registry. In Chapter 4, applying latent class growth analysis, I identified 6 distinct quality-of-life trajectories suggesting the presence of significant heterogeneity in longer term outcomes among total knee replacement patients. The results showed variable gains in quality-of-life and QALYs across different trajectory groups. Up to 55% of the cohort exhibited poor long-

term quality-of-life outcomes with small gains in health benefit. These findings have two important implications – firstly, although total knee replacement is widely regarded as a cost-effective procedure in general, this raised the question as to whether the procedure is necessarily good value for all. Secondly, it highlighted the need to re-evaluate current approaches when extrapolating utilities in economic models as utilities are unlikely to be homogenous with respect to patient characteristics and time.

The presence of heterogeneity in quality-of-life outcomes among total knee replacement patients was further explored in Chapter 5. Here, I employed multi-level modelling to investigate the differences in long-term quality-of-life patterns between patients with and without diabetes. I found that even after controlling for confounders such as age, sex, existing co-morbidities and socioeconomic status, patients with diabetes exhibit poorer outcomes following surgery compared to those without diabetes and these differences were sustained over time. This led me to conclude that cost-effectiveness results based on population averages may not adequately reflect the true value of the intervention and more needs to be done to identify vulnerable populations to improve the value of care provided.

In Chapter 6, I provided another methodological contribution by examining the relationship between quality-of-life and mortality and its influence on survival estimates. This study demonstrated that the inclusion of quality-of-life measures (at baseline and change from baseline) when extrapolating survival does matter. It can influence health outcomes such as life expectancy and QALYs, which are relevant in cost-effectiveness analysis. Current approaches of extrapolating survival based on patient risk factors alone may not completely capture true effects on survival. This is important because neglecting the correlation between QoL and mortality can lead to imprecise extrapolations and thus risk misleading results affecting subsequent decisions made by policy makers.

In Chapter 7, I conducted a matched case-control study to estimate the short- and long-term health care costs of sepsis in cancer patients using large population-linked administrative health datasets. Unsurprisingly, sepsis was found to be a high cost, high mortality condition. However, excess cost of care associated with sepsis was observed to be highest in the first month of cancer diagnosis and remained high throughout the first year. This indicated the urgent need for increased attention and strengthening of initiatives for prompt sepsis identification and treatment at this critical stage on the cancer pathway.

The cost of care of cancer patients with sepsis was at least double in patients with haematological malignancies, emphasising the substantial economic burden sepsis imposes on top of cancer care. There is real power in population-linked administrative datasets as it provides a whole of system view of the impact of sepsis. It also provides important real-world evidence that will be helpful in improving our understanding of the burden of sepsis along the cancer pathway and to guide targeted strategies to alleviate this burden. Importantly, this study contributes to current gap in literature by generating reliable cost estimates that can inform economic models for infection control or treatment strategies targeting sepsis in cancer patients.

A summary of the body of research covered in this thesis is presented in Table 8.2 which documents the health economics applications, methods employed, key contributions and suggestions for future directions from each of the six studies which will be discussed in the following sections.

Table 8.2: Overall summary

| | Chapter / Study | | Application | Methods of analysis | Key contributions | | Suggestions for future directions |
|---|---|---|---|---|---|---|---|
| | | | | | Methodology | Clinical and policy | |
| **I : EXTRAPOLATION OF COSTS** | | | | | | | |
| **Aggregate** | 2 | Incorporating future medical costs: Impact on CEA | Assess implications of incorporating future medical costs<br><br>Synthesise future cost inputs for economic model | + Cost-utility analysis<br>+ Decision tree analysis<br>+ Markov model | Demonstrate feasibility of appropriately including future medical costs | Provide evidence of cost-effectiveness of sepsis protocol and highlight potential differences in cost-effectiveness results | Promote greater awareness and implications of variation in types and sources of costs<br><br>Standardisation of cost inputs to improve quality and comparability |
| | 3 | National cost savings from an ambulatory program for LR FN patients | Leverage historical data for future trends | + Cost-effectiveness analysis<br>+ GLM regression<br>+ Cost projections | Undertake evaluation beyond cost-effectiveness analysis | Offer strong evidence for national implementation of a cost-effective program | Examine the value of including implementation considerations and costs of programs at scale |
| **II : MODELLING & TRANSLATING OUTCOMES** | | | | | | | |
| **Individual-level** | 4 | Using PROMs to guide patient-centred care and optimise outcomes | Uncover heterogeneity of QoL outcomes<br><br>Demonstrate value of care | + Latent class growth analysis<br>+ Multinomial logistic regression | Employ novel application of technique to uncover heterogeneity | Show important heterogeneity in longer-term outcomes and variations in the value of surgery for different patient groups | Thoroughly understand the real-world impact (value and equity) of heterogeneity in care delivery<br><br>Assess benefits of including patient perspectives in value assessments |
| | 5 | Co-morbidities and sex differences in long-term QoL | Modelling QoL outcomes by patient subgroups | + Multi-level modelling | Demonstrate method to assess patterns of change of repeated | Highlight notable differences in long-term QoL patterns | |

| | | | | | | |
|---|---|---|---|---|---|---|
| | outcomes among patients with and without diabetes | | | QoL measures over time and generate utility values for cost-effectiveness analyses | among specific patient subgroups (diabetes, females) and need for tailored post-surgery management | Incorporate patient-reported outcomes in decision making tools |
| 6 | Exploring the impact of QoL on survival | Examine correlation between QoL and survival<br><br>Assess implications on survival extrapolation | +Survival analysis<br>+Life table methods for life expectancy | Advance understanding of influence and consequence of correlations between QoL and mortality when extrapolating survival outcomes | Quantify impact of unaccounted correlation and heterogeneity on cost-effectiveness results | Examine the effect and implications of changes in QoL in other health economics disease progression models<br><br>Assess impact of QoL changes due to acute events or temporary health states on lifetime modelling |
| **Individual-level + Population-linked** | **III : GENERATING REAL-WORLD EVIDENCE** | | | | | |
| 7 | Economic burden of sepsis in cancer: Health care cost estimates from a population-based study | Quantify cost of cancer care and excess (net) cost of sepsis | +Matching (case-control)<br>+Panel data manipulation<br>+Survival-adjusted estimation of costs | Generate short- and long-term cost estimates | Provide key insights on burden of sepsis and useful inputs for future economic evaluations and resource allocation decisions | Maximise secondary use of administrative data to aid decision making; e.g. understand resource burden across health system, build and automate updating of repositories of inputs for economic and epidemiology modelling |

## 8.2. Implications and translational value of findings

Extending beyond contributions to health economics methodologies and research, the findings of this thesis also have important implications for policy and clinical practice. This thesis focused on two unique treatment populations – cancer patients with infections requiring medical management and patients with severe osteoarthritis requiring surgical intervention (total knee replacement). Both are high burden and high cost conditions necessitating expensive interventions. In view of burgeoning health care expenditure, the need to slow this growth without adversely affecting health outcomes is critical to ensuring sustainability of the health system. It is therefore prudent that health care dollars spent represent good value for money and that care provided delivers the best patient outcomes.

The decisions health care practitioners make will have important implications for patient outcomes. For both these conditions and many others, treatment decisions are often made based on available evidence guiding best practices (e.g. clinical guidelines, protocols) and clinical expertise incorporating patient's clinical characteristics. While clinical guidelines ought to be followed and can improve the consistency and quality of care [1, 2], evidence used to inform these guidelines are often not fully representative of real-world practices [3, 4]. The findings presented in this thesis highlighted the presence of important heterogeneity in the cost of care and outcomes across different patient populations (e.g. patients with different cancer types) and within the same treatment group (total knee replacement patients). This inevitably results in variations in the value of care provided and could mean sub-optimal care (i.e. low-value care) and inefficient use of limited resources for subpopulations of patients.

This thesis has shown the benefits of using real-world data to obtain insights not readily available from conventional clinical trials; for example, to monitor longer term consequences of treatment and uncover heterogeneity in treatment outcomes in routine clinical practice. Heterogeneity in treatment effects may be masked as a consequence of the strict inclusion and exclusion criteria to safeguard the rigour of clinical studies [5]. This was evident in the large variations in longer term quality-of-life outcomes of patients following total knee replacement (Chapters 4 and 5). The findings clearly demonstrated that not all patients benefit from the surgical intervention the same way, and

understanding this variability and identifying patient subgroups that are associated with poorer outcomes is an important step towards improving patient outcomes and optimising care provided. It also indicates that the prescribed standard surgical treatment and follow-up plans are unlikely to be adequate. The evidence generated from this research can be used to supplement clinical decision making in guiding management strategies based on patients' complex care needs and preferences. It can help facilitate delivery of individualised care through greater patient engagement and shared decision making to optimise outcomes for all patients.

Increasingly, health care providers internationally and across Australia are shifting towards a value-based healthcare system. In Australia, initiatives such as the New South Wales' Commissioning for Better Value and Leading Better Value Care programs [6] have been implemented to accelerate the move towards such models of care and other states such as Victoria [7] are following suit. As such, it is important to understand what value-based care delivery means. Whilst improving the health outcomes of patients remains paramount, ultimately health care resources are finite and devoting more resources to one may mean displacement or less for another. It is important for clinicians to recognise that treatment decisions will have considerable cost implications – to patients and the health system. A better understanding of cost-effective care (Chapter 2) and an appreciation of the true costs and consequences (Chapters 3 and 7) can help prepare clinicians make informed decisions to support better value in care delivery and rational allocation of resources.

Measuring and tracking outcomes and costs from real-world clinical practices are valuable in providing insights in patient preferences, practice variation and potential waste. However, it is also important that evidence generated has translational value to the healthcare community. This thesis presented six practical examples that show the utility and contribution of health economics research in supporting medical decision making and health policy design. Each study was built on ongoing research led by exemplary clinical research teams and was supported with input from physicians, surgeons, health economists and health services researchers. These studies are examples of translational research seeking to close the gap and improve patient outcomes in real-world practice. For instance, contributing towards informing a national grant application to initiate the roll-out of the life-saving and cost-effective sepsis protocol state-wide (Chapter 2) and

helping strengthen patient-clinician relationship by exploring the use of patient-reported outcome measures through shared decision making (Chapters 4 and 5). This was achieved through high levels of engagement and collaborative work between clinicians and health economists to generate ideas for improvements in patient outcomes and service delivery. Health and policy decision makers should encourage and initiate more engagements with health economists to develop and demonstrate high value health programs and services and should aim to embed health economists in research and implementation projects.

With the tremendous advances in information technology, rise in implementation of electronic health records and growing repositories of secondary data, the interest in using administrative health data to support health research and health care decision making is evident [8-12]. Globally, HTA agencies across Europe and North America are also incorporating the use of real-world data to provide evidence for relative effective assessment of medications and cost-effectiveness assessments for reimbursement decisions and timely access to new technologies [13-15]. The push towards using real-world evidence to inform decision making processes has been most evident in regulatory processes and HTA activities. This thesis has demonstrated a number of potential applications to support decision making across all levels of the health care system. Academic researchers and government bodies should be encouraged to harness the potential of such data for health economics research, methodological improvements and to evaluate real-world clinical and policy practices.

In Australia, infrastructure to facilitate health record linkage exists [16-18], but access to data continues to be a challenging and time consuming endeavour for many researchers [19-22]. This PhD research involved the use of individual-level population-linked administrative data sourced from Canada (Chapter 7) to estimate for the first time whole of system healthcare cost of cancer patients with and without sepsis. Access to an equivalent dataset in Australia would have been too costly and unfeasible within the timeframe of the PhD candidature. This represented just one of many research projects that signify the lost opportunity to maximise the potential of readily available data to effectively translate data into information for policy action, ultimately impacting patient outcomes of the Australian population. In tandem with lowering the barrier to safe and efficient access to health data, there also needs to be capacity development to maximise the use of the growing availability of large data in producing and conducting high-quality

and policy-relevant health economic analysis. This will need to be prioritised as we move towards a value-based healthcare model and/or incorporating real-world evidence in technology assessments for reimbursement decisions by the Medical Services Advisory Committee (MSAC) and PBAC.

## 8.3. Strengths, limitations and future research directions

One of the major strengths of this thesis was the ability to leverage existing health data from diverse sources to conduct numerous studies to answer specific research questions relevant to real-world settings. The wide population coverage allowed the access to information on patient groups who are often excluded or may be unlikely to participate in research, thereby increasing its relevance in informing policy decisions. By capitalising on these data sources, each of the studies made small but important contributions towards supporting improved medical decision making and better health policy design. Advancements in research literature included methodological research to improve consistency in extrapolating costs, utility inputs and modelling long-term outcomes, generating robust evidence for resource allocation decisions, promoting better understanding of real-world heterogeneity and approaches to optimise patient outcomes. It also aptly demonstrated the feasibility and opportunities to maximise the use of different data types (aggregate, individual-level, population-linked) to supplement health economics research by applying appropriate analytical methods.

There are also some limitations to this thesis that need to be considered. This thesis succumbed to many of the same limitations real-world and longitudinal data are prone to. This included irregularities in data quality, limited transparency in data collection, incomplete patient information and potential sources of error such as measurement and non-response errors [11, 23, 24]. Although steps were taken understand the data generation process and to resolve issues around confounding and missing data, clear answers were at times difficult to obtain and little can be done to instigate further clarification. This may have restricted the interpretability of the results. Furthermore, administrative data are not usually collected for the purposes of research thus does not capture all information relevant to the population or disease studied. Therefore, confounding due to unmeasured variables remains. Additionally, there can also be issues with the reliability of collected data for research purposes. For example, the sensitivity of

using International Classification of Disease codes for sepsis case-ascertainment can vary from 52% to 74% and often underestimates the rate of sepsis [25]. This was apparent in the estimation of health care cost of sepsis in cancer patients (Chapter 7). Therefore, to mitigate such limitations, robustness checks were necessary which included testing the implications of different combinations of diagnosis codes.

Incorporating heterogeneity in economic evaluations remains controversial due to ethical considerations. Subgrouping may lead to equity constrains in the provision of healthcare to certain populations and many may be uncomfortable with such approaches [26]. In recent years, cost-effectiveness analysis methods that incorporate health equity implications have been developed and used to help weigh up policy options and quantify equity impacts and trade-offs [27-30]. These analyses, however, do require data on demographics, health care utilisation and outcomes to understand underlying social distributions. As such, opportunities to employ real-world longitudinal data to equity-informative cost-effectiveness analysis should explored and can be a way forward in generating useful evidence for policy makers in making decisions that improve total health in an equitable manner.

While efforts have been made to highlight the consequences of inconsistent methodologies (e.g. impact of incorporating future medical costs or not fully capturing effects of quality-of-life on survival), this was illustrated for two selected diseases with specific interventions. The implications for different conditions and interventions may vary which warrants further investigation. For example, there is a need to test the correlation between quality-of-life and survival in working economic models in different disease areas given that evidence suggests important predictive value for survival over clinical and demographic baseline characteristics in other chronic diseases such as diabetes [31, 32] and end-stage renal disease [33]. With the increasing popularity and collection of patient-reported outcomes, there may be further opportunities to test this and it may impact the estimation of new risk equations that inform future health economics and risk prediction models.

The studies (Chapters 4-6) presented in this thesis used utility values derived from a single instrument, SF-12. Other generic preference-based measures such as EQ-5D (3- and 5-level), Health Utilities Index version 3 (HUI3) and Short Form 6 dimension (SF-6D) are more commonly used to derived utility values for economic evaluations [34]. Although

these measures all aim to capture health state utilities and are anchored at 1 for full health and 0 for 'dead', utility values derived from different measures can vary for the same patient [35-37], likely due to the constructs of these measures. This includes differences in dimensions of health covered, the number of levels and severity reflected for each dimension and in valuation sample and methods (population surveyed, theoretical and modelling approaches) [34, 38]. Another limitation of Chapters 4, 5 and 6 was that UK preference weights derived from the UK population were applied to the Australian generated SF-12 responses. Preference weights are known to vary across country populations, and this may have limited the interpretation of the results of the studies presented in this thesis. It is unclear if utility values from different instruments would provide the same level of distinction across different quality-of-life trajectories as shown in Chapter 4 and magnitude of impact on survival estimates in Chapter 6. Although utility values derived from instruments such as EQ-5D and HUI3 have similarly been shown to be strong predictors of mortality [31, 39], further research is required to examine if survival extrapolations using other instruments would give different results that could influence decision-making and compromise the comparability of cost-effectiveness analyses.

It remains challenging to enforce standardised approaches. Perhaps a more important question surrounds the case for further standardising of economic evaluation methodology. Standardisation can improve methodological quality of evaluations and facilitate fair comparisons and interpretations of results for different health care interventions and across different settings [40]. It can also lessen the focus on methodology and quality, allowing decision makers to concentrate on the policy implications instead [41]. However, the relevance of the context and perspective from which decisions are made differs from institution to institution and varies across countries and this invariably affects the inputs informing the economic model and approach of the evaluation. Furthermore, standardisation of practice may in turn lead to less generalisable results if clinical practice varies considerably [42]. As such, support of consistency in evaluation methods needs to be weighed against enforcing prescriptive methodological rules that might not be best suited to the decision problem at hand or existing constrains.

Standardisation is evident in most national HTA guidelines and through the use of a reference case [43-45] in ensuring a minimal standard of methodological quality and

transparency of approach. One component of economic evaluation that can benefit from standardising is cost, particularly when current guidelines regarding the types of costs to include are inconsistent and its impact can be substantial. Furthermore, the lack of reliable cost estimates is often cited as a limitation [46, 47]. In countries like the Netherlands, where guidelines on incorporation of costs are explicitly clear, resources to facilitate the inclusion of costs have been developed and made publicly available in an effort to preserve the quality and comparability of studies. Similarly, in Australia, a manual describing the recommended costing practices with published unit costs has been developed to ensure consistency and comparability of submissions to the PBAC [48]. These are positive steps towards standardisation; however, it remains challenging enforcing such standards on economic evaluations conducted for purposes beyond those required for formal assessments informing reimbursement decisions. For instance, economic evaluations are increasingly used to support decision making in policy development and health services planning at the state, hospital and clinical levels, whose setting and analytical viewpoints may differ. A possible approach to mitigate this would be to encourage the transparent reporting of the cost-effectiveness results for various cost scenarios as demonstrated in Chapter 2.

The increasing availability of access to individual-level population-linked data from routinely collected health data have opened up opportunities to capture healthcare resource use and generate health system cost estimates. This is evidenced by the numerous costing studies that have been published for different diseases and by socio-demographic characteristics and risk factors [49-55]. Moving forwards, HTA agencies should consider pooling these evidences together and developing repositories of cost estimates much like the Dutch costing manual which can be a cost-beneficial approach. In addition to alleviating the burden of scouring for reliable inputs, it can also help minimise uncertainties and avoid adopting potentially biased positions to elicit favourable results. Additionally, with the availability of a standardised cost resource, past cost-effectiveness analyses on similar interventions could be updated using a standardised procedure that includes homogenising costs to increase the value of existing evaluations and help inform current decision making [56]. As future costs will change depending on future technologies and innovations in care delivery, the building of cost repositories should also integrate mechanisms for periodic (and automated) updating.

While re-purposing administrative data to generate evidence to support medical and policy decision making can be a cost-effective approach leading to potential health outcome benefits and cost savings, this can only be achieved through thoughtful use of the data and application of appropriate analytic methods. This can be achieved through high levels of engagement and collaborative work between clinicians, health services researchers and health economists to identify and translate ideas for improvements in patient outcomes and service delivery. Transforming and analysis of administrative data for research purposes requires time and learned specialised techniques. This reiterates the need to develop capacity in this area to fully maximise the potential of using real-world data to generate credible and robust evidence. Growth in this area can be motivated by greater use to improve the rigor of methodology being applied to real-world studies, along with the increasing availability of higher-quality datasets. Additionally, conducting research to answer deep, insightful questions and increasing research outputs to demonstrate the enormous potential and impact of real-world data in supporting better decision making across at all levels of care may motivate funders and government bodies to fund more research using such data sources.

As the relevance and importance of health economics contributions towards better health policy and medical care continues to grow, so should the significance of conducting and producing high-quality research and evaluations. There should be greater promotion of awareness on the implications of variations in the conduct (methodology and types/sources of data inputs) of economic evaluations and its impact on cost-effectiveness results. Such efforts should be directed not only to emerging health economists, but clinicians as well as decision makers to increase confidence and credibility in the methods of cost-effectiveness analyses and their use in evidence-based decision making. Patient characteristics, access to care and health outcomes will invariably differ across populations, therefore distributive and equity questions are also important to address to improve total health in an equitable manner. More needs to be done to thoroughly understand the real-world impact (value and equity) of heterogeneity in care delivery as well as greater patient engagement and shared decision making to optimise outcomes for all patients.

## 8.4. Conclusions

This thesis includes six studies which demonstrated the usefulness and value of real-world longitudinal data in health economics research as a means to advance economic evaluation methodologies and directly contribute to the evidence base for better medical decision making. Collectively, these studies highlighted important variations in the cost and outcomes of health care delivery in real-world settings, provided useful insights into the implications of such variations and demonstration of translating research findings to implementation. They contributed to the research literature through methodological research to improve consistency in extrapolating costs, utility inputs and modelling long-term outcomes, generating robust evidence for resource allocation decisions, promoting better understanding of real-world heterogeneity and approaches to optimise patient outcomes. It is hoped that findings from this thesis will prompt greater considerations towards using real-world data to shape and support evidence in health policy and medical decision making.

## 8.5. References


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