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COST-EFFECTIVENESS OF GLUCOSAMINE, CHONDROITIN SULFATE, THEIR COMBINATION, CELECOXIB, NON-SELECTIVE NON- STEROIDAL ANTI-INFLAMMATORY DRUGS, AND PLACEBO IN TREATING KNEE OSTEOARTHRITIS

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by

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DISSERTATION

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DEDICATION

This dissertation is wholeheartedly dedicated to my parents whose life-long indefatigable efforts have helped me in achieving this success. I am proud and glad to be born as their child. They are my role models and source of inspiration in life.

I only vaguely remember how my mother has worked for 14 to 16 hours every day during my childhood, one year after another. Despite, I know exactly how much altruistic love and dedication she has put in behind my parenting. I love you, Mummy!

Papa, you are the best father in this world. You are my sole inspiration for pursuing a career in health care. I have seen you waking at 3:00 AM from your sleep to help patients in need, without any intention of making a profit out of their misery. I know precisely how many efforts you have put in to make sure I would receive the best possible education and have a prosperous life. I love you as well!

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COST-EFFECTIVENESS OF GLUCOSAMINE, CHONDROITIN SULFATE, THEIR COMBINATION, CELECOXIB, NON-SELECTIVE NON-STEROIDAL ANTI-INFLAMMATORY DRUGS, AND PLACEBO IN TREATING KNEE OSTEOARTHRITIS

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ABSTRACT

Background/Purpose: Knee osteoarthritis (KOA) affects 13.8% of the US population aged ≥26, causing significant burden-of-illness. We examined the cost-effectiveness of conventional medicines such as non-steroidal anti-inflammatory drugs (NSAIDs) and celecoxib and complementary and alternative medicines (CAM) therapies to treat KOA from the US health care payers' and patients' perspectives and from 24-week, 2-year, and 10-year time-horizons.

Methodology: We constructed a Markov cohort model (10-year analysis) and a decision-tree model (24-week and 2-year analyses). All costs were obtained from the published literature (converted to 2012 USD) and included both direct and indirect health care costs of medications, drugs associated adverse events, and total knee replacement surgery. Effectiveness was measured in Quality-adjusted life-years (QALYs) gained. Clinical efficacies for treatment strategies under study were obtained from the Glucosamine/CS Arthritis Intervention Trial (GAIT). Cost-effectiveness were estimated

by severity of baseline knee pain, categorized based on the data from GAIT into overall, mild pain only, and moderate-to-severe pain groups. Multiple published sources were used to obtain rest of the modeling parameters. Base-case results were varied in both one-way and probabilistic sensitivity analysis.

Results: We found that, in general, CAM therapies are cost-effective than conventional medicines to treat KOA in the US, with CS being the most cost-effective treatment. With CS as the reference, glucosamine was the most cost-effective, except for in mild pain only KOA patients group from 24-week time-horizon where celecoxib was the most cost-effective. Among the moderate-to-severe pain group, combination therapy of glucosamine and CS was the most cost-effective. A major driver of cost-effectiveness of CAM therapies over conventional medicines was the exclusion of the risk of adverse events associated with the former because of the lack of evidence.

Conclusion: CAM therapies are cost-effective than conventional medicines in treating KOA, both because of adverse events associated with latter and their higher drug utilization costs. Decision-makers could inform their treatment selection decisions from the findings of our study; however, future research is required to examine the long-term effectiveness and safety of CAM therapies in treating KOA.

TABLE OF CONTENTS

LIST OF FIGURES ..... **xv**

LIST OF TABLES ..... **xxii**

CHAPTER 1: INTRODUCTION **1**

Background 1

Specific Aims and Objectives 6

Theoretical Framework 9

Study Significance 12

Significant of Cost-Effectiveness Analysis for Healthcare Decision-Makers 12

Significance of Current Study for Health Care Policy and Decision-Makers 12

Significance of Current Study to the Literature 14

CHAPTER 2: LITERATURE REVIEW **16**

Overview of Knee Osteoarthritis 17

Epidemiology 17

Pathophysiology 17

Classification and Etiology 17

Diagnostic Evaluation 18

Treatment of Knee Osteoarthritis 19

Glucosamine as a Treatment Option for Knee Osteoarthritis 21

Approved Indications and Usage 21

Dosage and Administration of Glucosamine in Knee Osteoarthritis 21

Available Dosage Forms and Strengths 21

Contraindications 21

Serious Warnings and Precautions 22

Clinical Efficacy of Glucosamine in Knee Osteoarthritis 22

Chondroitin Sulfate as a Treatment Option for Knee Osteoarthritis 26

Approved Indications and Usage 26

Dosage and Administration of Chondroitin Sulfate in Knee Osteoarthritis.....26
Available Dosage Forms and Strengths 26
Contraindications.....26
Serious Warnings and Precautions 26
Clinical Efficacy of Chondroitin Sulfate in Knee Osteoarthritis.....27
Celecoxib as a Treatment Option for Knee Osteoarthritis 30
Approved Indications and Usage.....30
Dosage and Administration of Celecoxib in Knee Osteoarthritis 30
Available Dosage Forms and Strengths 30
Contraindications.....30
Serious Warnings and Precautions 31
Clinical Efficacy of Celecoxib in Knee Osteoarthritis 31
Non-Selective Non-Steroidal Anti-Inflammatory Drugs as a Treatment Option for Knee Osteoarthritis.....36
Approved Indications and Usage.....36
Dosage and Administration of Celecoxib in Knee Osteoarthritis 36
Available Dosage Forms and Strengths 37
Contraindications.....37
Serious Warnings and Precautions 38
Cost-Effectiveness of Glucosamine, Chondroitin Sulfate, Combination of Glucosamine and Chondroitin Sulfate, and Celecoxib in Knee 39
Celecoxib as the Primary Study Comparator 39
Glucosamine as the Primary Study Comparator 44
Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC).....45
Structure 45
Scoring.....45
Psychometric Properties 46
Reliability, test-retest 46
Reliability, internal consistency.....46
Reliability, rater 47
Validity, face.....47

Validity, criterion 47
Validity, construct 47
Validity, known-group 47
Responsiveness 48
Medical Outcomes Study (MOS) 36-item Short Form Health Survey (SF-36) 49
Structure 49
Scoring 50
Psychometric Properties 51
Reliability, test-retest 51
Reliability, internal consistency 51
Reliability, rater 51
Validity, face 51
Validity, criterion 52
Validity, construct 52
Validity, known-group 52
Responsiveness 52
Estimation of Quality-Adjusted Life-Years (QALYs) from SF-36 53
Utilization of SF-36 in GAIT 54
Glucosamine/chondroitin sulfate Arthritis Intervention Trial (GAIT) 54
Summary of Literature Review 56

CHAPTER 3: METHODS AND MATERIALS 57
Human Subjects Approval 57
Research Design and Data Sources 58
Study Population, Inclusion and Exclusion Criteria 59
For Objective 1 59
For Objectives 2 to 5 59
Sample Size Estimation 61
Sample Size Estimation in GAIT Study 62

Sample Size and Power Calculations Based on QALYs....63
Knee Osteoarthritis Treatment Strategies/Study Comparators....64
For Objective 1....64
For Objectives 2 to 5....65
Model Structure, Description, and Validation....67
Markov Cohort Model for Objective 1....67
Decision-Tree Model for Objectives 2 to 5....74
Model Validation....76
Time-Horizon, Study Perspective, and Discount Rates....77
Cost Measures....78
Drug Costs....78
Adverse Events Costs....79
Heart Failure....79
Stroke....79
Myocardial Infarction....79
GI Bleeding....80
Dyspepsia....80
Peptic Ulcer....80
Edema....81
Hypertension....81
TKR Surgery Costs....83
Indirect Health Care Costs....83
Effectiveness Measures....85
Health Utilities....86
Treatment Success, Respondents, Non-Respondents, Baseline, and No Treatment....86
Adverse Events....90
TKR Surgery....91
Transition Probabilities and Event Rates....92
Treatment Success, Response, and No Response....92
Adverse Events....96
TKR Surgery....101

Death Rates....102
Sensitivity Analysis....103
Parameter Sensitivity Analysis....103
Structural Sensitivity Analysis....104

CHAPTER 4: RESULTS....106
Section 1: Findings for Study Objective 1....106
Cost-Effectiveness of CAM Therapies vs. Conventional Medicines among Overall KOA Patients Group....106
Sensitivity Analysis....108
Cost-Effectiveness of CAM Therapies vs. Conventional Medicines among KOA Patients with Mild Pain....111
Sensitivity Analysis....113
Cost-Effectiveness of CAM Therapies vs. Conventional Medicines among KOA Patients with Moderate to Severe Pain....116
Sensitivity Analysis....118
Section 2: Findings for Study Objective 2....121
Cost-Effectiveness of CAM Therapies vs. Conventional Medicines among Overall KOA Patients Group....121
Sensitivity Analysis....123
Cost-Effectiveness of CAM Therapies vs. Conventional Medicines among KOA Patients with Mild Pain....126
Sensitivity Analysis....128
Cost-Effectiveness of CAM Therapies vs. Conventional Medicines among KOA Patients with Moderate to Severe Pain....131
Sensitivity Analysis....133
Section 3: Findings for Study Objective 3....136
Cost-Effectiveness of CAM Therapies vs. Conventional Medicines among Overall KOA Patients Group....136
Sensitivity Analysis....138
Cost-Effectiveness of CAM Therapies vs. Conventional Medicines among KOA Patients with Mild Pain....141

Sensitivity Analysis 143
Cost-Effectiveness of CAM Therapies vs. Conventional Medicines among KOA Patients with Moderate to Severe Pain 147
Sensitivity Analysis 149
Section 4: Findings for Study Objective 4 152
Cost-Effectiveness of CAM Therapies vs. Conventional Medicines among Overall KOA Patients Group 152
Sensitivity Analysis 154
Cost-Effectiveness of CAM Therapies vs. Conventional Medicines among KOA Patients with Mild Pain 157
Sensitivity Analysis 159
Cost-Effectiveness of CAM Therapies vs. Conventional Medicines among KOA Patients with Moderate to Severe Pain 162
Sensitivity Analysis 164
Section 5: Findings for Study Objective 5 167
Cost-Effectiveness of CAM Therapies vs. Conventional Medicines among Overall KOA Patients Group 167
Sensitivity Analysis 169
Cost-Effectiveness of CAM Therapies vs. Conventional Medicines among KOA Patients with Mild Pain 172
Sensitivity Analysis 174
Cost-Effectiveness of CAM Therapies vs. Conventional Medicines among KOA Patients with Moderate to Severe Pain 177
Sensitivity Analysis 179
Structural Sensitivity Analysis 182
Structural Sensitivity Analysis of Cost-Effectiveness of CAM Therapies vs. Conventional Medicines among Overall KOA Patients Group 182
Structural Sensitivity Analysis of Cost-Effectiveness of CAM Therapies vs. Conventional Medicines among Moderate to Severe KOA Patients Group 185
Structural Sensitivity Analysis of Cost-Effectiveness of CAM Therapies vs. Conventional Medicines among Mild Pain Only KOA Patients Group 188
Summary of Findings 191

CHAPTER 5: DISCUSSION 192
Interpretation of Study Findings 192
For Objective 1 195
Overall Knee Osteoarthritis Group 195
Knee Osteoarthritis Patients with Mild Knee Pain 195
Knee Osteoarthritis Patients with Moderate to Severe Pain 195
For Objective 2 196
Overall Knee Osteoarthritis Group 196
Knee Osteoarthritis Patients with Mild Knee Pain 196
Knee Osteoarthritis Patients with Moderate to Severe Pain 196
For Objective 3 197
Overall Knee Osteoarthritis Group 197
Knee Osteoarthritis Patients with Mild Knee Pain 197
Knee Osteoarthritis Patients with Moderate to Severe Pain 198
For Objective 4 198
Overall Knee Osteoarthritis Group 198
Knee Osteoarthritis Patients with Mild Knee Pain 199
Knee Osteoarthritis Patients with Moderate to Severe Pain 199
For Objective 5 199
Overall Knee Osteoarthritis Group 200
Knee Osteoarthritis Patients with Mild Knee Pain 200
Knee Osteoarthritis Patients with Moderate to Severe Pain 200
Adverse Events as a Driver of Cost-Effectiveness Ratios 201
Comparison with Previous Literature 203
Study Implications 205
Comparison with GAIT Findings 205
QALY as an Outcome Measure 207
Areas of Future Research 211
Societal Perspective 211
Analysis in Other Countries 212
Inclusion of Other Study Comparators 212

Different Therapeutic Doses of Glucosamine and/or Chondroitin Sulfate 213
Long-Term Clinical Data on Glucosamine and/or Chondroitin Sulfate 213
Study Limitations 214
Conclusion.....218

APPENDICES 219

APPENDIX1: INCLUSION AND EXCLUSION CRITERIA USED IN THE GAIT STUDY 219

APPENDIX 2: HUMAN RESEARCH AND REVIEW COMMITTEE STUDY APPROVAL LETTER 223

APPENDIX 3: MAIN EFFECTS MODEL 224

APPENDIX 4: MODELS WITH INTERACTION EFFECTS 225

REFERENCES.....227

LIST OF FIGURES

Figure 1: Schematic Diagram of the Markov Cohort Model 69

Figure 2: Markov Process for Conventional Medicines 71

Figure 3: GI Bleeding Management Pathway 72

Figure 4: Markov Process for Complementary and Alternative Medicines 73

Figure 5: Schematic Diagram of the Decision-Tree Model 75

Figure 6: Scatter Plot for Probabilistic Sensitivity Analysis Based on 10000 Simulations, in Overall Knee Osteoarthritis Patients Group from US Health care Payers' Perspective and 10-year Time-Horizon 109

Figure 7: Cost-Effectiveness Acceptability Curve, in Overall Knee Osteoarthritis Patients Group from US Health care Payers' Perspective and 10-year Time-Horizon 110

Figure 8: Scatter Plot for Probabilistic Sensitivity Analysis Based on 10000 Simulations, in Mild Pain Only Knee Osteoarthritis Patients Group from US Health care Payers' Perspective and 10-year Time-Horizon 114

Figure 8: Cost-Effectiveness Acceptability Curve, in Mild Pain Only Knee Osteoarthritis Patients Group from US Health care Payers' Perspective and 10-year Time-Horizon ... 115

Figure 10: Scatter Plot for Probabilistic Sensitivity Analysis Based on 10000 Simulations, in Moderate to Severe Pain Knee Osteoarthritis Patients Group from US Health care Payers' Perspective and 10-year Time-Horizon 119

Figure 11: Cost-Effectiveness Acceptability Curve, in Moderate to Severe Pain Knee Osteoarthritis Patients Group from US Health care Payers' Perspective and 10-year Time-Horizon 120

Figure 12: Scatter Plot for Probabilistic Sensitivity Analysis Based on 10000 Simulations, in Overall Knee Osteoarthritis Patients Group from US Health care Payers' Perspective and 24-Week Time-Horizon 124

Figure 13: Cost-Effectiveness Acceptability Curve, in Overall Knee Osteoarthritis Patients Group from US Health care Payers' Perspective and 24-Week Time-Horizon.125

Figure 14: Scatter Plot for Probabilistic Sensitivity Analysis Based on 10000 Simulations, in Mild Pain Only Knee Osteoarthritis Patients Group from US Health care Payers' Perspective and 24-Week Time-Horizon.....129

Figure 15: Cost-Effectiveness Acceptability Curve, in Mild Pain Only Knee Osteoarthritis Patients Group from US Health care Payers' Perspective and 24-Week Time-Horizon.....130

Figure 16: Scatter Plot for Probabilistic Sensitivity Analysis Based on 10000 Simulations, in Moderate to Severe Pain Knee Osteoarthritis Patients Group from US Health care Payers' Perspective and 24-Week Time-Horizon.....134

Figure 17: Cost-Effectiveness Acceptability Curve, in Moderate to Severe Pain Knee Osteoarthritis Patients Group from US Health care Payers' Perspective and 24-Week Time-Horizon.....135

Figure 18: Scatter Plot for Probabilistic Sensitivity Analysis Based on 10000 Simulations, in Overall Knee Osteoarthritis Patients Group from Patients' Perspective and 24-Week Time-Horizon.....139

Figure 19: Cost-Effectiveness Acceptability Curve, in Overall Knee Osteoarthritis Patients Group from Patients' Perspective and 24-Week Time-Horizon 140

Figure 20: Scatter Plot for Probabilistic Sensitivity Analysis Based on 10000 Simulations, in Mild Pain Only Knee Osteoarthritis Patients Group from Patients' Perspective and 24-Week Time-Horizon 145

Figure 21: Cost-Effectiveness Acceptability Curve, in Mild Pain Only Knee Osteoarthritis Patients Group from Patients' Perspective and 24-Week Time-Horizon .146

Figure 22: Scatter Plot for Probabilistic Sensitivity Analysis Based on 10000 Simulations, in Moderate to Severe Pain Knee Osteoarthritis Patients Group from Patients' Perspective and 24-Week Time-Horizon 150

Figure 23: Cost-Effectiveness Acceptability Curve, in Moderate to Severe Pain Knee Osteoarthritis Patients Group from Patients' Perspective and 24-Week Time-Horizon .151

Figure 24: Scatter Plot for Probabilistic Sensitivity Analysis Based on 10000 Simulations, in Overall Knee Osteoarthritis Patients Group from US Health care Payers' Perspective and 2-year Time-Horizon.....155

Figure 25: Cost-Effectiveness Acceptability Curve, in Overall Knee Osteoarthritis Patients Group from US Health care Payers' Perspective and 2-year Time-Horizon 156

Figure 26: Scatter Plot for Probabilistic Sensitivity Analysis Based on 10000 Simulations, in Mild Pain Only Knee Osteoarthritis Patients Group from US Health care Payers' Perspective and 2-year Time-Horizon 160

Figure 27: Cost-Effectiveness Acceptability Curve, in Mild Pain Only Knee Osteoarthritis Patients Group from US Health care Payers' Perspective and 2-year Time-Horizon 161

Figure 28: Scatter Plot for Probabilistic Sensitivity Analysis Based on 10000 Simulations, in Moderate to Severe Pain Knee Osteoarthritis Patients Group from US Health care Payers' Perspective and 2-year Time-Horizon 165

Figure 29: Cost-Effectiveness Acceptability Curve, in Moderate to Severe Pain Knee Osteoarthritis Patients Group from US Health care Payers' Perspective and 2-year Time-Horizon 166

Figure 30: Scatter Plot for Probabilistic Sensitivity Analysis Based on 10000 Simulations, in Overall Knee Osteoarthritis Patients Group from Patients' Perspective and 2-year Time-Horizon.....170

Figure 31: Cost-Effectiveness Acceptability Curve, in Overall Knee Osteoarthritis Patients Group from Patients' Perspective and 2-year Time-Horizon.....171

Figure 32: Scatter Plot for Probabilistic Sensitivity Analysis Based on 10000 Simulations, in Mild Pain Only Knee Osteoarthritis Patients Group from Patients' Perspective and 2-year Time-Horizon.....175

Figure 33: Cost-Effectiveness Acceptability Curve, in Mild Pain Only Knee Osteoarthritis Patients Group from Patients' Perspective and 2-year Time-Horizon.....176

Figure 34: Scatter Plot for Probabilistic Sensitivity Analysis Based on 10000 Simulations, in Moderate to Severe Pain Knee Osteoarthritis Patients Group from Patients' Perspective and 2-year Time-Horizon.....180

Figure 35: Cost-Effectiveness Acceptability Curve, in Moderate to Severe Pain Knee Osteoarthritis Patients Group from Patients' Perspective and 2-year Time-Horizon.....181

Figure 36: Scatter Plot for Probabilistic Sensitivity Analysis, in Overall KOA Patients Group from Healthcare Payers Perspective and 10-Year Time-Horizon 183

Figure 37: Cost-Effectiveness Acceptability Curve for Cost-Effectiveness Analysis, in Overall KOA Patients Group from Healthcare Payer's Perspective and 10-Year Time-Horizon 184

Figure 38: Scatter Plot for Probabilistic Sensitivity Analysis, in Moderate to Severe Pain KOA Patients Group from Healthcare Payers Perspective and 10-Year Time-Horizon.186

Figure 39: Cost-Effectiveness Acceptability Curve for Cost-Effectiveness Analysis, in Moderate to Severe Pain KOA Patients Group from Healthcare Payer's Perspective and 10-Year Time-Horizon.....187

Figure 40: Scatter Plot for Probabilistic Sensitivity Analysis, in Mild Pain Only KOA Patients Group from Healthcare Payers Perspective and 10-Year Time-Horizon.....189

Figure 41: Cost-Effectiveness Acceptability Curve for Cost-Effectiveness Analysis, in Mild Pain Only KOA Patients Group from Healthcare Payer's Perspective and 10-Year Time-Horizon.....190

LIST OF TABLES

Table 1: Treatment Modalities for Knee Osteoarthritis. 20

Table 2: Comparison of Efficacy of Glucosamine with Placebo. 23

Table 3: Comparison of Clinical Efficacy of Chondroitin Sulfate with Placebo. 28

Table 4: Comparison of Efficacy of Oral Celecoxib with Placebo 32

Table 5: List of FDA Approved Non-selective Non-Steroidal Anti-inflammatory Drugs for Prescription 36

Table 6: FDA Approved Dosages of NSAIDs in Treatment of Knee Osteoarthritis.....37

Table 7: Summary of Published Literature on Cost-Effectiveness of Celecoxib and Glucosamine. 39

Table 8: Structure of SF-36 Instrument 49

Table 9: Sample Size Estimation Based on QALYs. 63

Table 10: FDA Approved Dosages of NSAIDs in Treatment of Knee Osteoarthritis.....64

Table 11: Blinded Drugs Dispensed to the GAIT Study Participants 65

Table 12: Treatment Regimens for GAIT Study 66

Table 13: Model Inputs for Costs. 82

Table 14: Health Utility Values For Study Comparators Related Health States 89

Table 15: Model Inputs for Health Utility Values of Adverse Events 90

Table 16: Model Inputs for Health Utility Values. 91

Table 17: Markov Model Transition Probabilities for Treatment Success. 93

Table 18: Decision-Tree Model Rates for Study Comparators from 24-week Time-Horizon 94

Table 19: Decision-Tree Model Rates for Study Comparators from 2-Year Time-Horizon 95

Table 20: Transition Probabilities of Adverse Events. 97

Table 21: Search Terms Used in FAERS 99

Table 22: Total Knee Replacement Surgery Rates in the US 101

Table 23: Model Inputs for Age-Specific Mortality Rates, Based on US Life-tables. 102

Table 24: Parameters Distributions Used in Probabilistic Sensitivity Analysis 103

Table 25: Base Case Results for Cost-Effectiveness Analysis in Overall Knee Osteoarthritis Patients Group from US Health care Payers' Perspective and 10-year Time-Horizon, with Chondroitin Sulfate as the Reference Group. 107

Table 26: Probabilistic Sensitivity Analysis Results, in Overall Knee Osteoarthritis Patients Group from US Health care Payers' Perspective and 10-year Time-Horizon ...108

Table 27: Base Case Results for Cost-Effectiveness Analysis, in Mild Pain Only Knee Osteoarthritis Patients Group from US Health care Payers' Perspective and 10-year Time-Horizon, with Chondroitin Sulfate as the Reference Group. 112

Table 28: Probabilistic Sensitivity Analysis Results, in Mild Pain Only Knee Osteoarthritis Patients Group from US Health care Payers' Perspective and 10-year Time-Horizon.....113

Table 29: Base Case Results for Cost-Effectiveness Analysis, in Moderate to Severe Pain KOA Patients Group from US Health care Payers' Perspective and 10-year Time-Horizon, with Chondroitin Sulfate as the Reference Group. 117

Table 30: Probabilistic Sensitivity Analysis Results, in Moderate to Severe Pain Knee Osteoarthritis Patients Group from US Health care Payers' Perspective and 10-year Time-Horizon.....118

Table 31: Base Case Results for Cost-Effectiveness Analysis, in Overall Knee Osteoarthritis Patients Group from US Health care Payers' Perspective and 24-Week Time-Horizon, with Chondroitin Sulfate as the Reference Group. 122

Table 32: Probabilistic Sensitivity Analysis Results, in Overall Knee Osteoarthritis Patients Group from US Health care Payers' Perspective and 24-Week Time-Horizon.123

Table 33: Base Case Results for Cost-Effectiveness Analysis, in Mild Pain Only Knee Osteoarthritis Patients Group from US Health care Payers' Perspective and 24-Week Time-Horizon, with Chondroitin Sulfate as the Reference Group. 127

Table 34: Probabilistic Sensitivity Analysis Results, in Mild Pain Only Knee Osteoarthritis Patients Group from US Health care Payers' Perspective and 24-Week Time-Horizon.....128

Table 35: Base Case Results for Cost-Effectiveness Analysis, in Moderate to Severe Pain Knee Osteoarthritis Patients Group from US Health care Payers' Perspective and 24-Week Time-Horizon, with Chondroitin Sulfate as the Reference Group. 132

Table 36: Probabilistic Sensitivity Analysis Results, in Moderate to Severe Pain Knee Osteoarthritis Patients Group from US Health care Payers' Perspective and 24-Week Time-Horizon.....133

Table 37: Base Case Results for Cost-Effectiveness Analysis, in Overall Knee Osteoarthritis Patients Group from Patients' Perspective and 24-Week Time-Horizon, with Chondroitin Sulfate as the Reference Group. 137

Table 38: Probabilistic Sensitivity Analysis Results, in Overall Knee Osteoarthritis Patients Group from Patients' Perspective and 24-Week Time-Horizon 138

Table 39: Base Case Results for Cost-Effectiveness Analysis, in Mild Pain Only Knee Osteoarthritis Patients Group from Patients' Perspective and 24-Week Time-Horizon, with Chondroitin Sulfate as the Reference Group. 142

Table 40: Probabilistic Sensitivity Analysis Results, in Mild Pain Only Knee Osteoarthritis Patients Group from Patients' Perspective and 24-Week Time-Horizon .144

Table 41: Base Case Results for Cost-Effectiveness Analysis, in Moderate to Severe Pain Knee Osteoarthritis Patients Group from Patients' Perspective and 24-Week Time-Horizon, with Chondroitin Sulfate as the Reference Group. 148

Table 42: Probabilistic Sensitivity Analysis Results, in Moderate to Severe Pain Knee Osteoarthritis Patients Group from Patients' Perspective and 24-Week Time-Horizon .149

Table 43: Base Case Results for Cost-Effectiveness Analysis, in Overall Knee Osteoarthritis Patients Group from US Health care Payers' Perspective and 2-Year Time-Horizon, with Chondroitin Sulfate as the Reference Group. 153

Table 44: Probabilistic Sensitivity Analysis Results, in Overall Knee Osteoarthritis Patients Group from US Health care Payers' Perspective and 2-Year Time-Horizon 154

Table 45: Base Case Results for Cost-Effectiveness Analysis, in Mild Pain Only Knee Osteoarthritis Patients Group from US Health care Payers' Perspective and 2-Year Time-Horizon, with Chondroitin Sulfate as the Reference Group. 158

Table 46: Probabilistic Sensitivity Analysis Results, in Mild Pain Only Knee Osteoarthritis Patients Group from US Health care Payers' Perspective and 2-Year Time-Horizon 159

Table 47: Base Case Results for Cost-Effectiveness Analysis, in Moderate to Severe Pain KOA Patients Group from US Health care Payers' Perspective and 2-Year Time-Horizon, with Chondroitin Sulfate as the Reference Group.. 163

Table 48: Probabilistic Sensitivity Analysis Results, in Moderate to Severe Pain Knee Osteoarthritis Patients Group from US Health care Payers' Perspective and 2-Year Time-Horizon 164

Table 49: Base Case Results for Cost-Effectiveness Analysis, in Overall Knee Osteoarthritis Patients Group from Patients' Perspective and 2-Year Time-Horizon, with Chondroitin Sulfate as the Reference Group. 168

Table 50: Probabilistic Sensitivity Analysis Results, in Overall Knee Osteoarthritis Patients Group from Patients' Perspective and 2-Year Time-Horizon.....169

Table 51: Base Case Results for Cost-Effectiveness Analysis, in Mild Pain Only Knee Osteoarthritis Patients Group from Patients' Perspective and 2-Year Time-Horizon, with Chondroitin Sulfate as the Reference Group. 173

Table 52: Probabilistic Sensitivity Analysis Results, in Mild Pain Only Knee Osteoarthritis Patients Group from Patients' Perspective and 2-Year Time-Horizon.....174

Table 53: Base Case Results for Cost-Effectiveness Analysis, in Moderate to Severe Pain Knee Osteoarthritis Patients Group from Patients' Perspective and 2-Year Time-Horizon, with Chondroitin Sulfate as the Reference Group. 178

Table 54: Probabilistic Sensitivity Analysis Results, in Moderate to Severe Pain Knee Osteoarthritis Patients Group from Patients' Perspective and 2-Year Time-Horizon.....179

Table 55: Probabilistic Sensitivity Analysis Results, in Overall KOA Patients Group from Healthcare Payers Perspective and 10-Year Time-Horizon 182

Table 56: Probabilistic Sensitivity Analysis Results, in Moderate to Severe Pain KOA Patients Group from Healthcare Payers Perspective and 10-Year Time-Horizon.....185

Table 57: Probabilistic Sensitivity Analysis Results, in Mild Pain Only KOA Patients Group from Healthcare Payers Perspective and 10-Year Time-Horizon 188

Table 58: Summary of Cost-Effectiveness Findings 193

Table 58: QALYs Gained in Different Cost-Effectiveness Models 208

CHAPTER 1: INTRODUCTION

This chapter is divided into four sections. In the first section, we provide background of our study. In the second section, we discuss the specific aims and objectives for this study. These are followed by the theoretical framework for our study in section three. This chapter is concluded by providing significance of this study in section four.

Background

Knee osteoarthritis (KOA) has substantial burden-of-illness in the United States (US). It is the most common form of osteoarthritis, affecting 13.8% of the US population aged 26 or more.[1] Patients with KOA have significantly higher health care resource utilization, in comparison to healthy controls.[2, 3] More than half of KOA patients undergo total knee replacement (TKR) surgery during their life-time.[3] Further, the KOA patients have 6.0 times (95% CI=4.7 to 7.4) higher rates of physicians visits and 28% more hospitalizations.[2] KOA is a debilitating illness that significantly lowers both physical and mental quality-of-life of patients suffering from it.[4]

Although there is no currently known cure for KOA, its treatment options are focused on pain reduction, maintaining or improving joint mobility, and limiting functional impairment.[5] These treatment options include pharmacological modalities and complementary and alternate medicine (CAM) therapies such as glucosamine and chondroitin sulfate (CS). A commonly prescribed class of pharmacological modalities to treat KOA is the non-steroidal anti-inflammatory drugs (NSAIDs). These NSAIDs include both selective (e.g., celecoxib—a cyclooxygenase-2 [COX-2] only inhibitor) and

non-selective NSAIDs (e.g., diclofenac and naproxen—both cyclooxygenase-1 [COX-1] and COX-2 inhibitors).[6-8] The efficacies of these NSAIDs to manage KOA are well-established in several randomized, double-blinded, placebo-controlled, multi-center clinical trials.[9-24]

On the other hand, the effectiveness of commonly used CAM therapies such as glucosamine and CS to treat KOA is currently debated. A recent meta-analysis of ten randomized clinical trials with a total sample size of 3803 patients found no significant differences in joint pain reduction or joint space narrowing benefits between placebo and glucosamine, CS, or combination therapy of glucosamine and CS among the KOA patients.[25] However, this study is criticized for not studying the effect of CAM therapies on joint replacement rates and for using artificially back transformed effect sizes in making pool estimations for meta-analysis calculations.[26, 27] This study also didn't consider the risk reduction in TKR surgery (5-year relative risk=0.43; 95% CI=0.2-0.92) among those in the glucosamine group (who had taken 1500 mg glucosamine sulfate for 12-36 months) compared with placebo.[28] Moreover, another meta-analysis found effect size of 0.35 (95% CI=0.14 to 0.56) in favor of glucosamine.[29]

Despite several controversies surrounding the effectiveness of CAMs therapies (as described above), these are widely used to treat KOA in the US.[30] A recent marketing study reported 2008 sales of glucosamine totaling to $872 million in the US and $4 billion globally.[31] Another study reported 47% of KOA patients using CAM therapies at least once to treat their illness..[32] The National Health Interview Survey of 2007 further found a total of $14.8 billion were spent out-of-pocket on the non-vitamin, non-mineral, natural products that includes glucosamine and CS.[30]

The Glucosamine/CS Arthritis Intervention Trial (GAIT)—largest clinical trial examining efficacy of CAM therapies to treat KOA—compared celecoxib, glucosamine, CS, combination of glucosamine and CS, and placebo in a multi-center double-blind randomized study.[21] A total of 1583 individuals with symptomatic KOA were randomly assigned to receive daily doses of 1500 mg of glucosamine, 1200 mg of CS, both glucosamine and CS, 200 mg of celecoxib, or placebo for 24 weeks. The primary outcome measure was at least 20% reduction in pain from baseline enrollment, measured using the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain sub-scale. KOA patient groups were stratified by severity of knee pain at the baseline into mild and moderate to severe. Overall, glucosamine, CS, or their combination therapies were not significantly different from placebo in pain reduction, $p>0.05$. Among the moderate to severe pain stratum group of patients, however, the combination of glucosamine and CS was significantly better than placebo in treating KOA. On the other hand, celecoxib was better than placebo in both overall analysis and in mild-to-moderate pain stratum groups, but not in moderate-to-severe pain stratum.

A 2-year follow-up study of the GAIT—the ancillary structure modifying study—was also conducted on a sub-group of original participants.[24, 33] For this follow-up study, a total of 662 participants were randomly assigned to glucosamine (n=134), CS (n=126), combination of glucosamine and CS (n=129), celecoxib (n=142), and placebo groups (n=131). The primary outcome measure was the loss of joint space width (JSW) in the medial tibiofemoral joint compartment. The reduction in WOMAC pain sub-scale scores from baseline at 2 years was also recorded as a secondary outcome measure in this follow-up study. No significant differences were found between placebo and celecoxib,

glucosamine, CS, and combination of glucosamine and CS in reducing the loss of JSW or change in WOMAC pain sub-scale scores at 2-year follow-up, $p>0.05$.

Cost-effectiveness analysis is an important tool to compare health technologies based on their effectiveness and costs.[34, 35] An increasing number of both private and public healthcare systems in the US are utilizing the findings of these cost-effectiveness analyses to make their coverage decisions.[36-39] Requirements to examine the cost-effectiveness of CAM therapies in the US have been raised previously.[40] Currently, several US health plans provide coverage for CAM therapies, including herbal supplements.[41-4343,61,62] Physicians practicing in the US also have positive believes regarding benefits of CAM therapies in treating KOA; a recent survey concluded 39% of the rheumatologists in the US believe glucosamine and/or CS to be at least moderately beneficial.[44] A systematic review of PubMed was conducted (1996 to February 2013) to identify cost-effectiveness analyses comparing cost-effectiveness of glucosamine, CS, their combined therapy, celecoxib, NSAIDs, and placebo. From this search, no studies were found that have compared the cost-effectiveness of aforementioned therapies. Our study fills the knowledge gap in cost-effectiveness of CAM therapies and conventional medicines to treat KOA.

Specifically, the purpose of our study was to examine the cost-effectiveness of 1500 mg of glucosamine daily, 1200 mg of CS daily, combination of glucosamine 1500 mg and CS 1200 mg daily, 200 mg of celecoxib daily, US Food and Drug Administration (FDA) approved NSAIDs, and placebo in treating KOA. Separate analyses were conducted from health care payers' and patients perspectives. Time-horizons for our study were 24-weeks, 2 years, and 10 years. The costs measures included costs of

conventional drugs and CAM therapies utilization, drugs associated adverse events treatment, physician's office visits, and TKR surgery among the KOA patients. The effectiveness was measured as quality-adjusted life-years (QALYs) gained, based on its endorsement for the "reference case" cost-effectiveness analysis by the US Panel on Cost-Effectiveness in Health and Medicine (USPCEHM) and the National Institute of Clinical Excellence (NICE) of the United Kingdom (UK).[34, 45] Health utility values to estimate QALYs were obtained by mapping the short form (SF)-36 scores recorded in the GAIT study to SF-6 dimensions (SF-6D) instrument.

Two decision-analytic models—a decision-tree and a Markov cohort model—were constructed for the purpose of our study. While the decision-tree model was used for 24-week and 2-year analyses, Markov cohort model was utilized for 10-year time-horizon. One-way sensitivity analysis was performed on all model parameters. Probabilistic sensitivity analysis (PSA) was also conducted to account for the presence of second-order uncertainty in modeling parameters. The results were reported as incremental cost-effectiveness ratios.

Specific Aim and Objectives

The specific aim of our study was to compare the cost-effectiveness of CAM therapies (i.e., glucosamine, CS, and their combination) with conventional medicines (i.e., celecoxib and NSAIDs) and placebo in treating KOA from the perspectives of US health care payers' and patients' and from time-horizons of 24 weeks, 2 years, and 10 years.

Objective 1: To compare the incremental cost-effectiveness of CAM therapies (i.e., glucosamine, CS, and their combination) with conventional medicines (i.e., celecoxib and NSAIDs) for the treatment of KOA from the US health care payers' perspective and 10-year horizon, through a Markov model based analysis.

H_a=CAM therapies (i.e., glucosamine, CS, and their combination) are cost-effective at an incremental threshold of $50,000/QALY gained compared to conventional medicines (i.e., celecoxib and NSAIDs) for the treatment of KOA from the US health care payers perspective and 10-year horizon

Objective 2: To compare the incremental cost-effectiveness of CAM therapies (i.e., glucosamine, CS, and their combination), celecoxib, and placebo for treatment of KOA from the US health care payers' perspective and 24-week time-horizon, among the GAIT trial participants.

H_a=CAM therapies (i.e., glucosamine, CS, and their combination) were cost-effective among the GAIT trials participants at an incremental threshold of $50,000/QALY gained compared to conventional medicines (i.e., celecoxib and

NSAIDs) for the treatment of KOA from the US health care payers perspective and 24-week horizon

Objective 3: To compare the incremental cost-effectiveness of CAM therapies (i.e., glucosamine, CS, and their combination), celecoxib, and placebo for treatment of KOA from the US patients' perspective and 24-week time-horizon, among the GAIT trial participants.

H_a=CAM therapies (i.e., glucosamine, CS, and their combination) were cost-effective among the GAIT trials participants at an incremental threshold of $50,000/QALY gained compared to conventional medicines (i.e., celecoxib and NSAIDs) for the treatment of KOA from the US patients' perspective and 24-week horizon

Objective 4: To compare the incremental cost-effectiveness of CAM therapies (i.e., glucosamine, CS, and their combination), celecoxib, and placebo for treatment of KOA from the US health care payers' perspective and 2-year time-horizon, among the GAIT trial participants.

H_a=CAM therapies (i.e., glucosamine, CS, and their combination) were cost-effective among the GAIT trials participants at an incremental threshold of $50,000/QALY gained compared to conventional medicines (i.e., celecoxib and NSAIDs) for the treatment of KOA from the US health care payers perspective and 2-year horizon

Objective 5: To compare the incremental cost-effectiveness of CAM therapies (i.e., glucosamine, CS, and their combination), celecoxib, and placebo for treatment of

KOA from the US patients' perspective and 2-year time-horizon, among the GAIT trial participants.

H_a=CAM therapies (i.e., glucosamine, CS, and their combination) were cost-effective among the GAIT trials participants at an incremental threshold of $50,000/QALY gained compared to conventional medicines (i.e., celecoxib and NSAIDs) for the treatment of KOA from the US patients' perspective and 2-year horizon

Theoretical Framework

Cost-effectiveness analysis of health technologies informs resource allocation decisions. The theoretical foundations of cost-effectiveness analysis can be traced to a variety of fields such as decision analysis, operations research, and, most recently, welfare economics. The focus of this section is on welfare economics as the theoretical basis of cost-effectiveness analysis, since the USPCEHM deems welfare economics to provide a comprehensive framework that answers more theoretical questions arising in cost-effectiveness analysis than any other alternatives.[34] For instance, welfare economics provides guidance on several elements of cost-effectiveness analysis including how society should value resource costs and select discount rates for analysis.

Welfare economics is concerned with the means by which we can assess the desirability of alternative resource allocation. Welfare economics is based on two assumptions:

1. Individuals maximize a well-defined preference function. This means that an individual's sense of well-being (health utility function) depends on material consumption, among other things.
2. The overall welfare of the society is a function of these individuals' preferences.

Therefore, in order to measure the societal well-being, it is required to first measure the well-beings of individuals and thereafter aggregate these to the societal level.[34] In welfare economics, the individuals' preferences are represented by *individuals' utility function* that relates their well-being to their levels of consumption of several goods and services.[46]

Although several economics methods could be used to model individuals' preferences for the purpose of cost-effectiveness analysis, *expected utility theory* (EUT) is the principal approach as both health status and the effects of health care interventions involve substantial uncertainty.[47] According to the expected utility theory, alternative actions are characterized by a set of possible outcomes and a set of probabilities associated with each outcome. Each outcome can be assigned a quantitative representation of individuals' preferences, i.e. health utilities. The probability of an outcome when multiplied by its health utility, i.e. individuals' preference, provides the respective expected utility of that outcome. These numerical utility values, in theory, represent both ordinal rankings of outcomes and strength of individuals' preference for these outcomes under uncertainty.

The ultimate goal of welfare economics is to maximize the *social utility function,* defined as the aggregate of individuals' utility preferences. However, currently there is no consensus on how to combine individuals' preferences to form the social utility function. Nonetheless, the currently used benchmark concept behind determining the social utility function is *Pareto optimality*.[48] According to this concept, a resource is considered to be Pareto-optimal when it is not possible to make anyone better without making at least one other worse off.. On the other hand, if the resource relocation makes at least one person better off without others being worse off, it is said to be *Pareto improvement.* Therefore, in absence of knowledge of the social utility function, but not of the individuals' preferences, the Pareto criterion can be used to determine if social welfare has improved.

In the real-world, however, it is rarely possible to benefit someone without harming others; for example, in order to implement a public health program taxes or

other mechanisms are used that impose costs on some people to benefit others. A less restrictive standard, called *compensation test* (also known as *potential Pareto improvement* or *Kaldor-Hicks criterion*), is used in situations that have both gainers and losers. Under this theory, social welfare can still be improved if the gainers are willing to pay enough to compensate the losers. The welfare economics provides the conditions under which the theoretical bases of cost-effectiveness ratios are in the theory of compensation test. Garber and Phelps work show that individuals optimally set priorities for health care expenditures by selecting those with cost/quality-adjusted life-year (QALY) ratios less than some threshold. For this reason, the USPCEHM and the National Institute of Clinical Excellence of the UK has endorsed QALYs as the effectiveness measure for the "reference case" during the cost-effectiveness analysis. The QALYs gained was also used as the primary outcome measure in this study.

Study Significance

Significant of Cost-Effectiveness Analysis for Healthcare Decision-Makers

CEAs are widely utilized in the US as well as the rest of the world for the purpose of health technology assessments. The 2009 report of the Institute of Medicine justifies use of economic analysis, especially CEA, in comparative effectiveness research stating that the overall value of a strategy can be understood best only by considering costs and benefits together.[49] A real-world example of use of CEA in health technology assessment in the US is its incorporation into the Academy of Managed Care Pharmacy (AMCP) drug dossiers. These drug dossiers are frequently utilized by managed care organizations (87.5%) to inform their formulary decisions.[50] Submitted by pharmaceutical companies, these dossiers commonly contain CEA studies (39.3%) and budget-impact models (53.5%) to describe value of a drug.

In another example, the UK Department of Health has commissioned the National Institute of Clinical Excellence (NICE) to make health technology assessments on the basis of both clinical effectiveness and cost-effectiveness.[51] The NICE believes that on its own the clinical effectiveness is insufficient for maintaining or introducing any health technology and that cost must also be taken into account.[52]

Significance of Current Study for Health Care Policy and Decision-Makers

Comparing glucosamine and CS, alone as well as combination therapies, to conventional medicines, our study is the first to provide evidence on the incremental cost-effectiveness of these agents for health care policy makers as well as for the clinical decision-makers such as the rheumatologists.

Currently billions of dollars are spend on CAM therapies in the US. A total of $33.9 billion were spent out-of-pocket on CAM therapies in 2007, equaling to 11.2% of the total out-of-pocket health care expenditures in the US.[30] Of these out-of-pocket expenditures, 43.7% of the total amount was spent on non-vitamin, non-mineral natural products that include glucosamine and CS. Globally, the glucosamine market was valued at $4 billion in 2008, with the US sales totaling to $872 million.[31]

Several health plans in the US also currently provide coverage for the CAM therapies, including various herbal supplements.[41-43,61,62] For example, the Blue Cross Blue Shield provides discounts on herbal supplements as well as other CAM therapies to its beneficiaries in various states, including Illinois, South Carolina, and Idaho.[43, 53, 54] The Kaiser Permanente of Ohio also provides discounts on various herbal supplements.[41]

The clinical decision-makers in the US are also currently divided on the efficacy of CAM therapies to treat KOA. In a survey of 345 rheumatologists in the US, 39% of the physicians were reported to believe glucosamine and/or CS to be at least moderately beneficial in treating KOA.[44] When asked about recommending glucosamine and/or CS to the patients, 57% of these rheumatologists said that they were likely to recommend these agents to their patients.

There is an unmet and important need to evaluate therapeutic approaches for osteoarthritis in terms of their cost-effectiveness.[55] The evidence from randomized clinical trials is central to efficacy testing. However, failing to translate the endpoints from these trials into measures that are valued by patients, providers, insurers, and the general public could lead to misleading decisions.[56] Since an increasing number of health

care payers are utilizing evidence from cost-effectiveness analyses in their decision-making, the findings from our study could be crucial to such stakeholders.

Significance of Current Study to the Literature

A systematic review of PubMed was conducted to identify studies that have compared the cost-effectiveness of glucosamine, CS, their combination, celecoxib, and NSAIDs from 1966 to February 2013. The MeSH terms "knee osteoarthritis", "cost-benefit analysis", "glucosamine", "chondroitin sulfate", "celecoxib", and "non-steroidal anti-inflammatory agents" were separately combined with the keywords "cost-effectiveness analysis", "cost-utility analysis", and "quality-adjusted life-years." The Boolean operators AND, OR, and NOT were used to combine the above listed MeSH terms and keywords. No other limits were applied to the search strategy.

No studies comparing the cost-effectiveness of glucosamine, CS, their combination, celecoxib, NSAIDs were found. Nonetheless, some cost-effectiveness analysis studies were found that compared the incremental cost-effectiveness of celecoxib with other therapies.[57-67] Further, one study comparing the incremental cost-effectiveness of glucosamine with paracetamol and placebo was also identified.[68, 69] Glucosamine was found to be highly cost-effective in this study, by dominating the paracetamol strategy and with incremental cost-effectiveness of €4,285/quality-adjusted life-year (QALY) gained in comparison to placebo. Further details of these studies are provided in the literature review section, under sub-section "cost-effectiveness of glucosamine, CS, combination of glucosamine and CS, and celecoxib in KOA."

Our study was the first cost-effectiveness analysis to compare cost-effectiveness of glucosamine, CS, their combination therapy, celecoxib, NSAIDs, and placebo. In fact, our study was the first to compare the cost-effectiveness of any selective or NSAIDs with CAM therapies. It was also the first study to compare cost-effectiveness of CS or combination of glucosamine and CS with each other and with other therapy options in the treatment of KOA.

CHAPTER 2: LITERATURE REVIEW

This chapter is divided into ten sections. In the first section, we begin by providing the overview of KOA that constitutes its epidemiology, pathophysiology, classification and etiology, diagnosis and treatment. In sections two to five, we discuss celecoxib, NSAIDs, glucosamine, and CS as treatment options for KOA in terms of their respective approved doses, indications, mode of administration, contraindications, associated serious warnings and precautions, and clinical efficacies. Section six provides review of the cost-effectiveness of celecoxib, NSAIDs, glucosamine, CS, and combination of glucosamine and CS in treating KOA. Sections seven and eight provide review of the structure, scoring, and psychometric properties of the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) and Medical Outcomes Study 36-item Short Form Health Survey (SF-36), respectively. Section nine describes the Glucosamine/chondroitin sulfate Arthritis Intervention Trial (GAIT), which is the source of clinical data in our study. Finally, this chapter is concluded by a summary of the literature review section.

Overview of KOA

Epidemiology

KOA is the most common type of osteoarthritis in the US, affecting 13.8% of the US population aged 26 or more.[1] The incidence and prevalence of KOA (age and sex-standardized) in the US are 240 and 900 cases per 100,000 person years, respectively.[70, 71] This prevalence increases throughout the elderly years, more so in women than in men, reaching to 37.4% among persons aged 60 years or more.[71, 72] Women have significantly more Kellgren-Lawrence Grade 3-4 changes (12.9% vs. 6.5% in men); however, symptomatic KOA do not differ by gender.[71] In recent years, the prevalence of KOA has increased dramatically, doubling among women and tripling among men during the period of the last 20 years.[73]

Pathophysiology

KOA, initially believed to be the result of aging, is now proven to result from complex interactions of multiple physical and biochemical factors.[74, 75] Abnormal or compromised cartilage of knee joint, alone or in combination with abnormal stresses on knee joint, initiate a cascade of proliferative and inflammatory processes that lead to further damage this joint.[76] Proinflammatory mediators fuel changes in the synovial membrane and alter the chondrocyte metabolism, causing progression of KOA.[76, 77]

Classification and Etiology

KOA is most commonly classified by Kellgren-Lawrence scale that divides KOA into five grades (0, normal to 4, severe).[78-80] The World Health Organization (WHO) has

also adopted these classification criteria for the radiological classification of KOA as the standard for epidemiological studies of this pathology.[81]

Based on its etiology, KOA can also be classified into primary (idiopathic) and secondary osteoarthritis.[82] While the etiology of idiopathic KOA is unknown, the common causes of secondary KOA are post-traumatic, congenital, malposition, post-operative, metabolic abnormalities, endocrine disorders, and aseptic osteonecrosis conditions.[82]

Diagnostic Evaluation

The major elements to diagnose KOA are history, physical examination, and imaging studies of the patients.[82] Historical criteria that are specific to KOA are presence of pain (beginning of movement, during movement, permanent/nocturnal, or early morning), loss of function (stiffness, limited range of joint movement, impaired daily activities), and other symptoms, including crepitation, elevated sensitivity to cold and/or damp weather, and stepwise progression of disease. Physical examination includes findings on inspection and palpation, testing of range of movement, and special functional tests (for example, ligament stability, meniscus test, and gait analysis). Imaging studies by X-ray are used for both primary diagnosis and to assess the progression of the disease. Other radiological studies to diagnose KOA include MRI, to demonstrate the hyaline cartilage, ^{99m}Tc bone scanning, to assess metabolic activity in the subchondral bone, and ultrasonography, to demonstrate the soft-tissues and fluid-filled spaces.

Treatment of KOA

KOA is not a curable disease at present; therefore, its treatment is intended to reduce pain, maintain and/or improve joint mobility, and limit functional impairment.[5] The recommended approaches for treating KOA include nonpharmacological modalities, pharmacological modalities, surgical modalities, and CAM therapies (Table 1).[83]

Table 1: Treatment Modalities for KOA.[5, 83, 84]

Non-pharmacological Modalities
Patient education
Self-management programs
Personalized social support through telephone contact
Weight loss
Aerobic exercise programs
Physical therapy range-of-motion exercises
Muscle-strengthening exercises
Assistive devices for ambulation
Patellar taping
Appropriate footwear
Lateral-wedged insoles bracing
Occupational therapy
Joint protection and energy conservation
Assistive devices for activities of daily living
Pharmacological Modalities
Acetaminophen as initial oral analgesic for treatment of mild to moderate pain
NSAIDs at lowest effective dose in symptomatic KOA patients
Topical NSAIDs and capsaicin as adjunctives and alternatives to oral analgesic/anti-inflammatory agents in KOA
IA Corticosteroids injections
IA Hyaluronate injections
Weak opioids and narcotic analgesics
Surgical Modalities
Knee replacement surgery
Complementary and Alternate Medicines Therapies
Acupuncture
Dietary supplements
Glucosamine
CS
Methylsulfonylmethane
Risedronate
Diacerein

CS=Chondroitin Sulfate; KOA=Knee osteoarthritis; IA=Inferior alveolar; NSAIDs= Non-steroidal anti-inflammatory drugs

Glucosamine as a Treatment Option for KOA

Approved Indications and Usage

In the US, glucosamine is considered a dietary supplement and is currently not approved by the FDA for diagnosis, treatment, cure or prevention of any disease. In most of the European Union (EU), however, glucosamine hydrochloride is approved as a medical drug, indicated for the relief of symptoms in mild to moderate KOA.[85]

Dosage and Administration of Glucosamine in KOA

In the EU, the approved dosage of glucosamine is 1250 mg/day, taken orally. No specific dosage of glucosamine is approved or recommended by the US FDA. Previous clinical trial studies of glucosamine have used its daily doses ranging from 1200 mg to 1500 mg.[21, 24, 69, 86-98]

Available Dosage Forms and Strengths

In EU and the US, glucosamine is available as a tablet (400 mg, 625 mg, and 1500 mg) as well as in the power form for oral solution (1178 mg, 1500 mg).[99]

Contraindications

Glucosamine is contraindicated in patients: (1) with known hypersensitivity to glucosamine or any other ingredient of glucosamine; (2) shellfish allergy; (3) who suffer from impaired glucose intolerance; (4) who have known risk factor for cardiovascular disease; and (5) who suffer from asthma.[99]

Serious Warnings and Precautions

Glucosamine may be associated with risk of the following adverse events, however no conclusive evidence currently exists: asthma attack, rise of blood sugar level in people with diabetes, and shellfish allergy.[99]

Clinical efficacy of Glucosamine in KOA

Several randomized, double-blind, placebo-controlled, clinical trials have examined the efficacy of glucosamine in treating KOA.[21, 24, 69, 86-98] Many of these studies found glucosamine to be significantly better than placebo ($p<0.05$) to treat KOA.[69, 87-96] Most widely used primary outcome measures in these clinical trials of glucosamine are the mean loss of joint space width (JSW), change in Lequesne index score, change in WOMAC pain sub-scale score, change in visual analogue scale (VAS) score, and patient's global assessment of response to therapy (PGART). Table 2 displays the summaries of all published randomized clinical trial studies of glucosamine.

Table 2: Comparison of Efficacy of Glucosamine with Placebo.*

Study	Duration (in weeks)	Treatment	Total Sample size	Primary Endpoint(s)	Results
Crolle et al. 1980[87]	3	Glucosamine 1500 mg/d	30	Symptom score reduction	80%
		Placebo			21%
Pujalte et al. 1980[92]	6-8	Glucosamine 1500 mg/d	20	Pain reduction	80%
		Placebo			20%
Drovanti et al. 1980[88]	4	Glucosamine 1500 mg/d	80	Symptom score reduction	71%
		Placebo			-
Vajaradul 1981[96]	9	One intra-articular glucosamine injection/week for 5 weeks	54	Pain reduction	88%
		Placebo			54%
Rovati et al. 1992[95]	4	Glucosamine 1500 mg/d	252	Lequesne index reduction of at least 3	52%
		Placebo			37%
Reichelt et al 1994[94]		Glucosamine intramuscular injection twice a week for 6 weeks	155	Lequesne index reduction of at least 3	55%
	8	Placebo			33%
Noack et al. 1994 [90]		Glucosamine 1500 mg/d	252	Lequesne index reduction of at least 3	52%
	4	Placebo			37%
Rindone et al. 2000+[98]	8	Glucosamine 1500 mg/d	98	Pain score reduction on VAS scale	24%
		Placebo			16%
Reginster et al. 2000[93]	162	Glucosamine 1500 mg/d	212	Loss of mean JSW	-0.06 mm (-0.22 to 0.09)

Study	Duration (in weeks)	Treatment	Total Sample size	Primary Endpoint(s)	Results
		Placebo			-0.31 mm (95% CI=-0.48 to -0.13)
Pavelka et al. 2002[91]	162	Glucosamine 1500 mg/d	202	Loss of mean JSW	0.04 mm (95% CI=-0.06 to 0.14)
		Placebo			-0.19 mm(95% CI=-0.29 to 0.09)
Hughes et al.+ 2002[97]	6 months	Glucosamine 1500 mg/d	80	PGART	Mean difference= 0.15 mm (95% CI=-8.78 to 9.07)
		Placebo			
McAlindon et al.+ 2004[89]	12	Glucosamine 1500 mg/d	205	WOMAC pain score	2.0±3.4
		Placebo			2.5±3.8
Cibere et al.+ 2004[86]	6 months	Glucosamine 1500 mg/d	137	Proportion of patients with disease flare after drug discontinuation	45%
		Placebo			42%
Herrero-Beaumont et al. 2007[69]	6 months	Glucosamine 1500 mg/d	210	Change in Lequesne index	-3.1 (95% CI=-3.8 to -2.3)
		Placebo			-1.9 (95% CI=-2.6 to -1.2)
Clegg et al. 2006+[21]	24	Glucosamine 1500 mg/d	630	Patients with 20% decrease in WOMAC pain score	64.0%
		Placebo			60.1%

Study	Duration (in weeks)	Treatment	Total Sample size	Primary Endpoint(s)	Results
Sawitzke et al. 2008+[24]	108	Glucosamine 1500 mg/d	147	Mean change in JSW	-0.153 (95% CI=-0.379 to 0.074)
		Placebo			-0.055 (95% CI=-0.279 to 0.170)

*=Efficacy results from only glucosamine and placebo arms of the trials are reported.
+=No significant difference between placebo and glucosamine on primary outcome measure at $p<0.05$
JSW=Joint space width; PGART=Patient global assessment of response to therapy; VAS=Visual analogue scale; WOMAC=Western Ontario and McMaster Universities Osteoarthritis Index

In summary, glucosamine is currently not approved by the US FDA and is marketed as a dietary supplement in the US. In EU, however, glucosamine is approved in most of the countries as a medical drug to treat KOA patients with mild to moderate pain. The recommended daily dose of glucosamine in EU to treat KOA is 1500 mg/day, taken orally. Many randomized, double-blinded, placebo-controlled, clinical trials have examined efficacy of glucosamine for relief of symptoms of KOA. Based on these studies, currently, the efficacy of glucosamine to treat KOA is not well-established.

CS as a Treatment Option for KOA

Approved Indications and Usage

CS is currently used as a dietary supplement in both the US and the Europe.[100] However, the European League Against Rheumatism (EULAR) recommends CS as a symptomatic slow acting drug for all forms of osteoarthritis.[101]

Dosage and Administration of CS in KOA

Currently, there is no US FDA or European Medicine Agency (EMA) approved or recommended dose of CS. In clinical trials studies, however, the commonly used doses of CS have ranged from 800 mg to 1200 mg per day, taken orally. [22,25,103-108]

Available Dosage Forms and Strengths

Currently, there is no officially approved dosage form and strength of CS. Nonetheless, CS is commonly available as tablets or capsules in strengths 400 mg, 800 mg, and 1200 mg.[102]

Contraindications

CS is contraindicated in patients: (1) with prostate cancer, or at increased risk of prostate cancer, (2) with hypersensitivity to CS products, (3) who have shellfish allergy, or (4) who suffer from asthma.[103]

Serious Warnings and Precautions

The CS is deemed to be well-tolerated for up to 3 years, as no conclusive evidence currently exist that associates risk of any serious adverse events with it.[103, 104]

Clinical efficacy of CS in KOA

Several randomized, double-blinded, placebo-controlled, clinical trials have examined the clinical efficacy of CS in treating KOA, Table 3.[21, 24, 105-110] Some of these studies found CS to be significantly better than placebo ($p<0.05$) for the treatment of KOA.[105-110] Overall, however, the efficacy of CS to treat KOA is currently not well-established, as reported in an recent meta-analysis.[25] Most commonly used primary outcome measures in clinical trial studies of CS are change in Lequesne index scores, change in VAS pain scores, joint space narrowing, and change in WOMAC pain sub-scale scores.

Table 3: Comparison of Clinical Efficacy of Chondroitin Sulfate with Placebo.

Study	Duration	Treatment	Total N	Primary Endpoint(s)	Results
Uebelhart et al. 1998[105]	12 months	CS 800 mg/d	42	Change in degree of spontaneous joint pain	At 6 months: 57%
		Placebo			At 6 months: 25%
Bourgeois et al. 1998[106]	3 months	CS 1200 mg/d	127	Change in Lequesne index, change in pain score on VAS	45%, 50%
		Placebo			10%, 20%
Bucsi et al. 1998[107]	6 months	CS 800 mg/d	80	Change in Lequesne index	58%
		Placebo			3%
Michel et al. 2005[108]	24 months	CS 800 mg/d	300	Mean change in JSW	0.00±0.53 mm
		Placebo			0.14±0.61 mm
Mazieres et al.+ 2001[109]	6 months	CS 1000 mg/d for 3 months Placebo for 3 months	130	Lequesne Index	CS group had non-significantly better outcomes than placebo group
Conrozier et al. 1998[110]	12 months	CS 800 mg/d	104	Lequesne Index	Functional impairment was reduced by 50%
		Placebo			-
Clegg et al. 2006+[21]	24 weeks	CS 1200 mg/d	621	Patients with 20% decrease in WOMAC pain score	65.4%
		Placebo			60.1%
Sawitzke et al. 2008+[24]	24 months	CS 1200 mg/d	141	Mean change in JSW	Difference from placebo: -0.059 (95% CI=-0.287 to 0.169)
		Placebo			

*=Results from only glucosamine and placebo arms of the trials are reported.
+=No significant difference between placebo and glucosamine on primary outcome measure at $p<0.05$

CS=Chondroitin Sulfate; JSW=Joint Space Narrowing; VAS=Visual Analogue Scale; WOMAC= Western Ontario and McMaster Universities Osteoarthritis Index

In summary, CS is currently used as an oral dietary supplement in both the US and EU. Several randomized clinical trials have examined the efficacy of CS to treat KOA. Based on the findings from these clinical trials, the efficacy of CS to manage symptoms of KOA is currently not well-established.[21, 24, 25, 105-111]

Celecoxib as a Treatment Option for KOA

Approved Indications and Usage

Celecoxib is a selective NSAID (i.e., a COX-2 only inhibitor) approved by the US FDA for relief of signs and symptoms of osteoarthritis, rheumatoid arthritis (including juvenile rheumatoid arthritis), and ankylosing spondylitis.[8] Celecoxib is also approved for the management of acute pain in adults and treatment of primary dysmenorrhea. It was the first selective COX-2 inhibitor to be introduced into the clinical practice.[112]

Dosage and Administration of Celecoxib in KOA

Celecoxib is recommended in oral doses of 200 mg once a day or 100 mg twice a day for relief of signs and symptoms of KOA.[8] These doses can be administered without regards to the timings of meals.

Available Dosage Forms and Strengths

Celecoxib is marketed as capsules of strength 50 mg, 100 mg, 200 mg, and 400 mg.[8]

Contraindications

Celecoxib is contraindicated in patients: (1) with known hypersensitivity to celecoxib, aspirin, or other NSAIDs; (2) who have demonstrated allergic-type reactions to sulfonamides; (3) who have experienced asthma, urticaria, or allergic-type reactions after taking aspirin or other NSAIDs; and (4) for the treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery.[8]

Serious Warnings and Precautions

Celecoxib is associated with risk of serious and fatal cardiovascular thrombotic events, myocardial infarction, and stroke.[8] It is also associated with serious gastrointestinal (GI) adverse events including bleeding, ulceration, and dyspepsia.[8]

Clinical efficacy of Celecoxib in KOA

Several randomized clinical trials have examined the efficacy of celecoxib to treat KOA.[9-11, 13-24, 113] All of these clinical trial studies have found celecoxib to be significantly better than placebo to treat KOA ($p<0.05$). Table 4 summarizes the published studies that have examined the clinical efficacy of oral celecoxib with placebo in randomized, double-blind, placebo-controlled, clinical trials for the treatment of symptomatic KOA.

Table 4: Comparison of Efficacy of Oral Celecoxib with Placebo.*

Study	Duration (in weeks)	Treatment	N	Primary Endpoint(s)	Mean change (improvement) From Baseline
Birbara et al. 2005[9]	6	Cel 200 mg/d	157	PGART	2.29
		Placebo	78		1.61
Birbara et al. 2005[9]	6	Cel 200 mg/d	169	PGART	2.28
		Placebo	85		1.61
Gibofsky et al. 2003[10]	6	Cel 200 mg/d	189	VAS, WOMAC	34 mm, -22.1
		Placebo	96		21.2 mm, -12.6
McKenna et al. 2001[11]	6	Cel 200 mg/d	63	VAS, WOMAC, PGA improvement %	39 mm, -26, 79
		Placebo	60		25 mm, 18, 50
Smugar et al. 2006[113]	6	Cel 200mg/d	456	WOMAC pain score	-37.5
		Placebo	150		-25.0
Smugar et al. 2006[113]	6	Cel 200mg/d	460	WOMAC pain score	-33.0
		Placebo	151		-21.0
Pincus et al. 2004[13]	6	Cel 200 mg/d	370	Patients preferences for treatment	54%
		Placebo	354		24%
Bensen et al. 1999[14]	12	Cel 100 mg/d		PGA,	27, 9.5±1.11
		Cel 200 mg/d		WOMAC total score	35, -13.3±1.17
		Cel 400 mg/d			36, -12.0±1.22
		Placebo			24, -6.1±1.09
McKenna et al. 2001[11]	6	Cel 200 mg/d	201	VAS, WOMAC, PGA improvement %	-34.9±28.1, -18.8±17.5, 50%
		Placebo	200		-23.1±28.0, -11.5±17.8, 34%

Study	Duration (in weeks)	Treatment	N	Primary Endpoint(s)	Mean change (improvement) From Baseline
Rother et al. 2007[15]	6	Cel 200 mg/d	132	WOMAC pain score, WOMAC physical function score, PGA excellent %	-20.7±22.7, -18.1±22.5, 14±10.6
		Placebo	127		-12.4±20.8, -12.3±19.2, 5±3.9
Bingham III et al. 2007[16]	26	Cel 200 mg/d	241	WOMAC pain score, WOMAC physical function score, PGA	-3.12, -1.74, -4.05
		Placebo	127		
Bingham III et al. 2007[16]	26	Cel 200 mg/d	247	WOMAC pain score, WOMAC physical function score, PGA	0.14, -0.08, 0.06
		Placebo	117		
Fleischmann et al. 2006[17]		Cel 200 mg/d	444	VAS, PGA, WOMAC pain score, WOMAC total score	-24.5±27.38, -3.5±4.11, -16.0±18.19
		Placebo	231		-16.1±27.45, -2.3±3.90, -9.3±16.15
Lehmann et al. 2005[18]	13	Cel 200 mg/d		PGA, WOMAC total score	-22.9±24.64, -14.7±15.81
		Placebo			-18.9±24.70, -11.3±18.27
Sheldon et al. 2005[19]	13	Cel 200 mg/d	393	VAS, WOMAC functional score	-24.1±26.40, -10.8±13.07
		Placebo	382		-18.1±25.51, -6.3±11.80

Study	Duration (in weeks)	Treatment	N	Primary Endpoint(s)	Mean change (improvement) From Baseline
Tannenbaum et al. 2004[20]	13	Cel 200 mg/d	481	VAS, PGA, WOMAC pain score, and WOMAC total score	-25.2±24.7, -22.4±25.7, -3.1±3.8, -13.4±15.8
		Placebo	243		-19.8±26.1, -15.7±26.1, -2.4±3.8, -9.4±16.1
Hochberg et al. 2011[23]	12	Cel 200 mg/d	243	WOMAC pain score, WOMAC function score, and PGA	-41.1±26.2, -36.0±26.4, 22.4 ±28.7
		Placebo	124		-34.0± 25.3, -28.9±24.9, 12.4±28.9
Hochberg et al. 2011[23]	12	Cel 200 mg/d	245	WOMAC pain score, WOMAC function score, and PGA	-43.6±25.2, -37.7±27.5, 26.4±30.3
			122		-37.3±26.1, -30.9±28, 22.4±31.3
Sawitzke et al. 2008[24]	108	Cel 200 mg/d	80	Mean change in JSW	-0.055 mm (95% CI=-0.279, 0.170)
		Placebo	70		-
Clegg et al. 2006[21]	24	Cel 200 mg/d	318	Patients with 20% decrease in WOMAC pain score	70.1%
		Placebo	313		60.1%
DeLemos et al. 2011[22]	12	Cel 200 mg/d	202	WOMAC pain score, WOMAC function score, and PGA	130.0±9.0, 429.2±29.3, 28.6±2.0
		Placebo	200		94.9±8.9, 290.1±29.1, 20.2±2.0

*=Results from only celecoxib and placebo arms of the trials are reported.

Cel=Celecoxib; CI=Confidence interval; JSW=Joint space width; PGA=Patient global assessment score; PGART=Patient global assessment of response to therapy; VAS=Visual analogue scale; WOMAC=Western Ontario and McMaster Universities Osteoarthritis Index

In summary, celecoxib is currently approved by the US FDA for symptomatic pain relief in KOA patients. The recommended daily doses of celecoxib to treat KOA are 200 mg, taken orally. Several randomized, double-blind, placebo-controlled, clinical trials have established the efficacy of celecoxib to relief symptoms of KOA.

NSAIDs as Treatment Options for KOA

The discussion in this section is focused on the US FDA approved prescription NSAIDs all of which are listed in Table 5.[114]

Table 5: List of FDA Approved Non-selective Non-Steroidal Anti-inflammatory Drugs for Prescription.

FDA Approved Non-Steroidal Anti-inflammatory Drugs (NSAIDs)		
Diclofenac	Flurbiprofen	Naproxen
Diflunisal	Indomethacin	Oxaprozin
Etodolac	Ketoprofen	Piroxicam
Fenoprofen	Meloxicam	Sulindac

Approved Indications and Usage

The NSAIDs class of drugs are approved by the US FDA to treat pain and redness, swelling, and heat (inflammation) from medical conditions such as arthritis, including KOA, and menstrual cramps.[114]

Dosage and Administration of NSAIDs in KOA

Different NSAIDs have different FDA approved doses for treating KOA, as displayed in Table 6.[115]

Table 6: FDA Approved Dosages of NSAIDs in Treatment of KOA.

Drug	Recommended FDA Dosage to Treat KOA
Diclofenac	100-150 mg/day in divided doses (50 mg BID, TID or 75 mg BID)
Diflunisal	500-1000mg/day in two divided doses
Etodolac	300 mg BID, TID or 400 mg BID or 500 mg BID
Fenoprofen	Up to 3,200 mg/day (3 to 4 times a day)
Flurbiprofen	200-300 mg/day
Ibuprofen	400 to 800 mg orally every 6 to 8 hours
Indomethacin	Up to 150-200 mg/day
Ketoprofen	Up to 200 mg/day (75 mg TID or 50 mg BID)
Ketorolac	10 mg 4 times a day orally as needed
Mefenamic acid	500 mg orally followed by 250 mg every 6 hours as needed
Meloxicam	Up to 15 mg/day
Nabumetone	Up to 2000 mg per day
Naproxen	Up to 500 mg/day in divided doses, BID
Oxaprozin	1200 mg/day in divided doses, BID
Piroxicam	20 mg/day
Sulindac	300 mg/day, BID

BID=Twice a day; FDA=Food and Drug Administration; KOA=Knee osteoarthritis; TID=Thrice a day

Available Dosage Forms and Strengths

The US FDA approved dosage forms and strengths of NSAIDs vary by specific drugs. These agents are available in dosage forms such as tablets, capsules, suspension, and power. Their approved strengths vary from 7.5 mg for meloxicam to 600 mg oxaprozin.[115]

Contraindications

Similar to celecoxib, NSAIDs are contraindicated in patients : (1) with known hypersensitivity to aspirin or any NSAIDs; (2) who have demonstrated allergic-type reactions to sulfonamides; (3) who have experienced asthma, urticaria, or allergic-type reactions after taking aspirin or other NSAIDs; and (4) for the treatment of peri-operative pain in the setting of CABG surgery.[114]

Serious Warnings and Precautions

Similar to celecoxib, NSAIDs are associated with risk of serious cardiovascular events, including heart failure, stroke, and myocardial infarction. These NSAIDs are also associated with risk of serious GI events, including dyspepsia, peptic ulcer, and bleeding and perforation.[114]

Cost-Effectiveness of Glucosamine, CS, Combination of Glucosamine and CS, and Celecoxib in KOA

Based on a systematic review of PubMed, to our knowledge, no previously published study has compared the cost-effectiveness of glucosamine, CS, their combination, celecoxib, and NSAIDs in treating KOA. However, a few published studies have compared the cost-effectiveness of celecoxib with other treatment options (Table 7). One study has also compared the cost-effectiveness of glucosamine with paracetamol (acetaminophen) and placebo.[68] The focus of this section is on describing these published studies.

Celecoxib as the Primary Study Comparator

A total of 11 studies have previously compared the cost-effectiveness of celecoxib with other treatment strategies in osteoarthritis patients (hip and/or knee), Table 7.[57-67] Treatment options compared with celecoxib in these studies included NSAIDs (alone or in combination with Misoprostol [Arthrotec], proton pump inhibitors, histamine-2 receptor antagonists, and prophylaxis), acetaminophen, rofecoxib, and hyalouronan. Countries of focus in these studies were Mexico, Netherlands, United States, Taiwan, Canada, Switzerland, Sweden, and Norway. All except for one study utilized decision-tree models for conducting cost-effectiveness analysis—this one exception used an Markov model.[63] All except two studies were conducted from the 6-months' time-horizon. These rest of the two studies were conducted from the life-time of the patients.[59] Perspectives under evaluation were health care payers' and societal.

Table 7: Summary of Published Literature on Cost-Effectiveness of Celecoxib and Glucosamine.

Author, year	Comparators	Primary outcome measure	Methodology	Base Case Results	Comments
Celecoxib as the Primary Comparator					
Iris et al. 2008[57]	• Celecoxib • NSAIDs • Acetaminophen	Cost per number of patients with pain control	• Time horizon: 6 months • Decision-tree model • Perspective: health care payer • Country: Mexico	Celecoxib dominated the rest of the two comparators	• Patient population: OA of knee or hip • Study funded by pharmaceutical company (Pfizer)
Al et al. 2008[58]	• Celecoxib • NSAIDs • NSAIDs + Misoprostol • NSAIDs + H_2RA • NSAIDs + PPI • Arthrotec	• Cost/number of averted GI events • Cost/life-years saved	• Time horizon: 6 months • Decision-tree model • Perspective: societal • Country: Netherlands	Celecoxib ICER was €56,667/life-year saved	• Patient population: OA or RA • Study funded by pharmaceutical company (Pfizer)
Loyd et al. 2007[59]	• Celecoxib • NSAIDs	• Cost/QALY gained	• Time horizon: life-time • Decision-tree model • Perspective: societal • Country: United States	Celecoxib ICER was $31,097/QALY gained in comparison to NSAIDs	• Patient population: OA patients aged 60 years or more • Study funded by pharmaceutical company (Pfizer)

Author, year	Comparators	Primary outcome measure	Methodology	Base Case Results	Comments
Schaefer et al. 2004[60]	• Celecoxib • Rofecoxib • NSAIDs	• Cost per clinically significant upper GI event averted (CSUGIE) • Cost per QALY gained	• Time horizon: 1 year • Decision-tree model • Perspective: Veterans Affairs Administration • Country: United States	Celecoxib: • Cost/CSUGIE= $7,476 • Cost/QALY gained= <$50,000	• Patient population: OA patients with previous history of perforation/ ulcer/bleed
Spiegel et al. 2003[61]	• Celecoxib • NSAIDs	• Cost per QALY gained	• Time horizon: Life-time • Decision-tree model • Perspective: Health care payer • Country: United States	Celecoxib ICER was $275,809/QALY gained in comparison to NSAIDs	• Patient population: OA or RA patients • No funding source declared
Yen et al. 2004[62]	• Celecoxib • NSAIDs • Hyalouronan	• Cost per QALY gained	• Time horizon: 6 months • Decision-tree model • Perspective: Societal • Country: Taiwan	Celecoxib ICER was $21,226/QALY gained in comparison to NSAIDs	• Patient population: 60-years old women with knee OA • Study funded by a governmental organization

Author, year	Comparators	Primary outcome measure	Methodology	Base Case Results	Comments
Maetzel et al. 2003[63]	• Celecoxib • Rofecoxib • NSAIDs	• Cost per QALY gained	• Time horizon: 5-years • Markov model • Perspective: Health care payers • Country: Canada	• *In average-risk patients:* Celecoxib was dominated by NSAIDs • *In high-risk patients:* Celecoxib was cost-effective at <$Can 50,000 per QALY gained	• Patient population: OA or RA patients with no prior history of GI events (average-risk) or prior history of GI events (high-risk) • Study funded by a governmental organization
Kamath et al. 2003[64]	• Celecoxib • Rofecoxib • NSAIDs • NSAIDs + prophylaxis • Acetaminophen	• Cost/number of upper GI events averted • Cost/number of patients achieving pain relief	• Time horizon: 6 months • Decision-tree model • Perspective: Health care payer • Country: United States	• *For GI events avoided:* Acetaminophen dominates all other strategies • *For pain relief:* Acetaminophen, followed by Rofecoxib have lowest ICER	• Patient population: patients with symptomatic knee OA • Study funded by a private organization

Author, year	Comparators	Primary outcome measure	Methodology	Base Case Results	Comments
Chancellor et al. 2001[65]	• Celecoxib • NSAIDs • NSAIDs + Misoprostol • NSAIDs + H_2RA • NSAIDs + PPI • NSAIDs + Misoprostol	• Cost/number of averted GI events	• Time horizon: 6 months • Decision-tree model • Perspective: Health care payers • Country: Switzerland	• *Cost/number of averted GI events:* Celecoxib dominated NSAIDs alone	• Patient population: OA or RA • Study funded by pharmaceutical company (Pfizer)
+Haglund et al. 2000[66]	• Celecoxib • NSAIDs • NSAIDs + Misoprostol • NSAIDs + H_2RA • NSAIDs + PPI • Arthrotec	• Cost/number of averted GI events • Cost/life-years saved	• Time horizon: 6 months • Decision-tree model • Perspective: Health care payers • Country: Sweden	Celecoxib dominated all other comparators	• Patient population: OA and RA patients • No funding source declared

Author, year	Comparators	Primary outcome measure	Methodology	Base Case Results	Comments
+Svarvar et al. 2000[67]	• Celecoxib • Rofecoxib • NSAIDs • NSAIDs + Misoprostol • NSAIDs + H_2RA • NSAIDs + PPI • Arthrotec	• Cost per number of averted GI events • Cost per life-years saved	• Time horizon: 6 months • Decision-tree model • Perspective: Health care payers • Country: Norway	Celecoxib dominated all other comparators	• Patient population: OA and RA patients • No funding source declared
Glucosamine as the primary Comparator					
Scholtissen et al. 2010[68]	• Glucosamine • Paracetamol • Placebo	• Cost/QALY gained	• Time horizon: 6 months • Clinical trial data[69] • Perspective: Health care payers • Country: Spain	ICER: • Glucosamine dominated paracetamol • Glucosamine vs. placebo: €4,285/QALY gained	• Patient population: patients with knee OA • Study funded by a grant from ESCEO-Amgen

+=Only osteoarthritis results are reported.
GI=Gastrointestinal; H_2RA=Histamine-2 receptor antagonists; ICER=Incremental cost-effectiveness ratio; NSAIDs=Non-steroidal anti-inflammatory drugs; OA=Osteoarthritis; PPI=Proton pump inhibitor; QALY=Quality-adjusted life-years; RA=Rheumatoid Arthritis

The findings on cost-effectiveness of celecoxib vary by studies. Celecoxib dominated all other treatment strategies in four studies;[57, 65-67] whereas, it was dominated by NSAIDs [63] and acetaminophen in one study each.[64]

Glucosamine as the Primary Study Comparator

Only one published study has previously examined the cost-effectiveness of glucosamine. Scholtissen et al. compared the cost-effectiveness of glucosamine with paracetamol and placebo in treating KOA, based on the data from a randomized clinical trial.[68, 69] This cost-effectiveness analysis study was conducted from 6 months' time-horizon and health care payers' perspective of the Spanish population. No decision-analytic model was used in this study. Cost/QALY gained was used as the primary outcome measure of effectiveness in this study. Glucosamine was found to be highly cost-effective, by dominating the paracetamol strategy and with incremental cost-effectiveness ratio of €4,285/QALY gained in comparison to placebo.

In summary, to our knowledge, no published study has compared the cost-effectiveness of celecoxib, glucosamine, CS, and combination of glucosamine and CS. We found a few cost-effectiveness studies that have compared celecoxib to other treatment strategies such as the NSAIDs alone or in combination with other agents (e.g., rofecoxib and hyalouronan). The findings on cost-effectiveness of celecoxib vary by studies. We also found one study that compared the incremental cost-effectiveness of glucosamine with paracetamol and placebo. This study concluded glucosamine to be a highly cost-effective therapy option in treating KOA. No published study has compared the cost-effectiveness of CS or alone or in combination with glucosamine.

Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)

The WOMAC was developed in 1980s as a disease-specific clinical index for assessing the pain, stiffness, and physical function among the osteoarthritis patients.[116] It is widely used and easily-administered instrument to evaluate the outcomes of KOA patients.[117] WOMAC is also incorporated into the clinical trials guidelines of the Osteoarthritis Research Society International (OARSI) as an index relevant to outcome measurement in osteoarthritis.[118]

Structure

The WOMAC consists of 24 items divided into 3 sub-scales:

1) Pain (5 items): during walking on flat surface, using stairs, in bed, sitting or lying, and standing upright
2) Stiffness (2 items): after first awakening and later in the day
3) Physical function (17 items): descending stairs, ascending stairs, rising from sitting, standing, bending, walking on flat surface, getting in/out of the bath, sitting, getting on/off toilet, heavy domestic duties, light domestic duties, shopping, rising from bed, lying in bed, putting on socks/stockings, taking off socks or stockings, getting in/out of a car or bus.

Scoring

The WOMAC is currently available in two versions: Likert scale and visual analogue scale (VAS). The possible ranges of scores on the Likert scale version of WOMAC are: 0 to 20 (pain); 0 to 8 (stiffness); and 0 to 68 (physical function). On the

other hand, the possible ranges of scores on the VAS version of the WOMAC for each item are from 0 to 100. Therefore, the possible ranges of total scores on the three sub-scales are: 0 to 500 (pain); 0 to 200 (stiffness); and 0 to 1700 (physical function). The WOMAC 3.1 Veterans Affairs (VA) 100 mm VAS version was used in the GAIT study.

Psychometric Properties

A recent systematic review of 43 published articles examined the reliability, validity, and responsiveness of the WOMAC instrument in measuring outcomes among hip osteoarthritis or KOA patients.[117]

Reliability, test-retest:

Overall, the test-retest reliability of the WOMAC meets the minimum standards.[119-124] One study examining this psychometric property of the WOMAC found the global score on test-retest reliability to be 0.64, with sub-scale scores being 0.64, 0.61, and 0.72 for pain, stiffness, and physical function, respectively.[125] Another study reported internal consistencies for WOMAC sub-scales to be 0.83 (pain), 0.87 (stiffness), and 0.96 (physical function).[121]

Reliability, internal consistency:

Findings from several studies suggest that the WOMAC sub-scales are internally consistent and that the items on each sub-scale are related to each other.[117, 126] One such study reported internal consistency of the pain sub-scale to be 0.89, as estimated through the Chronbach's alpha.[125]

Reliability, rater:

The Intraclass correlation coefficients (ICCs) for WOMAC range from 0.53 to 0.78 and 0.62 to 0.90 for intra-rater reliability and inter-rater reliability of WOMAC, respectively, in a study of patients undergoing hip replacement.[127]

Validity, face:

The WOMAC has been face validated through the expert opinion of rheumatologists and epidemiologists, reviews of previous instruments, and survey of hip osteoarthritis and KOA patients.[128]

Validity, criterion:

Several studies have examined and established the criterion validity for WOMAC.[129-131] For example, one study with knee arthroplasty patient population found statistically significant Spearman correlations between patient satisfaction and WOMAC's pain (r =0.67), stiffness (r =0.63), and function (r =0.64) subscales.[129]

Validity, construct:

Convergent construct validity for WOMAC has also been examined and established by several studies.[122, 123, 131-136]

Validity, known-group:

One study has examined the known-group validity of WOMAC scale.[131] Studying the total knee arthroplasty population, this study found that WOMAC differentiates on

the pain and physical function subscales and on the global scores in a variety of different groups.

Responsiveness:

The WOMAC's responsiveness varies by its sub-scales.[117] For example, among the six hip arthroplasty studies examining this property, the effect size for WOMAC's pain, stiffness, and physical function sub-scales were large and ranged from 1.7 to 2.58, 1.0 to 2.17, and 1.8 to 2.9, respectively.[132, 133, 137-140]

Utilization of WOMAC in GAIT

WOMAC scores were used as a secondary outcome measure in the GAIT study. A complete WOMAC questionnare including patient assessments of pain, stiffness, and function were done at each visit, i.e. at baseline; weeks 4, 8, 16, 24; and months 9, 12, 15, 18, 21 and 24.

In summary, WOMAC is a disease-specific clinical index used for assessing disease status of the hip osteoarthritis or KOA patients. The WOMAC consists of 24 items divided into 3 sub-scales, i.e. pain, stiffness, and physical function. The WOMAC is available in both the Likert scale and VAS formats. Both of these versions are well validated and are tested for reliability and responsiveness in many studies.

Medical Outcomes Study (MOS) 36-item Short Form Health Survey (SF-36)

Structure

The MOS SF-36 (better known as SF-36) is a generic quality-of-life index, with 36 items divided into 8 sub-domains (i.e., physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental health), Table 8.[141-143] These sub-domains, in turn, can be summarized into two composite scores, i.e. physical component summary (PCS) and mental component summary (MCS). Previous studies based on factor analysis have confirmed that the physical and mental health summary composite scores account for 80-85% of the reliable variance in the eight sub-domains in the US general population,[144] MOS patients, [102,105] and populations of other countries.[145-149] The SF-36 is available to administer by self, computer, or a trained interviewer in person or by telephone, to persons age 14 and older.

Table 8: Structure of SF-36 Instrument.

Summary Measures	Number of Items	Meaning of Scores	
		Low	High
Physical Component	21		
Physical Functioning	10	Limited a lot in performing all physical activities	Performs all types of physical activities
Role-Physical	4	Problems with work or other daily activities due to physical health	No problems with work or other daily activities due to physical health, past 4 weeks
Bodily pain	2	Very severe and extremely limiting pain	No pain or limitations due to pain, past 4 weeks
General Health	5	Believes personal health is poor and likely to get worse	Believes personal health is excellent
Mental Component	14		

Summary Measures	Number of Items	Meaning of Scores	
		Low	High
Vitality	4	Feels tired and worn out all of the time	Feels full of pep and energy all of the time, past 4 weeks
Social Functioning	2	Extreme and frequent interference with normal social activities	Performs normal social activities without interference, past 4 weeks
Role-Emotional	3	Problems with work or other daily activities due to mental health	No problems with work or other daily activities due to mental health, past 4 weeks
Mental Health	5	Feeling of nervousness and depression all of the time	Feels peaceful, happy, and calm all of the time, past 4 weeks

Scoring

Higher PCS and MCS summary scores on the SF-36 indicate better physical and mental health status, respectively. The following description provides overview of the scoring algorithm for the SF-36v2 (version 2). Items of the physical functioning sub-domain consist of three levels, ranging from 'limited a lot' to 'not limited at all'. Items on the role physical sub-domain consist of five levels in the SF-36v2, varying from 'all of the time' to 'none of the time.' This is different from the version 1 where these items use to have only two levels, i.e. yes and no. Bodily pain sub-domain has six levels for the first question (from none to very severe) and five levels for the second question (from 'not at all' to 'extremely'). The general health sub-domain has five levels for all five items. The vitality sub-domain has five levels in the SF-36v2 (ranging from 'all of the time' to 'none of the time'), differing from the six level items in the version 1 of this instrument. Items in the social functioning sub-domains have five levels. Items on the role emotional sub-domain also have five levels in the SF-36v2, ranging from 'all of the time' to 'none of the time.' This is different from the version 1 of SF-36, in which these

items had only two levels (yes and no). The mental health sub-domain has five level items in both of the version 1 and 2 of the SF-36.

Psychometric Properties

Reliability, test-retest:

The SF-36's test-retest reliability has been tested in more than 200 studies.[150] Reliability statistics have exceeded the minimum standards of 0.70 or even 0.80 in most of these studies.

Reliability, internal consistency:

Findings from a systematic review suggest that the median reliability for each of the eight scales of the SF-36 are at least 0.80, except for the social functioning scale that would found to have an median reliability of 0.76.[151] These statistics indicate that the SF-36 is internally consistent.

Reliability, rater:

Several studies have examined the inter- and intra-rater reliabilities of the SF-36.[152-157] Most of these studies have found moderate to high inter-and intra-rater reliabilities for this quality-of-life instrument.

Validity, face:

The SF-36 has been compared to other widely used generic quality-of-life instruments.[158] Content of the SF-36 instrument includes eight of the most frequently measured health concepts, ensuring its face validity.

Validity, criterion:

Numerous studies have evaluated the criterion validity of the SF-36 instrument;[141, 144, 148, 159-163] all of these studies found SF-36 to meet the standards of criterion validity.

Validity, construct:

The construct validity of SF-36 has been examined by various studies.[102,105,109,120-124] These studies have reported that the SF-36's construct validity varies from 0.85 (physical function) to 0.69 (general health) for the PCS and from 0.87 (mental health) to 0.65 (vitality) for the MCS summary scores.

Validity, known-group:

Several studies have found evidence of known-group validity of the SF-36. A recent systematic review focused on examining the use of SF-36 in schizophrenia population found 11 studies comparing SF-36 scores with normative values.[164] All of the 11 studies found statistically significant ($p<0.05$) differences in SF-36 composite scores (PCS and MCS) and dimension scores between individuals with schizophrenia and normative values. Two studies found significant difference for all eight sub-domains, except for the bodily pain.[165]

Responsiveness:

The responsiveness of SF-36 has been examined and established in several studies.[166-170] For example, one study examined Sf-36's responsiveness in four common chronic conditions of low back pain, menorrhagia, suspected peptic ulcer, and varicose

veins.[166] This study found that the changes across health status were significantly associated with the changes in SF-36 scores, establishing the responsiveness of SF-36.

In summary, the SF-36 is a generic quality-of-life instrument, with 36 items divided into 8 sub-domains that can be summarized into two component scores, i.e. PCS and MCS. Many studies have established the validity, reliability, and responsiveness of the SF-36 instrument.

Estimation of Quality-Adjusted Life-years (QALYs) From SF-36

As described before in the introduction chapter, the individuals' preferences are represented by *individuals' utility function* that relates their well-being to their levels of consumption of several goods and services. In health economics, this preference-based *individuals' utility function* is known as health utility, which is used to estimate QALYs for the purpose of a CEA study.

The SF-36 instrument cannot be directly used to estimate QALYs as the former is not a preference-based instrument, but a descriptive one. Therefore, in order to estimate QALYs from SF-36 its scores must be mapped on to a preference based instrument like SF-6 Dimensions (SF-6D) or EuroQol 5-Dimensions (EQ-5D). Pickard et al. have previous compared several mapping algorithms (n=9) for estimating preference-based health utilities from the SF-36 and concluded Brazier Index to be the best.[171, 172] Brazier index is a preference-based measure of health from the SF-36 instrument that was derived by mapping UK's national population measures on to SF-6D through the standard gamble approach.[173] Further details of mapping SF-36 scores to SF-6D and, in turn, estimate QALYs for the purpose of current study are provided in the methods section.

Utilization of SF-36 in GAIT

SF-36 scores were used as a secondary outcome measure in the GAIT study. The SF-36 scores were recorded at each visit, i.e. at baseline; weeks 4, 8, 16, 24; and months 9, 12, 15, 18, 21 and 24.

Glucosamine/chondroitin sulfate Arthritis Intervention Trial (GAIT)

GAIT was the largest clinical trial examining efficacy of CAM therapies to treat KOA. This trial compared glucosamine, CS, their combination, celecoxib, and placebo in a multi-center double-blind randomized study.[21] All patients were screened at the screening visit for several inclusion and exclusion criteria (Appendix 1). This was followed by a randomization visit and follow-up visits at weeks 4, 8, 16, and 24 (GAIT 24-week study) and at months 9, 12, 15, 18, and 24 (GAIT 2-year follow-up study).

For the GAIT 24-week study, a total of 1583 individuals with symptomatic KOA were randomly assigned to receive daily doses of 1500 mg of glucosamine, 1200 mg of CS, both glucosamine and CS, 200 mg of celecoxib, or placebo for 24 weeks. KOA patient groups were stratified by severity of knee pain at the baseline into mild and moderate to severe. The primary outcome measure was at least 20% reduction in pain from baseline enrollment, measured using the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain sub-scale. The secondary outcome measures were: 1) WOMAC stiffness and function subscales, 2) patient's global assessment of disease status, 3) patient global assessment of response to therapy, 4) investigator global assessment of disease status, 5) investigator global assessment of

response to therapy, 6) study joint evaluation, 7) SF-36 scores, 8) modified health assessment questionnaire (mHAQ), beck depression inventory, 9) use of rescue analgesic, and 10) discontinuation of study medication due to adverse event. Overall, glucosamine, CS, or their combination therapies were not significantly different from placebo in pain reduction, $p>0.05$. Among the moderate to severe pain stratum group of patients, however, the combination of glucosamine and CS was significantly better than placebo in treating KOA. On the other hand, celecoxib was better than placebo in both overall analysis and in mild-to-moderate pain stratum groups, but not in moderate-to-severe pain stratum.

The GAIT 2-year follow-up study—the ancillary structure modifying study—was conducted on a sub-group of original participants.[24, 33] For this follow-up study, a total of 662 participants were randomly assigned to glucosamine (n=134), CS (n=126), combination of glucosamine and CS (n=129), celecoxib (n=142), and placebo groups (n=131). The primary outcome measure was the loss of joint space width (JSW) in the medial tibiofemoral joint compartment. The reduction in WOMAC pain sub-scale scores from baseline at 2 years was also recorded as a secondary outcome measure in this follow-up study. No significant differences were found between placebo and celecoxib, glucosamine, CS, and combination of glucosamine and CS in reducing the loss of JSW or change in WOMAC pain sub-scale scores at 2-year follow-up, $p>0.05$.

Summary of Literature Review

KOA has substantial burden of illness in the US, affecting 13.8% of the population aged 26 years or more. Currently, there is no cure for KOA; all available treatment options are intended to reduce pain, maintain and/or improve joint disability, and limit functional impairment. Both CAM therapies and conventional medicines are widely used in the US to treat KOA. Several previous clinical trials have examined and established the efficacy and safety of conventional medicines such as celecoxib to treat KOA. On the other hand, the efficacy and safety of CAM therapies like glucosamine and CS is still debatable after several clinical trials. There is a high unmet need to compare the cost-effectiveness of CAM therapies with conventional medicines in treating KOA in the US.

CHAPTER 3: METHODS AND MATERIALS

The aim of our study was to compare the incremental cost-effectiveness of glucosamine, CS, combination of glucosamine and CS, celecoxib, NSAIDs and placebo therapies to treat KOA. We begin this section by discussing the human subjects' approval for this study. This is followed by the discussion on research design and data sources; study population; inclusion and exclusion criteria; sample size estimation; strategies to manage KOA; model structure, description, and validation; study perspective, time horizon and discounting rates; costs measures, effectiveness measures; health utilities; transition probabilities and event rates; and sensitivity analysis. Wherever necessary, the aforementioned sections have separate sub-sections for different study objectives to differentiate between their respective applicable methodologies.

Human Subjects Approval

We submitted this study for the departmental review through the University of New Mexico, College of Pharmacy. After seeking the departmental approval, this study was submitted to the Human Research and Review Committee (HRRC) under the exempt category. The HRRC approved this study on November 7, 2012. The approval letter for this study is presented in Appendix 2.

Research Design and Data Sources

Two decision-analytic models were constructed to examine the cost-effectiveness of CAM therapies and conventional medicines in treating KOA: (1) A Markov cohort model to compare the cost-effectiveness of CAM therapies and conventional medicines from 10-year time-horizon, and (2) A decision-tree model to compare cost-effectiveness of CAM therapies and conventional medicines from 24-weeks and 2-year time-horizons. Below is a brief of all data sources utilized in this study; the specific details of these, however, are provided in the later sections of this chapter.

For the Markov cohort model, efficacies of CAM therapies and conventional medicines were based on 1-year WOMAC pain sub-scale reduction outcomes from the GAIT study and were defined as at least 20% reduction in pain sub-scale scores from the baseline, as described later in this chapter.[174] Health utility values were estimated by mapping SF-36 scores to the SF-6D instrument. Drug costs were obtained from the published literature sources such as Red Book, Wal-Mart Prescription Program, and CVS Generic Pharmacy.[175-178] Published literature was also used to obtain risks rates of drugs associated adverse events,[63, 179-208] their costs[59, 176, 209-216] and their health utility values,[63, 217-222] and total knee replacement surgery rates and its costs. [39,40,63, 217-224]

For the decision-tree model drug efficacies data were based on 24-week and 2-year WOMAC pain sub-scale reduction outcomes from the GAIT study , for respective time-horizons of 24-weeks and 2-year. Similar to the Markov model, the health utility values were estimated by mapping SF-36 scores to the SF-6D instrument and the drug costs were obtained from the published literature sources such as Red Book, Wal-Mart

Prescription Program, and CVS Generic Pharmacy.[175-178] Since no significant difference in serious adverse events between CAM therapies and celecoxib was observed in the GAIT study, none were modeled in the decision-tree.[24, 33, 174]

Study Population, Inclusion and Exclusion Criteria

For Objective 1

The inclusion criteria used for our study population are being male or female, age of at least 50 years, and clinical diagnosis of primary KOA. No other inclusion or exclusion criteria apply to this study population, as multiple data sources from the literature were utilized for objective 1.

For Objectives 2 to 5

Study population for objectives 2 & 3 and 4 & 5 consist of the GAIT 24-week and GAIT 2-year follow-up studies participants, respectively.[21, 33] The inclusion criteria for our study are same as the inclusion and exclusion criteria from the GAIT study (Appendix 1).[21, 33]

Sample Size Estimation

We did not conduct formal sample size estimations and power for our study because of the following reasons. First, the foundation of cost-effectiveness analysis is based on the concepts of estimation rather than hypothesis testing.[34, 225, 226] Unlike other types of studies, the uncertainties in cost-effectiveness analysis studies are addressed through sensitivity analysis rather than the formal power calculations.[34] If any, the usage of power calculations and sample size estimation in cost-effectiveness analyses are limited to those studies that are conducted alongside clinical trials.[227] Even the economic evaluations alongside clinical trials are commonly underpowered, as recognized by a recent good practices report by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Randomized Clinical Trials (RCT) Cost-Effectiveness Analysis Task Force.[228] Further, all currently published literature on sample size estimation and power calculation is based on cost-effectiveness analysis studies conducted alongside clinical trials.[227, 229-234] Our study was not a cost-effectiveness analysis alongside a clinical trial because no cost data were collected in the GAIT study and we utilized multiple data sources to populate our decision-analytic models. Therefore, the sample size estimation formulas valid for cost-effectiveness analysis studies alongside the clinical trials are not applicable to our study.

Second, to address the parameter uncertainty among the decision-model inputs, we performed second order Monte Carlo simulation (probabilistic sensitivity analysis) on all of our decision-analytic models. Further details on the probabilistic sensitivity analysis are provided later in this chapter.

Third, sample size estimation is most beneficial at the time of designing a study so that sufficient study participants can be recruited accordingly.[235] As the GAIT study is already closed out, no further participants recruitment or data collection is possible at this point.[21] Therefore, estimation of sample size based on the cost-effectiveness ratios at this stage for our study would not be fruitful, and, more importantly, would be of least scientific importance.

Sample Size Estimation in GAIT Study

In the GAIT 24-weeks study, a total of 1583 patients with symptomatic KOA were randomly assigned to glucosamine (n=317), CS (n=318), combination of glucosamine and CS (n=317), celecoxib (n=318), or placebo (n=313).[21] These group assignments were based on the statistical power of 85% to detect at least one clinically meaningful difference between the placebo group and groups of glucosamine, CS, combination of glucosamine and CS, and celecoxib.[21, 235] The rate of response for these calculations was assumed to be 35% in placebo group and the overall rate of withdrawal from study was assumed to be 20%.[21]

The GAIT 2-year ancillary structural study consisted of sub-population of GAIT 24-week study.[24, 33] Nine of the sixteen centers from the latter participated in this 2-year follow-up study (Arthritis Research Center, Wichita; University of Arizona; Case Western Reserve University; Cedars-Sinai Medical Center; Indiana University; University of California, Los Angeles; University of California, San Francisco; University of Pittsburgh; and the University of Utah). For the 2-year follow-up study, a total of 662 participants were randomly assigned to glucosamine (n=134), CS (n=126),

combination of glucosamine and CS (n=129), celecoxib (n=142), and placebo (n=131) groups.

Sample Size and Power Calculations Based on QALYs

As described before, no formal sample size and power calculations were conducted in our study. Nonetheless, we here discuss if the currently available sample size from the GAIT study was sufficient to determine the minimum important difference (MID) in QALYs gained among the KOA patients for the study of objectives 2 to 5.

Walters and colleagues estimated the MID in SF-6D based health utility values among the KOA patients from a prospective study.[236] They found a difference of 0.032 to be the MID, with standard deviation of 0.066 and 95% CI of 0.015 to 0.049. Based on these statistics, the required sample size per group and the total required sample size (5 groups) are displayed in Table 9. These statistics indicate that the data available from the GAIT study were sufficient to estimate MID in QALYs gained (mean=0.032, 95% CI=0.015 to 0.049) at 90% power.

Table 9: Sample Size Estimation Based on QALYs.[236]

Power	MID*; Mean (95% CI)	Required Sample Size Per Group: LCI, M, UCI	Total Required Sample Size: LCI, M, UCI
0.80	0.032 (0.015 to 0.049)	610, **136**, 60	3650, **680**, 300
0.85	0.032 (0.015 to 0.049)	698, **156**, 68	3490, **780**, 340
0.90	0.032 (0.015 to 0.049)	816, **182**, 80	4080, **910**, 400

*Standard Deviation=0.066

CI=Confidence Interval; LCI=Estimates as per the Lower Confidence Interval; M=Estimates as per the mean; QALYs=Quality-Adjusted Life-years; UCI=Estimates as per the Upper Confidence Interval

KOA Treatment Strategies/Study Comparators

For Objective 1

We compared the incremental cost-effectiveness of 1500 mg of glucosamine daily, 1200 mg of CS daily, combination of glucosamine 1500 mg and CS 1200 mg daily, 200 mg of celecoxib daily, and US FDA approved prescription NSAIDs in the treatment of KOA. The list of these US FDA approved prescription NSAIDs is provided in Table 10.

Table 10: FDA Approved Dosages of NSAIDs in Treatment of KOA.

Drug	Recommended FDA Dosage to Treat KOA
Diclofenac	100-150 mg/day in divided doses (50 mg BID, TID or 75 mg BID)
Diflunisal	500-1000mg/day in two divided doses
Etodolac	300 mg BID, TID or 400 mg BID or 500 mg BID
Fenoprofen	Up to 3,200 mg/day (3 to 4 times a day)
Flurbiprofen	200-300 mg/day
Ibuprofen	400 to 800 mg orally every 6 to 8 hours
Indomethacin	Up to 150-200 mg/day
Ketoprofen	Up to 200 mg/day (75 mg TID or 50 mg BID)
Ketorolac	10 mg 4 times a day orally as needed
Mefenamic acid	500 mg orally followed by 250 mg every 6 hours as needed
Meloxicam	Up to 15 mg/day
Nabumetone	Up to 2000 mg per day
Naproxen	Up to 500 mg/day in divided doses, BID
Oxaprozin	1200 mg/day in divided doses, BID
Piroxicam	20 mg/day
Sulindac	300 mg/day, BID

BID=Twice a day; FDA=Food and Drug Administration; KOA=Knee osteoarthritis; TID=Thrice a day

For Objectives 2 to 5

We compared the incremental cost-effectiveness of 1500 mg of glucosamine daily, 1200 mg of CS daily, combination of glucosamine 1500 mg and CS 1200 mg daily, 200 mg of celecoxib daily, and placebo in the treatment of KOA. These comparators are per the dosage regimen used in the GAIT study protocol. Further details of the aforementioned drugs dispensed to the blinded groups in the GAIT study are provided in Table 11.

Table 11: Blinded Drugs Dispensed to the GAIT Study Participants.

Treatment	**Strength**	**Dosage Form**	**Dose/Day (number of capsules/day)**
Glucosamine	250 mg	Capsules	1500 mg (six capsules/day)
CS	200 mg	Capsules	1200 mg (six capsules/day)
Glucosamine + CS	250 mg Glucosamine + 200 mg CS	Capsules	Glucosamine: 1500 mg (six capsules/day) + CS: 1200 mg (six capsules/day)
Celecoxib	200 mg	Capsules	200 mg (one capsule/day)
Placebo I	0 mg	Capsules	0 mg (six capsules/day)
Placebo II	0 mg	Capsules	0 mg (one capsule/day)

CS=Chondroitin Sulfate; GAIT=Glucosamine/Chondroitin Arthritis Intervention Trial

At each visit during the GAIT study, participants were dispensed two bottles of the blinded drugs. The first bottle consisted of glucosamine, CS, combination of glucosamine and CS, or placebo I to be taken three times a day. The second bottle consisted of celecoxib or placebo II to be taken once a day. The details of the treatment regimens during the GAIT study are provided in Table 12.

Table 12: Treatment Regimens for GAIT Study.

Treatment Group	**Treatment**	**Bottle 1 Dose/Day** (Dosage regimen: 2 capsules 3 times a day)	**Bottle 2 Dose/Day** (Dosage regimen: one capsule a day)
1	Glucosamine	Glucosamine 1500 mg	Placebo II 0 mg
2	CS	CS 1200 mg	Placebo II 0 mg
3	Glucosamine + CS	Glucosamine 1500 mg + CS 1200 mg	Placebo II 0 mg
4	Celecoxib	Placebo I 0 mg	Celecoxib 200 mg
5	Placebo	Placebo I 0 mg	Placebo II 0 mg

GAIT=Glucosamine/Chondroitin Arthritis Intervention Trial

Placebo was included as one of the comparators in our study as it is commonly prescribed among the KOA patients and its use is viewed ethical among the US physicians.[237, 238] A recent survey of 679 internists and rheumatologists practicing in the US found that 46-58% of these physicians prescribe placebo to their patients on a regular basis.[237] Majority of these physicians (62%) also believe the practice of prescribing placebo to be ethically permissible. In addition, these physicians most commonly describe placebo to their patients as potentially beneficial treatment (68%); only rarely do they explicitly describe these as placebos (5%). Further, a systematic review of 22 studies from 12 countries further found the use of placebos to range from 17% to 80% among physicians.[238]

Model Structure, Description, and Validation

Mathematical modeling is widely used in health economic evaluations of the pharmaceuticals as well as of other health technologies.[56] The types of decision-analytic models used in our study for objective 1 was a Markov cohort model and two decision-tree models for examining objectives 2 to 5. Both of these types of models had provisions for probabilistic sensitivity analysis.

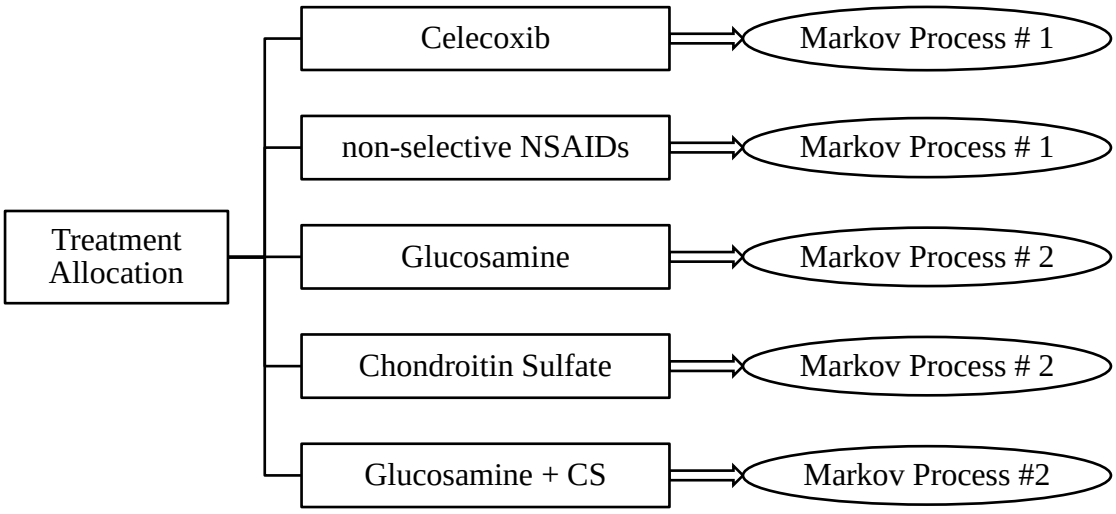
Two different types of models (i.e., Markov and decision-tree models) were constructed in this study for the following reason: The purpose of studying objective 1 was to compare the long-term (10 years) cost-effectiveness of CAM therapies with conventional medicines in real-world where a patient may experience adverse events or death during its treatment journey. On the other hand, the purpose of objectives 2 to 5 was to compare the cost-effectiveness of KOA treatment strategies by exclusively simulating the world of GAIT clinical trial. For the same reason, no adverse events or deaths were modeled in any decision-tree, as none occurred in the GAIT study.

Markov Cohort Model for Objective 1

A Markov cohort model was constructed to mathematically simulate clinical scenarios of treating KOA patients with CAM therapies and conventional medicines from 10-year time-horizon (1-year Markov cycles) and healthcare payers' perspective (Figure 1 to 4). Clinically diagnosed KOA patients entered the Markov model at age 50 years to be allocated to one of the following treatment groups: celecoxib, NSAIDs, glucosamine, CS, or combination of glucosamine and CS. Unlike the other four objectives, no placebo arm was modeled in the Markov model because the purpose of the Markov model based

analysis was to compare cost-effectiveness of FDA approved conventional medicines with CAM therapies in a broader group of US population. Whereas, for decision-tree model based analyses, the purpose was to examine which therapy (including placebo) was most cost-effective in the GAIT study population. Patients entered different Markov processes based on their initial allocations to CAM therapies or conventional medicines, as displayed in Figure 1. No medication augmentation or switching was allowed in the model.

Figure 1: Schematic Diagram of the Markov Cohort Model.



CS=Chondroitin Sulfate; NSAIDs=non-selective Non-Steroidal Anti-Inflammatory Drugs

Patients allocated to conventional medicines, i.e. celecoxib or NSAIDs, progressed through the Markov process displayed in Figure 2 (Markov Process # 1). Beginning at the celecoxib/NSAIDs health state, the KOA patients progressed to one of the following Markov health states: treatment success, TKR surgery, adverse events, and death. Treatment success was defined as at least 20% reduction on WOMAC pain sub-scale scores from baseline at the end of one year, these data were obtained from 1-year outcomes of the GAIT study. TKR surgery rates were obtained from a large US joint replacement registry of the Kaiser Permanente and varied by age-groups and gender. Included adverse events were serious cardiovascular (i.e., heart attack, stroke, myocardial infarction, and hypertension) and GI adverse events (i.e., GI bleeding, peptic ulcer, and

dyspepsia) for conventional medicines.[63, 179-208] After experiencing a GI bleeding event, KOA patients were modeled to be managed either in outpatient or inpatient settings, as per the recommendations and previously published evidence.[179-184] Among the inpatients, the treatment of GI bleeding may have included surgery.[63] Progressing through the Markov process, death was modeled to occur because of one of the following five reasons: heart failure, stroke, myocardial infarction, GI bleeding, and aging. A patient may have progressed to death due to aging from any of the Markov health states. Death was not modeled in any of the decision-tree models, as these models were exclusively populated without any extrapolation from the GAIT study outcomes in which no deaths occurred.[185-196, 239, 240]

Figure 2: Markov Process (1-year cycles) for Conventional Medicines (Markov Process # 1 in figure 1).

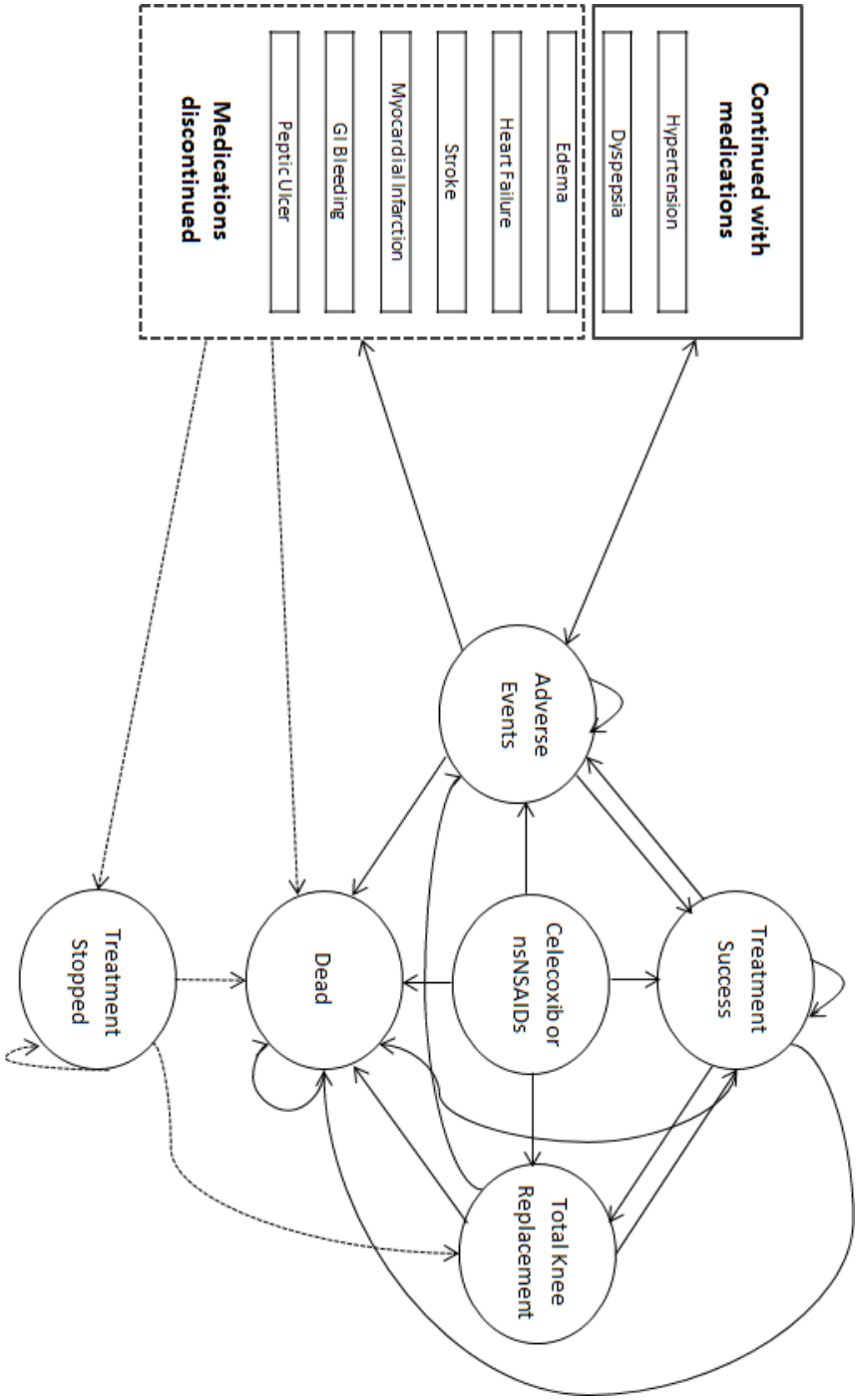
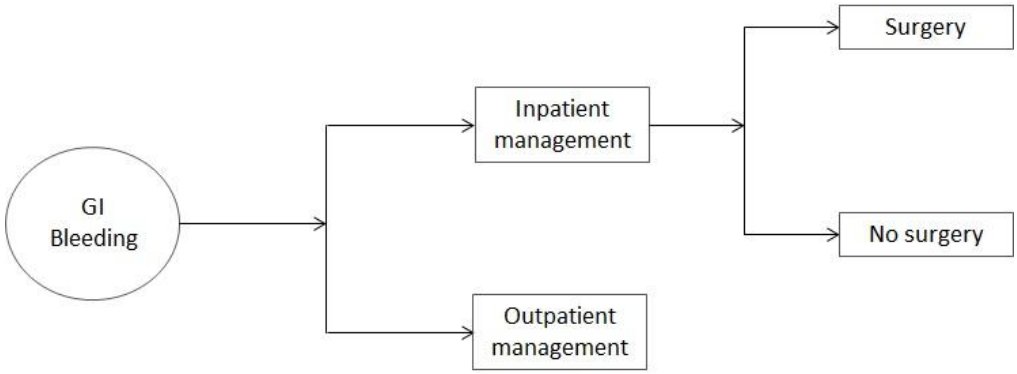


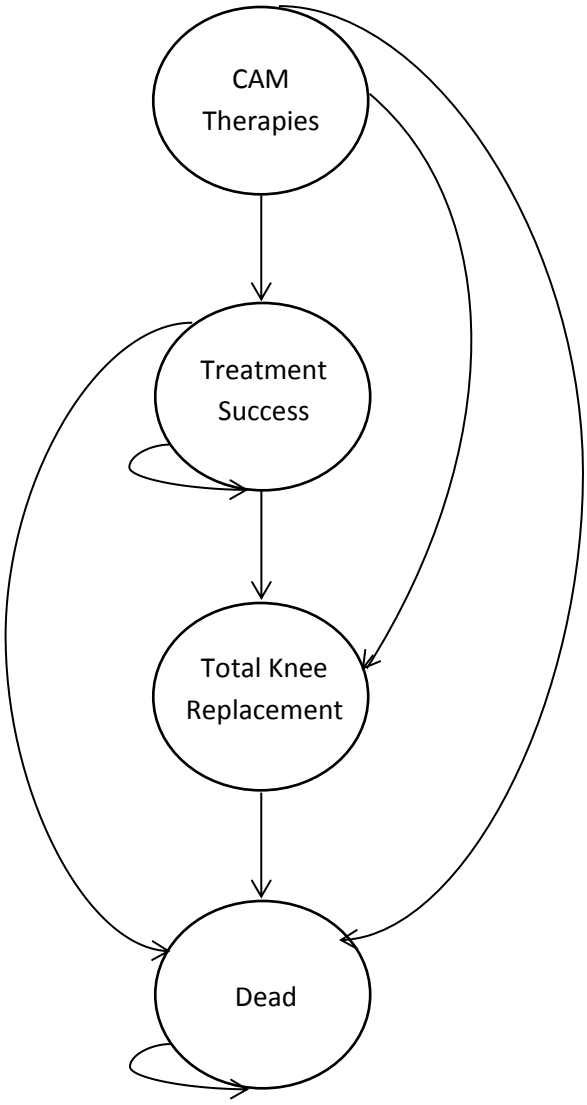
Figure 3: GI Bleeding Management Pathway



GI=Gastrointestinal

Patients allocated to CAM therapies, i.e. glucosamine, CS, or combination of glucosamine and CS, entered the Markov process shown in Figure 4 (Markov process # 2 in Figure 1). Only difference between the Markov processes for conventional medicines and CAM therapies is the absence of risks of adverse events associated with the latter (The reasons for not associating any serious adverse events with CAM therapies are described later in this chapter). In the Markov process for CAM therapies, KOA patients began in the model at the CAM therapies health state and progressed to one of the following: treatment success, TKR, and death. Treatment success was defined in the same manner as for the conventional medicines group, i.e. at least 20% reduction on WOMAC pain sub-scale scores from baseline to end of one year. TKR risks and death rates were also based on same data sources as that for the conventional medicines group.

Figure 4: Markov Process for CAM Therapies (Markov Process # 2 in figure 1).



CAM=Complementary and alternate medicine

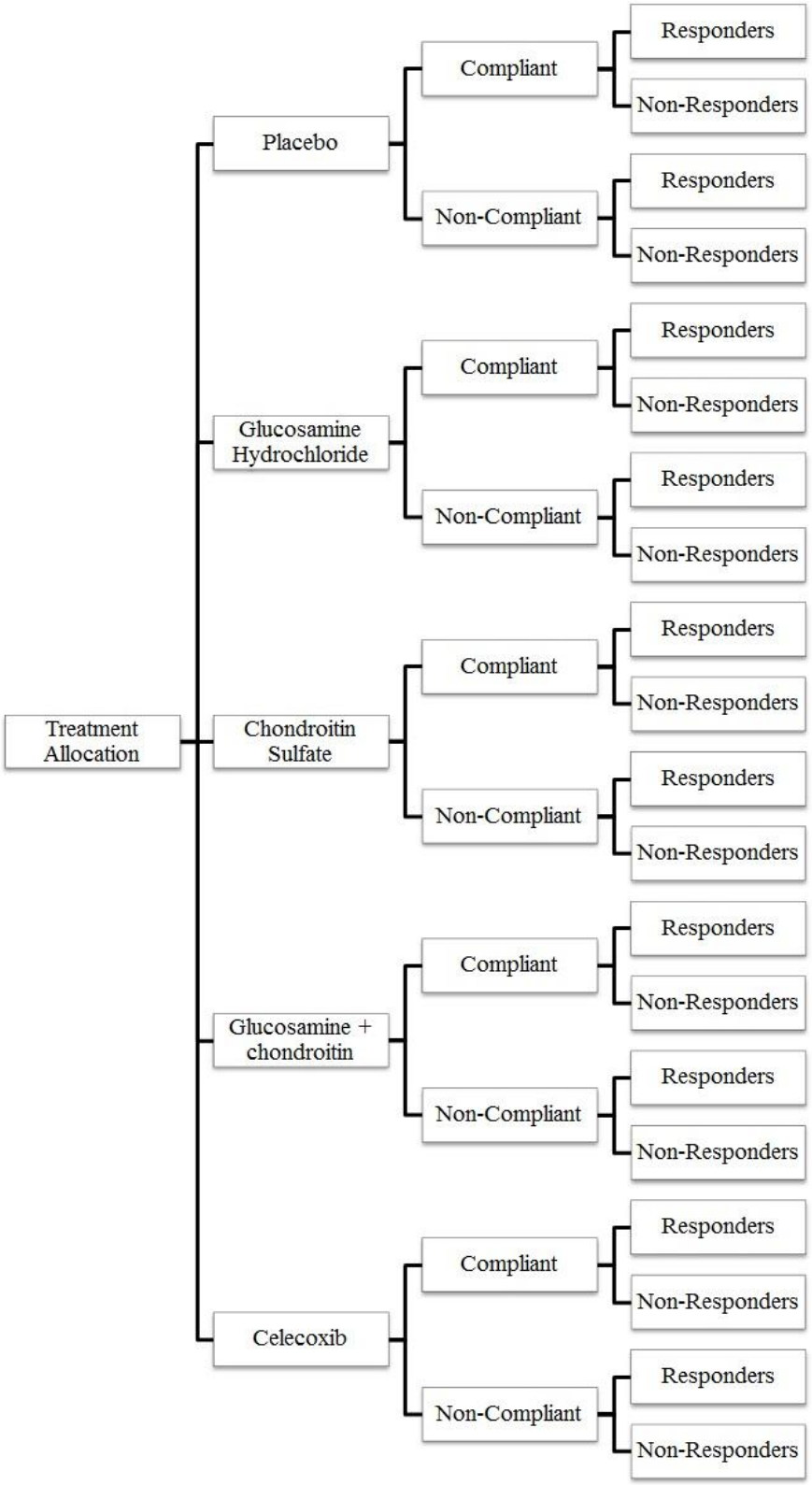
Decision-Tree Model for Objectives 2 to 5

In addition to the Markov cohort model described earlier, two decision-tree models were constructed to compare the cost-effectiveness of CAM therapies and conventional medicines from 24-weeks and 2-year time-horizons (one decision-tree for each). The schematic framework of these decision-tree models is displayed in Figure 5.

All KOA patients entered the model at the decision branch "treatment allocation." From this decision branch, patients were allocated to one of the following five branches, as per their respective blinded treatment groups in the GAIT study: glucosamine, CS, combination of glucosamine and CS, celecoxib, or placebo. From these five decision branches patients progressed to either "compliant" or "non-compliant" chance branches.[21, 241, 242] Since the GAIT study was conducted in well-controlled clinical trial settings, compliance rates during GAIT study may have differed from the real-world settings. To account for potential bias in decision-tree model parameters due to this issue, the compliance for all study parameters was arbitrarily assumed to be 75%. This estimate was varied by ±25% in the sensitivity analysis.[243]

From the compliant/non-compliant event branches, the patients entered "responders" or "non-responders" terminal chance branches. "Responders" were defined as the patients that achieved at least 20% reduction on the WOMAC pain sub-scale scores from baseline at the end of 24-weeks or 2-years, for the respective study time-horizons.[21] Patients who did not achieve at least 20% reduction on the pain sub-scale of the WOMAC instrument from baseline to endpoint were defined as "non-responders."

Figure 5: Schematic Diagram of the Decision-Tree Model.



Models Validation

Health economic models were based on specific assumptions related to their structure and parameters; therefore, model validation is important for decision-makers to judge regarding applicability of these models while making their decisions.[244, 245] Several different types of model validations are required as it is not possible to specify a criterion that a model must meet to be declared valid. *Verification (internal validity)* was performed by examining all model equations and parameters against their sources, after building the final decision-analytic models.[245] *Cross-validation* was conducted by comparing the study models with the previously published related cost-effectiveness models.[62, 63, 246, 247] *External validation* was conducted by extrapolating the decision-model to 1 year based on the data from the GAIT 24-weeks study and comparing these results with the GAIT ancillary study results.

Time Horizon, Study Perspective, and Discounting Rates

Our study was conducted from three different time-horizons: 24-weeks, 2-years, and 10-years. The selection of first two time-horizons was as per the studied time periods in the GAIT.[24, 33, 174] The 10-year time horizon was used to compare long-term cost-effectiveness of CAM therapies and conventional medicines among the KOA patients.

Separate cost-effectiveness analyses were conducted from healthcare payers and patients perspectives for the purpose of 24-week and 2-year time-horizon analyses. Healthcare payers' perspective was used to study cost-effectiveness of CAM therapies and conventional medicines from 10-year time-horizon.

The base case discounting rate of 3% was used in all of our analyses, as recommended by the USPCEHM.[34] This rate was varied from 0% to 5% in the sensitivity analysis, as described later in this chapter.

Cost Measures

All costs were estimated in the 2012 US dollars, adjusting previous years costs for inflation through the consumer price index (CPI).[34, 248] These costs include drug costs; adverse events management costs for heart failure, stroke, myocardial infarction, GI bleeding, peptic ulcer, dyspepsia, edema, and hypertension; and TKR surgery costs. For objectives 3 and 5, we also included indirect healthcare costs incurred among the KOA patients, as described later in this section. Any other health care costs excluded from our study as they would be similar between all study comparators.[21, 33, 249-251] Table 13 lists all costs included in our study.

Drug Costs

Multiple literature sources were utilized to obtain annual drug costs for the study comparators. Drug costs for celecoxib and NSAIDs were obtained from the generic prescription drug programs of the Wal-Mart and CVS.[175, 176] Drugs costs of glucosamine and CS were obtained from the published literature.[178] The average wholesale prices of glucosamine and chondroitin combination therapy obtained from the Red Book was used as its drug cost.[176] Placebo costs were assumed to be equal to the mean of costs of all other study comparators. Costs related to the physicians' office visit were based on the 2012 Medicare fee schedule estimated using the *Current Procedural Terminology* (CPT) codes.[252, 253]

Adverse Events Costs

Heart Failure

Costs of heart failure treatment were obtained from the published literature and were inclusive of 90-days post heart failure inpatient and outpatient management costs.[209] These heart failure treatment costs were estimated from a large employer-based commercial insurance database. From this database, the costs of treating heart failure were measured as the total healthcare costs for patients with heart failure claims minus the total healthcare costs among matched control groups without heart failure claims.

Stroke

Costs of treating stroke include separate short-term and long-term direct healthcare expenditures.[210, 211, 254] Short-term (i.e., day 0 to 30 post-stroke) direct healthcare costs during hospitalization ranged from $8,531 to $24,526.65.[210] Long-term (i.e., after 30 days post-stroke) direct care stroke costs after hospital discharge ranged from $5,482 to $27,195.[211] All stroke related costs were estimated from large retrospective claims databases.

Myocardial Infarction

Costs of treating myocardial infarction were obtained from the US estimates of an international, multisite registry of patients presented with acute myocardial infarction.[212] These costs were based on diagnosis-related group (DRG) codes and are adjusted to reflect length of hospital stay and physicians' efforts for each procedure performed. These procedures include CABG, percutaneous transluminal coronary angioplasty

(PTCA), coronary catheterization (CC), intra-aortic balloon pump (ABP), and automatic implantable cardiac defibrillator (AICD).

GI Bleeding

Costs of treating GI bleeding included 12-month healthcare costs post a GI bleeding event, estimated from a large US national health plan claims database.[213] These costs include total healthcare, medical, and pharmacy costs incurred in both inpatients and ambulatory care settings for patients experienced a GI bleeding event.

Dyspepsia

Costs of managing dyspepsia were based on the American College of Gastroenterology recommendations to treat dyspepsia.[255] The dyspepsia treatment strategy followed was of empiric trial of acid suppression with a proton pump inhibitors (PPIs) for a month. All dyspeptic patients over 55 years of age additionally underwent esophagogastroduodenoscopy (EDG). The cost of EDG was obtained from 2012 Medicare physicians fee reimbursement schedule.[214] The cost of PPI was obtained from the published literature.[59]

Peptic Ulcer

Similar to costs of managing dyspepsia, the costs of managing peptic ulcer were based on the guidelines of the American Association of Family Physicians.[256] All patients with peptic ulcer discontinued NSAIDs/celecoxib, underwent test for *Helicobactor Pylori* (*H. Pylori*) and took PPIs for 2 months. Furthermore, all patients aged over 55 years underwent EDG. The cost of EDG and *H. Pylori* testing were based on the 2012

Medicare physician fee reimbursement schedule and the cost of PPIs was obtained from the published literature.[59, 214]

Edema

Costs of treating edema were also based on the treatment guidelines of the American Association of Family Physicians.[257] All patients experiencing edema discontinued NSAIDs/celecoxib and were treated with diuretics for 4 to 6 weeks. Costs of diuretics were based on the Wal-Mart Prescription Program.[176]

Hypertension

Hypertension management is based on the recommendations of the National Institute of Clinical Excellence (NICE).[258] All patients experiencing hypertension continued on their KOA medications and were started on a concomitant anti-hypertensive therapy.[258-260] Costs of anti-hypertensive therapy were based on the Wal-Mart Prescription Program for generic drugs.[176]

Table 13: Model Inputs for Costs.

Parameter	Base Case (SA Range)	Reference
Drugs (annual)		
Celecoxib	$456.16 ($339.76 to $957)	CVS Generic Pharmacy[175]
NSAIDs	$40 ($30 to $ 50)	Wal-Mart Prescription Program[176]
Glucosamine	$ 286.20 ($214.65 to $429.30)	Gregory et al.[178]
CS	$ 227.88 ($170.92 to $284.84)	Gregory et al.[178]
Glucosamine + CS	$ 499.44 ($374.58 to $624.30)	Red Book[177]
Placebo	$367.42 ($274.97 to $573.86)	Assumption
Physicians' office visit cost (4 times/year)	$75.77±25%	CPT code: 99214[252]
Adverse Events Costs		
Heart Failure	$7,926.67 ($5,945.01 to $9,908.33)	Zhao et al.[209]
Stroke		
Short-term care (up to 30 days)	$15,995.12 ($11,997.01 to $19,993.75)	Qureshi et al.[210]
Long-term care (after 30 days)	$21,713 ($16,284.76 to $27,141.24)	Kind et al.[211]
Myocardial Infarction	$11,898.72 ($8,924.04 to $14,873.40)	Kauf et al.[212]
GI Bleeding		
Inpatient Management	$16,294.94 ($12,223.20 $20,366.67)	Cryer et al[213]
Outpatient Management	$5037.34 ($3,778.01 to $6,296.67)	Cryer et al[213]
Peptic Ulcer		
Esophagogastroduodenoscopy	$315 ($256.28 to $373.72)	HCPCS code=43235[214]
PPI for 2 months	$40.4 ($33.0 to $49.2)	Loyd et al.[59]
Test for *Helicobacter Pylori*	$87.12 ($52.49 to $121.75)	HCPCS code=83013[215]
Dyspepsia		
Esophagogastroduodenoscopy	$315 ($256.28 to $373.72)	HCPCS code=43235[214]
PPI for one month	$20.2 ($16.5 to $24.6)	Loyd et al.[59]
Edema		
Diuretics	$4 ($2 to $ 5)	Wal-Mart Prescription Program[176]
Hypertension		
Anti-hypertensive drugs	$40 ($30 to $50)	Wal-Mart Prescription Program[176]
Total Knee Replacement	$11,660 ($5,830 to $17,490)	Robinson et al.[216]

CS=Chondroitin Sulfate; NSAIDs= Non-steroidal anti-inflammatory drugs; PPI=Proton pump inhibitors; SA=Sensitivity analysis
Average length of stay for bleeding=5.56 days[261]

TKR Surgery Costs

Costs of TKR surgery were obtained from the claims records of commercial and Medicare beneficiaries from 61 hospitals in the US.[216] These costs include device costs as well as procedure costs, adjusted for patient age, principal diagnoses (i.e., fracture, osteoarthritis, rheumatoid arthritis, and osteonecrosis), number of comorbidities, discharge destination, and number of in-hospital complications. Table 13 displays the costs of TKR surgery.

Indirect Health Care Costs

To compare the cost-effectiveness of CAM therapies with conventional medicines from patients' perspective, in addition to all of the costs described eariler, we also included indirect health care costs of treating KOA in the analysis (i.e., for examining objectives 3 and 5).

Several studies have previously examined indirect healthcare costs incurred among KOA patients in different countries; however, none of these studies are focused on the US population.[262-267] For the purpose of our analysis, we used indirect healthcare costs estimated by Gupta et al in Canada because: (1) the Canadian healthcare systems was assumed to most closely represent the US system and, (2) authors also reported their findings in terms of US dollars. The annual average indirect healthcare costs were

$13,624.37 (SD±$6,416.7). These indirect healthcare costs include formal and informal productivity lost costs and caregiver time costs.

Effectiveness Measure

Quality-adjusted life-years (QALYs) gained was used as the primary effectiveness measure in our study. Selection of QALYs as the effectiveness measure for our study is based on QALYs' endorsement for "reference case" by the USPCEHM and the NICE of the UK.[34, 45] While using QALY as the effectiveness measure, the assumption of the decision-makers objective of maximizing the health or health improvements across the population subject to resource constraints is made.

Health Utilities

Treatment Success, Respondents, Non-Respondents, Baseline, and No Treatment

Health utilities for all studied therapies (i.e., KOA treatment strategies) related treatment success, response and, non-response were obtained from the GAIT study. However, GAIT study did not collect any preference-based data, which are required to estimate health utilities and, in turn, QALYs. As a result, data from the GAIT study could not be directly converted into health utilities. Nonetheless, the short form (SF)-36, which is a descriptive index, was used in the GAIT study to determine quality-of-life changes among the GAIT study participants. In order to estimate QALYs from GAIT study, SF-36 scores were mapped on SF-6 Dimensions (SF-6D), which is a preference-based quality-of-life instrument. These SF-6D scores were then converted into health utilities from which QALYs were estimated.

More specifically, in the first step Brazier's index was used to map SF-36 scores on SF-6D based preference-scores, thus estimating the patient-level health utility values among the GAIT participants.[172] In the second step, using the health utility values obtained from the above procedure, QALYs gained were estimated among the GAIT study participants.[34, 268] In sensitivity analysis, these health utilities were varied by ±25% to account for uncertainty in the parameters, as described later in this chapter.[243]

Several studies have previously mapped the descriptive SF-36 questionnaire on to the preference-based measurements. Some examples include mapping SF-36 on to the quality of well-being index,[269] EuroQol-5D (EQ-5D),[270] Health Utility Index (HUI),[271] and Short Form-6 Dimensions (SF-6D).[172] The published algorithm of converting SF-36

scores to SF-6D based health utilities was utilized in this study.[172] This was because a recent study comparing multiple algorithms to convert SF-36 scores to preference-based scores concluded Brazier's index to have the strongest methodological and theoretical basis among all other conversion algorithms.[171]

Brazier et al. derived preference-based measure of health (i.e., health utilities) from the SF-36 instrument for use in economic evaluations.[172] A sample of 249 states from the SF-6D was valued by a representative sample of the UK's national population and mapped to the preference-based measures through standard gamble approach.[173] A trained and experienced interviewer conducted the interviews in the respondent's own home. Each respondent was asked to rank, and then value, six of the 249 sample SF-6D states using a variant of the standard gamble technique. Several exploratory models (mean and individual-level) were tested with the aim to construct model to predict health states valuations based on the SF-6D. Appendix 3 displays the ordinary least squares (OLS), random error, mean, and median models tested in the study. Appendix 3 also displays the random error model and mean model with intercept forced to unity, as recommended for estimating health utility values. Appendix 4 displays the random error and mean models, with and without forcing intercept to unity. Based on the evaluation of predictive ability of these models, Brazier and colleagues recommend using the mean model with interaction effects that has the intercept forced to unity for the purpose of estimating health utilities.

The following equation summarizes this aforementioned recommended mean model:

$$\textit{Health utility scores} = 1 + (\textbf{-0.053})\, PF2_i + (\textbf{-0.011})PF3 + (\textbf{-0.040})PF4 + (\textbf{-0.054})PF5 + (\textbf{-0.111})PF6 + (\textbf{-0.053})RL2 + (\textbf{-0.055})RL3 + (\textbf{-0.050})RL4 + (\textbf{-0.055})SF2 + (\textbf{-0.067})SF3 + (\textbf{-0.070})SF4 + (\textbf{-0.087})SF5 + (\textbf{-0.047})PAIN2 + (\textbf{-0.025})PAIN3 + (\textbf{-0.056})PAIN4 + (\textbf{-0.091})PAIN5 + (\textbf{-0.167})PAIN6 + (\textbf{-0.049})MH2 + (\textbf{-0.042})MH3 + (\textbf{-0.109})MH4 + (\textbf{-0.128})MH5 + (\textbf{-0.086})VIT2 + (\textbf{-0.061})VIT3 + (\textbf{-0.054})VIT4 + (\textbf{-0.091})VIT5 + error$$

Where,

PF=Physical Functioning

RL=Role Limitation

SF=Social Functioning

Pain=Bodily Pain

MH=Mental health, and

VH=Vitality

There were no significant differences ($p<0.05$) in baseline SF-36 scores between glucosamine, CS, their combination, celecoxib, and placebo groups;[21] therefore, an overall baseline mean utility score, rather than differential means for each study comparator, was used to populate the decision-analytic model for the purpose of our analysis. Table 14 displays the mean health utility scores for baseline, treatment success, and no treatment groups.

Table 14: Health Utility Values For Study Comparators Related Health States.

Health State	Utility Value (SA Range)	Data Source
Baseline*	0.65 (0.49 to 0.81)	GAIT study at baseline
Responders*		
At 24-Weeks	0.70 (0.52 to 0.87)	GAIT study 24-weeks outcomes
At 2-Years	0.71 (0.53 to 0.89)	GAIT study 2-years outcomes
Non-Responders*		
At 24-Weeks	0.64 (0.48 to 0.80)	GAIT study 24-weeks outcomes
At 2-Years	0.64 (0.48 to 0.80)	GAIT study 2-years outcomes
Annual Treatment Success┼	0.70 (0.54 to 0.86)	GAIT study 1-year outcomes
No Treatment┼	0.65 (0.51 to 0.79)	GAIT study 1-year outcomes

*=For decision-tree model
┼=For Markov model
GAIT=Glucosamine/chondroitin sulfate Arthritis Intervention Trial; SA=Sensitivity analysis

Adverse Events

Health utility values for adverse event health states to populate the Markov cohort model were obtained from the published literature (Table 15). All base case health utility values were varied by ±25% in the sensitivity analysis to account for parameter uncertainty.[243]

Separate health utility values were used for year one and thereafter for stroke and myocardial infarction.[218, 219, 223]

Table 15: Model Inputs for Health Utility Values of Adverse Events.

Health State	Utility Value; Base Case (SA Range)	Reference
Heart Failure	0.66 (0.58 to 0.75)	Miller et al.[217]
Stroke		Pickard et al.[223]
First Year	0.31 (0.16 to 0.46)	
Subsequent Years	0.62 (0.31 to 0.93)	
Myocardial Infarction		
First Year	0.37 (0.28 to 0.46)	Squires et al.[218]
Subsequent Years	0.91 (0.68 to 1.00)	Crespin et al.[219]
GI Bleeding	0.46 (0.34 to 0.57)	Maetzel et al.[63]
Peptic Ulcer	0.55 (0.41 to 0.69)	Maetzel et al.[63]
Dyspepsia	0.73 (0.55 to 0.91)	Maetzel et al.[63]
Edema	0.98 (0.74 to 1.00)	Revicki et al.[220]
Hypertension	0.96 (0.72 to 1.00)	Mclntyre et al.[221]
Inpatient Treatment of Bleeding	0.31 (0.23 to 0.39)	Moore et al.[222]
Outpatient Treatment of Bleeding	0.38 (0.28 to 0.47)	Moore et al.[222]
Surgery Given Inpatient Treatment of Bleeding	0.20 (0.15 to 0.25)	Moore et al.[222]

GAIT= Glucosamine/chondroitin sulfate Arthritis Intervention Trial; GI=Gastrointestinal; KOA=Knee osteoarthritis; SA=Sensitivity analysis

TKR Surgery

Health utility values for TKR surgery were obtained from a large randomized clinical trial (n=2352 participants).[224, 272, 273] These health utility values differed from each other based on the number of years a KOA patient has spent in the post TKR surgery health state. All base case health utility values were varied by ±25% in the sensitivity analysis to account for parameter uncertainty.[243] Table 16 displays values of health utilities used in the Markov cohort model.

Table 16: Model Inputs for Health Utility Values.

Total Knee Replacement	Utility Value (SA Range)	Reference
After 1 year	0.71 (0.53 to 0.88)	224, 272, 273
After 2 years	0.68 (0.51 to 0.85)	224, 272, 273
After 3 years	0.66 (0.49 to 0.82)	224, 272, 273
After 4 years	0.63 (0.47 to 0.79)	224, 272, 273
After 5 or more years	0.61 (0.46 to 0.76)	224, 272, 273

GI=Gastrointestinal; KOA=Knee osteoarthritis; SA=Sensitivity analysis

Transition Probabilities and Event Rates

Treatment Success, Response, and No Response

Transition probabilities for treatment success health state in the Markov model and event rates for response and no response branches in our decision-tree model were based on the drug efficacies data obtained from the GAIT study.[33, 174] Specifically, transition probabilities for treatment success to populate the Markov model were based on 1-year outcomes on WOMAC pain sub-scale as found in the GAIT study, as described earlier in this chapter. Similarly, event rates for 24-weeks and 2-year time-horizon decision-tree models were based on the WOMAC pain-subscale outcomes during the respective GAIT study time-periods.

The treatment success for the Markov model and response/non-response for the decision-tree model were defined as at least 20% reduction in WOMAC pain sub-scale scores from baseline at 24-weeks, 1-year, and 2-years respectively for 24-weeks, 10-year (1 year Markov cycles), and 2-year time-horizons decision-analytic models. This definition is same as was used for the primary outcome measure in the GAIT study.[24, 33, 174]

Table 17 displays the transition probabilities for the Markov cohort model. With rationale of utilizing the best available data source for population the models, 1-year, not 24-weeks, GAIT data were used reflecting longer-term efficacies of all KOA treatment strategies in the Markov model. Separate transition probabilities were used for overall KOA patients group, KOA patients with mild pain, and KOA patients with moderate to severe pain at the baseline. Mild pain was defined as baseline WOMAC pain sub-scale

score of 125 to 300. Similarly, moderate to severe pain was defined as baseline WOMAC pain sub-scale score of 301 to 400.

Table 17: Markov Model Transition Probabilities For Treatment Success.

Study Comparators	Annual Transition Probability; Base case* (SA Range)	References
Overall KOA Patients		
Celecoxib	0.4584 (0.4446 to 0.4784)	GAIT study[33, 174]
NSAIDs	0.4584 (0.4446 to 0.4784)	Latimer et al.[247]
Glucosamine	0.4509 (0.4421 to 0.4762)	GAIT study[33, 174]
CS	0.4393 (0.4340 to 0.4567)	GAIT study[33, 174]
Glucosamine+ CS	0.4560 (0.4526 to 0.4729)	GAIT study[33, 174]
KOA Patients with Mild Pain[┼]		
Celecoxib	0.4615 (0.4481 to 0.4788)	GAIT study[33, 174]
NSAIDs	0.4615 (0.4481 to 0.4788)	Latimer et al.[247]
Glucosamine	0.4529 (0.4440 to 0.4768)	GAIT study[33, 174]
CS	0.4395 (0.4350 to 0.4611)	GAIT study[33, 174]
Glucosamine+ CS	0.4399 (0.4376 to 0.4578)	GAIT study[33, 174]
KOA Patients with Moderate to Severe Pain[‡]		
Celecoxib	0.4451 (0.4297 to 0.4747)	GAIT study[33, 174]
NSAIDs	0.4451 (0.4297 to 0.4747)	Latimer et al.[247]
Glucosamine	0.4399 (0.4318 to 0.4715)	GAIT study[33, 174]
CS	0.4387 (0.4307 to 0.4543)	GAIT study[33, 174]
Glucosamine+ CS	0.5124 (0.5050 to 0.5260)	GAIT study[33, 174]

*=based on change in WOMAC pain-subscale scores improvement from baseline at 1-year: base case=20% (range=12% to 22%) in the GAIT study[24, 33, 174, 274]

┼=Mild pain stratum is defined as baseline WOMAC pain subscale score of 125 to 300.[174]

‡= Moderate to severe pain stratum is defined as baseline WOMAC pain subscale score of 301 to 400.[174]

CS=Chondroitin Sulfate; GAIT= Glucosamine/chondroitin sulfate Arthritis Intervention Trial; KOA=Knee osteoarthritis; nsNSAIDs= non-steroidal anti-inflammatory drugs; SA=Sensitivity analysis

Table 18 shows the response rates for the 24-week time-horizon study, to populate the decision-tree model. Different response rates were used for the compliant and non-compliant KOA patients in the decision-tree model. For the purpose of estimating response rates, patients were defined as compliant if they were adherent to their study medications 80% to 110% of the times during the study period.[275] Similar to

the Markov model, separate rates of response were used for overall KOA patient group, KOA patients with mild pain, and KOA patients with moderate to severe pain.

Table 18: Decision-Tree Model Rates for Study Comparators from 24-week Time-Horizon.

Study Comparators	**Response Rates* (SA Range)**		
	Overall KOA Patients	*KOA Patients with Mild Pain*┼	*Mild to Moderate Pain KOA Patient* ‡
Celecoxib			
Compliant	78.17% (75.13% to 82.74%)	77.07% (74.52% to 80.89%)	82.50% (77.50% to 90.00%)
Non-Compliant	53.68% (51.58% to 57.89%)	56.72% (53.73% to 61.19%)	44.44% (44.44% to 48.15%)
Glucosamine			
Compliant	78.95% (77.19% to 81.29%)	75.56% (74.07% to 78.52%)	91.43% (88.57% to 91.43%)
Non-Compliant	46.13% (45.54% to 49.11%)	50.00% (50.00% to 52.33%)	34.62% (30.77% to 38.46%)
CS			
Compliant	71.43% (71.43% to 78.57%)	72.66% (72.66% to 79.14%)	65.52% (65.52% to 75.86%)
Non-Compliant	51.28% (50.43% to 52.99%)	50.56% (49.44% to 51.69%)	53.57% (53.57% to 57.14%)
Glucosamine + CS			
Compliant	70.00% (69.44% to 75.56%)	64.75% (64.75% to 69.78%)	87.80% (85.37% to 95.12%)
Non-Compliant	56.19% (55.24% to 60.95%)	51.81% (51.81% to 55.42%)	72.73% (68.18% to 81.82%)
Placebo			
Compliant	69.89% (69.89% to 76.34%)	72.79% (72.79% to 77.55%)	58.97% (58.97% to 71.79%)
Non-Compliant	40.00% (37.78% to 45.56%)	39.44% (38.03% to 45.07%)	44.44% (38.89% to 50.00%)

*=based on change in WOMAC pain-subscale scores changes between baseline and 24 weeks: base case=20% (range=12% to 22%) in the GAIT study[24, 33, 174, 274]
┼=Mild pain is defined as baseline WOMAC pain subscale score of 125 to 300.[174]
‡= Moderate to severe pain is defined as baseline WOMAC pain subscale score of 301 to 400.[174]
CS=Chondroitin Sulfate; KOA=Knee osteoarthritis; nsNSAIDs=NSAIDs non-steroidal anti-inflammatory drugs; SA=Sensitivity analysis

The response rates for all study comparators, stratified by compliance/non-compliance and pain stratum, from 2-year time-horizon are displayed in Table 19.

Table 19: Decision-Tree Model Rates for Study Comparators from 2-Year Time-Horizon.

Study Comparators	**Response Rates* (SA Range)**		
	Overall KOA Patients	*KOA Patients with Mild Pain*┼	*KOA Patients with Mild to Moderate Pain*‡
Celecoxib			
Compliant	62.64% (61.54% to 65.93%)	57.33% (56.00% to 61.33%)	87.50% (87.50% to 87.50%)
Non-Compliant	50.00% (50.00% to 50.00%)	62.50% (62.50% to 62.50%)	16.67%§ (16.67% to 16.67%)
Glucosamine			
Compliant	77.14% (77.14% to 78.57%)	80.00% (80.00% to 81.82%)	66.67% (66.67% to 66.67%)
Non-Compliant	59.26% (55.56% to 59.26%)	68.18% (63.64% to 68.18%)	20.00%§ (20.00% to 20.00%)
CS			
Compliant	64.29% (61.43% to 64.29%)	65.00% (61.67% to 65.00%)	60.00% (60.00% to 60.00%)
Non-Compliant	41.67% (41.67% to 50.00%)	43.75% (43.75% to 56.25%)	37.50%§ (37.50% to 37.50%)
Glucosamine + CS			
Compliant	54.24% (50.85% to 61.02%)	54.76% (52.38% to 61.90%)	52.94% (47.06% to 58.82%)
Non-Compliant	34.48% (34.48% to 34.48%)	33.33% (33.33% to 33.33%)	40.00%§ (40.00% to 40.00%)
Placebo			
Compliant	62.16% (60.81% to 62.16%)	59.32% (57.63% to 59.32%)	73.33% (73.33% to 73.33%)
Non-Compliant	54.17% (54.17% to 54.17%)	52.63% (52.63% to 52.63%)	75.00%§ (75.00% to 75.00%)

*=based on change in WOMAC pain-subscale scores changes between baseline and 24 weeks: base case=20% (range=12% to 22%) in the GAIT study[24, 33, 174, 274]

┼=Mild pain stratum is defined as baseline WOMAC pain subscale score of 125 to 300.[174]

‡= Moderate to severe pain stratum is defined as baseline WOMAC pain subscale score of 301 to 400.[174]

§=Cell count is less than 5

CS=Chondroitin Sulfate; KOA=Knee osteoarthritis; NSAIDs= non-steroidal anti-inflammatory drugs; SA=Sensitivity analysis

Adverse Events

PubMed literature searches were conducted to obtain transition probabilities for adverse events for populating the Markov model. Based on these searches, data sources for transition probabilities of adverse events associated with NSAIDs and celecoxib included large clinical trials such as Celecoxib Long-term Arthritis Safety Study (CLASS), Multinational Etoricoxib Versus Diclofenac Arthritis Long-Term Study (MEDAL) study, and MONItor trends in CArdiovascular disease (MONICA) study and large prospective cohort studies like the Framingham Heart Study.[195-198, 239]

Modeled adverse events include risk of serious cardiovascular (i.e., heart failure, stroke, myocardial infarction, and hypertension) and GI (peptic ulcer, GI bleeding, and dyspepsia) adverse events associated with NSAIDs and celecoxib. All KOA patients on celecoxib or NSAIDs experiencing any adverse event except for hypertension and dyspepsia were modeled to discontinue their medications.

Patients experiencing GI bleeding adverse events were modeled to be treated in either outpatient or inpatient settings.[179-184] If hospitalized, the patients were modeled to undergo surgery to manage a GI bleeding event, based on the published rates of surgery for GI bleeding after hospitalization.[63] The risk of GI bleeding was modeled to increase with age, based on the reviewed literature.[204, 205, 207, 276-278]

Increased risk of mortality after an event of GI bleeding, heart failure, stroke, or myocardial infarction was incorporated in the model, based on the published literature.[185-193, 195, 196, 239]

Table 20: Transition Probabilities of Adverse Events.

Model Inputs for Adverse Events	Annual Transition Probability; Base case (SA Range)	Reference
Heart Failure		
Celecoxib	0.0044 (0.0032 to 0.0058)*	MEDAL study[197]
NSAIDs	0.0026 (0.0017 to 0.0037)	MEDAL study[197]
Stroke		
Celecoxib	0.0100 (0.0087 to 0.0112)	CLASS study[198]
NSAIDs	0.0296 (0.0259 to 0.0332)	CLASS study[198]
Myocardial Infarction		
Celecoxib	0.0112 (0.0084 to 0.0140)	Caldwell et al.[199]
NSAIDs	0.0129 (0.0097 to 0.0161)	Rodirguez et al.[200]
GI Bleeding		
Celecoxib	0.0134 (0.0075 to 0.0221)	CLASS study[201]
NSAIDs	0.0270 (0.0216 t0 0.0334)	CLASS study[201]
Peptic Ulcer		
Celecoxib	0.0082 (0.0048 to 0.0114)	[202-208]
NSAIDs	0.0106 (0.0048 to 0.0159)	[202-208]
Dyspepsia		
Celecoxib	0.0463 (0.0420 to 0.0506)*	MEDAL study[197]
NSAIDs	0.0704 (0.0650 to 0.0759)	MEDAL study[197]
Edema		
Celecoxib	0.0106 (0.0086 to 0.0127)*	MEDAL study[197]
NSAIDs	0.0070 (0.0054 to 0.0088)	MEDAL study[197]
Hypertension		
Celecoxib	0.0229 (0.0200 to 0.0260)*	MEDAL study[197]
NSAIDs	0.0153 (0.0129 to 0.0179)	MEDAL study[197]
Age-related increased risk of Bleeding/year	0.0421 (0.0247 to 0.0592)	[204, 205, 207, 276-278]
Hospitalization rate for bleeding	0.5934 (0.5507 to 0.6321)	[179-184]
Surgery after hospitalization for bleeding	0.0815 (0.0392 to 0.3002)	Maetzel et al.[63]
Mortality for GI bleeding	0.0769	[185-193]
Mortality for post heart failure	0.3750	Framingham Heart Study[239]
Mortality for post myocardial infarction	0.0344	Framingham Heart Study[195]
Mortality post stroke	0.3363	MONICA study[196]

Adverse event rates for glucosamine, chondroitin sulfate, and their combination therapy are assumed to be zero in the model, based on previously published meta-analyses and analysis of the Food and Drug Administration's Adverse Event Reporting System database.

*=Transition probabilities for celecoxib were based on events rates for Etoricoxib

CLASS=Celecoxib Long-term Arthritis Safety Study; MEDAL= Multinational Etoricoxib Versus Diclofenac Arthritis Long-Term Study; MONICA=MONItor trends in CArdiovascular disease; NSAIDs= Non-Steroidal Anti-inflammatory Drugs; SA=Sensitivity Analysis

No risk of serious adverse events associated with CAM therapies were incorporated in the Markov model based on evidence from the following two sources:

1. Food and Drug Administration Adverse Event Reporting System (FAERS) database

The FDA's post-marketing safety surveillance program plays a crucial role in identifying the safety problems associated with a drug after its market launch. One of the main tools employed by the FDA to support this surveillance program is MedWatch that consists of voluntarily reported adverse drug reactions to the FDA by patients, health professionals, pharmaceutical manufacturers, and other such sources.[279, 280] The FAERS is the electronic database that summarizes these adverse events MedWatch reports.[279, 281] This FAERS database is updated quarterly and more than 300,000 MedWatch cases are currently added each year.

We searched the FAERS database for glucosamine or CS associated adverse events reported to the FDA. Specifically, the World Health Organization (WHO) drug dictionary based preferred and trade names of glucosamine, CS, and combination of glucosamine and CS were searched separately in the FAERS to review reports of serious adverse events associated with these agents. The list of the trade and preferred names of these CAM therapies searched in the FAERS is displayed in Table 21.

Table 21: Search Terms Used in FAERS

Search Terms in FAERS	Term Type
Glucosamine only	
Terrastatin (glucosamine hydrochloride, nystatin, oxytetracycline)	Preferred
Osteoeze bone & joint care (calcium carbonate, glucosamine hydrochloride, phytomenadione, vitamin D NOS)	Preferred
Glucosamine with methylsulfonylmethane (glucosamine, methylsulfonylmethane)	Preferred
Glucosamine with methylsulfonylmethane	Trade
Glucosamine sulfate with chondroitin	Trade
Glucosamine sulfate sodium chloride	Preferred
Glucosamine sulfate potassium chloride	Preferred
Glucosamine sulfate	Preferred
Glucosamine hydrochloride	Preferred
Glucosamine (cod-liver oil, glucosamine, minerals NOS, salmon oil, vitamins NOS)	Preferred
Glucosamine	Preferred
Dona 200 tablet (glucosamine hydroiodide, glucosamine sulfate)	Preferred
Dona (glucosamine sulfate)	Trade
Arthryl (acetyl-glucosamine, diethanolamine, sodium sulfate)	Preferred
Arthrochoice (glucosamine, minerals NOS, vitamins NOS)	Preferred
Aflexa (glucosamine hydrochloride, glucosamine sulfate)	Preferred
CS only	
Kashiwadol (chondroitin sulfate sodium, salicylate sodium)	Preferred
Chondroitin sulfate sodium	Preferred
Chondroitin sulfate	Preferred
Chloroquine chondroitin sulfate	Preferred
Blutal (chondroitin sulfate sodium, ferric chloride)	Preferred
Combination of Glucosamine and CS	
Osteo bi-flex (chondroitin sulfate, glucosamine hydrochloride)	Preferred
Joint food (chondroitin sulfate, glucosamine sulfate)	Preferred
Glucosamine with chondroitin sulfate (chondroitin sulfate, glucosamine)	Preferred
Glucosamine with chondroitin sulfate/magnesium/vitamin C (ascorbic acid, chondroitin sulfate, glucosamine sulfate, manganese)	Preferred
Glucosamine with chondroitin sulfate/ magnesium/vitamin C	Trade
Glucosamine with chondroitin (chondroitin sulfate, glucosamine)	Preferred
Glucosamine sulfate w/chondroitin	Trade
Flex-a-min (chondroitin sulfate, glucosamine sulfate, methylsulfonylmethane)	Preferred
Cosamin ds (ascorbic acid, chondroitin sulfate sodium, glucosamine hydrochloride, manganese ascorbate)	Preferred

Search Terms in FAERS	Term Type
Cosamin (chondroitin sulfate, glucosamine hydrochloride, manganese ascorbate)	Preferred
Chondroitin with glucosamine (chondroitin, glucosamine)	Preferred
Chondroitin sodium sulfate with glucosamine HCL (chondroitin sulfate sodium, glucosamine hydrochloride)	Preferred
Chondroitin sodium sulfate with glucosamine HCL	Trade
Blackmores joint glucosamine, chondroitin (chondroitin sulfate sodium, glucosamine hydrochloride, manganese gluconate, sodium borate decahydrate)	Preferred

CS=Chondroitin Sulfate; FAERS=Food and Drug Administration Adverse Event Reporting System; NOS=Not otherwise specified

Based on the analysis of the FAERS described above, no serious cardiovascular or GI adverse events were found to be associated with glucosamine, CS, or their combination therapies.

2. *Meta-analyses of previously conducted clinical trials of one or more of glucosamine and CS.*[25, 29]

A recent meta-analysis of ten randomized clinical trials with a total sample size of 3803 patients reported no significantly higher risk of serious adverse events associated with glucosamine, CS, or their combination therapies among the KOA patients.[25] Similar findings were reported in a previously published-meta-analysis study.[29]

Based on the evidence from the above described two sources, we assumed no risk of serious cardiovascular and GI adverse events associated with CAM therapies in the Markov cohort model.

TKR Surgery

Transition probabilities for TKR surgery were obtained from on a large US joint replacement registry of Kaiser Permanente.[282] These transition probabilities for TKR surgery vary by age and gender, as displayed in Table 22.

Table 22: Total Knee Replacement Surgery Rates in the US.

Age Group	Males (95% CI)	Females (95 % CI)
50 to 64 years	6.4% (3.0% to 9.7%)	8.1% (4.5% to 11.8%)
65 to 84 years	11.9% (6.7% to 17.0%)	10.9% (6.5% to 15.3%)
85 or more years	3.0% (1.7% to 4.3%)	2.7% (1.6% to 3.8%)

CI=Confidence interval

Death Rates

KOA patients were modeled to die either because of adverse events (i.e., health failure, stroke, myocardial infarction, and GI bleeding) or aging. The transition probabilities for death due to adverse events were obtained from multiple literature sources and are displayed in Table 20. The transition probabilities for death due to aging were obtained from the National Vital Statistics Reports US life-tables.[240] These transition probabilities for death due to aging are shown in Table 23.

Table 23: Model Inputs for Age-Specific Mortality Rates, Based on US Life-tables.[240]

Age (in years)	Annual Probability of Death
50	0.004337
51	0.004709
52	0.005091
53	0.005474
54	0.005863
55	0.006275
56	0.006726
57	0.007220
58	0.007773
59	0.008389
60	0.009081

Sensitivity Analysis

Parameter Sensitivity Analysis

We performed both one-way sensitivity analysis and probabilistic sensitivity analysis on all modeling parameters. These parameters include costs, drug efficacies, health utilities, adverse events probabilities, TKR surgery rates, medication compliance rates, and discounting rates (for study of first objective). The sensitivity analysis ranges for all of these parameters are listed in tables in earlier sections of this chapter.

Probabilistic sensitivity analysis (second-order Monte Carlo simulation) was also performed to account for the parameter uncertainty in the decision-tree model inputs. The parameter distributions used for conducting probabilistic sensitivity analysis are displayed in Table 24.

Table 24: Parameters Distributions Used in PSA.

Type of Parameter	Type of Distribution
Transition Probabilities	Beta
Costs	Gamma
Health Utilities	Beta
Compliance	Log-normal
Discount Rate	Uniform

PSA=Probabilistic Sensitivity analysis.

The base case definition of treatment success in the Markov model and response rate in the decision-tree model was at least 20% reduction on WOMAC pain sub-scale from the baseline. In sensitivity analysis, this definition was varied from treatment success/response being 12% to 22% reduction in WOMAC pain sub-scale from the baseline. This variation is based on a prospective cohort study that estimated minimal

clinically important differences (MCID) of effects measured by the WOMAC in patients with osteoarthritis of the lower extremities.[274]

All health utility values and adverse event probabilities were varied by ±25% from the base case in the sensitivity analysis to account for parameter uncertainties arising due to factors such as differences in patient populations and in methods and instruments of measurements. These variations of ±25% from baseline are as per the good practices recommendations of the International Society for Pharmacoeconomics and Outcomes Research-Society for Medical Decision Making (ISPOR-SMDM) modeling task force.[243]

Rates for TKR surgery were varied per the 95% confidence interval reported in the findings from the analysis based on a large US joint replacement registry of the Kaiser Permanente.[283] The base case medication compliance rate of 75% in the decision-tree model was varied from 50% (poor compliance) to 100% (excellent compliance) in the sensitivity analysis. The base case discounting rate of 3% was varied from 0% to 5%.[34]

Structural Sensitivity Analysis

In addition to performing the parameter sensitivity analysis, structural sensitivity analysis was performed to account for the robustness of assumption of no risk of adverse events associated with CAM therapies. In this regard, ICERs were estimated by excluding all drug associated adverse events from the 10-year Markov models, thereby leaving both CAM therapies and conventional medicines without any risk of adverse events.

CHAPTER 4: RESULTS

This chapter is divided into seven sections, describing results for objectives 1 to 5 of this study (one objective per section) and results for the structural sensitivity analysis. Sections 1 to 5 are further divided into three sub-sections each providing study findings for KOA patients: (1) overall, (2) with mild baseline pain (defined by WOMAC pain subscale being between 150 and 300), and (3) with moderate to severe baseline pain (defined by WOMAC pain subscale being between 301 and 400). Finally, this chapter is concluded by a summary of findings section.

Section 1: Findings for Study Objective 1:

The first objective of our study was to compare the incremental cost-effectiveness of CAM therapies (i.e., glucosamine, CS, and their combination therapy) with conventional medicines (i.e., celecoxib and NSAIDs) to treat KOA from the US health care payers' perspective and 10-years horizon of the patients, through a Markov model based analysis. Tables 25 to 30 display results for cost-effectiveness comparison of CAM therapies with conventional medicines among different study groups of KOA patients.

Cost-Effectiveness of CAM Therapies vs. Conventional Medicines among Overall KOA Patients Group

Table 25 displays the base case results for incremental cost-effectiveness of CAM therapies and conventional medicines among the overall KOA patients group (i.e., KOA patients with baseline WOMAC pain sub-scale scores between 150 and 400) from US health care payers' perspective and 10-year time-horizon. In general, CAM therapies were found to be cost-effective than conventional medicines in treating KOA.

Specifically, while both NSAIDs and celecoxib were dominated by CS in treating KOA from the US health care payers' perspective and 10-year time-horizon; the incremental cost-effectiveness of glucosamine, in comparison to CS, was found to be $120,367.90/QALY gained.

CS alone therapy was used as the reference group in our analysis based on the recommendations of the USPCEHM—this panel recommends using that strategy as the reference group which has the lowest total costs (i.e., CS alone therapy in our analysis).[34] In this analysis, the absolute value of the cost-effectiveness of CS alone therapy was found to be $1,332.32/QALY gained.

Table 25: Base Case Results for Cost-Effectiveness Analysis in Overall KOA Patients Group from US Health care Payers' Perspective and 10-year Time-Horizon, with Chondroitin Sulfate as the Reference Group.

Study Comparator	Total Cost	Total QALYs gained┼	Incremental Cost	Incremental QALYs gained	ICER (Cost/QALY gained)
CS	$7,571	5.6833			
Glucosamine	$8,033	5.6872	$461	0.0038	$120,367
Glucosamine + CS	$9,719	5.6877	$1,686	0.0005	$3,250,047
Celecoxib	$19,759	4.8567	$10,040	-0.8310	-$12,083*
NSAIDs	$21,274	4.7765	$11,555	-0.9112	-$12,682*

*=Dominated therapies
┼=All QALYs are based on SF-6D based health utilities mapped from SF-36
CS=Chondroitin Sulfate; ICER=Incremental cost-effectiveness ratio; NSAIDs= Non-steroidal anti-inflammatory drugs; QALYs=Quality-adjusted life-years

Sensitivity Analysis

In one-way sensitivity analysis, the following parameters were found to impact the expected value of the cost-effectiveness model: discount rate; utilities of treatment success, no response, and TKR surgery at baseline; transition probability of TKR surgery, response to CS, and response to glucosamine; and cost of TKR surgery, glucosamine, and CS.

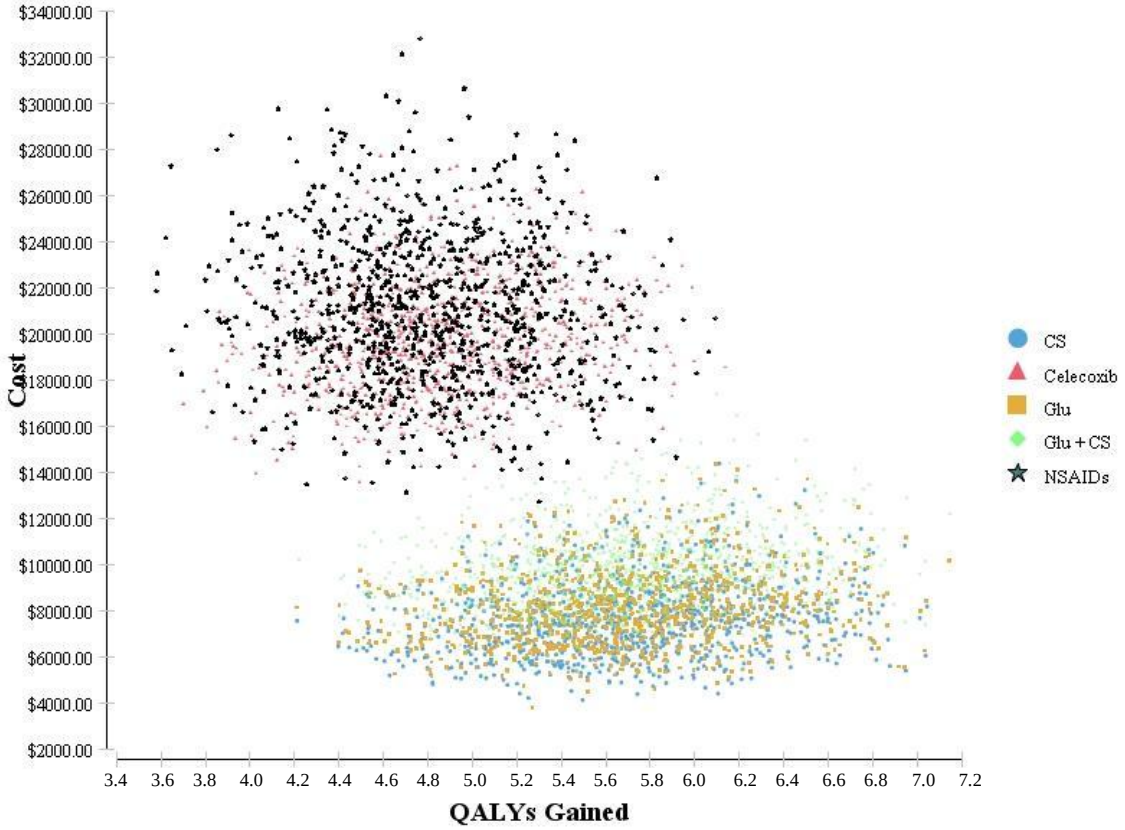
Table 26 displays the detailed results of probabilistic sensitivity analysis on all model inputs and Figure 6 presents its scatter plot based on 10000 second-order Monte Carlo simulations.

Table 26: Probabilistic Sensitivity Analysis Results, in Overall KOA Patients Group from US Health care Payers' Perspective and 10-year Time-Horizon.

	Parameters	**CS**	**Glucosamine**	**Glucosamine + CS**	**NSAIDs**	**Celecoxib**
Cost	*Mean*	$7,598	$8,057	$9,748	$21,026	$19,715
	SD	$1,607	$1,612	$1,679	$3,136	$2,306
	Min	$3,174	$3,588	$5,246	$11,144	$11,160
	2.50%	$4,913	$5,352	$6,883	$15,270	$15,537
	10%	$5,648	$6,114	$7,707	$17,078	$16,849
	Median	$7,440	$7,917	$9,608	$20,892	$19,602
	90%	$9,705	$10,168	$11,962	$25,053	$22,701
	97.50%	$1,120	$11,627	$13,398	$27,658	$24,624
	Max	$15,983	$16,349	$18,067	$38,902	$29,726
QALYs gained┼	*Mean*	5.7070	5.7108	5.7113	4.8067	4.8799
	SD	0.5131	0.5144	0.514498	0.4369	0.4231
	Min	3.9063	3.9075	3.9064	3.3014	3.3411
	2.50%	4.7156	4.7209	4.7193	3.9761	4.0712
	10%	5.0526	5.0533	5.0528	4.2548	4.3425
	Median	5.6973	5.7003	5.7015	4.7954	4.8699
	90%	6.3811	6.3888	6.3854	5.3785	5.4341
	97.50%	6.7147	6.7181	6.7187	5.6910	5.7156
	Max	7.6564	7.6726	7.6702	6.5346	6.4528

┼=All QALYs are based on SF-6D based health utilities mapped from SF-36
CS=Chondroitin Sulfate; NSAIDs= Non-steroidal anti-inflammatory drugs; QALYs=Quality-adjusted life-years

Figure 6: Scatter Plot for Probabilistic Sensitivity Analysis Based on 10000 Simulations, in Overall KOA Patients Group from US Health care Payers' Perspective and 10-year Time-Horizon.

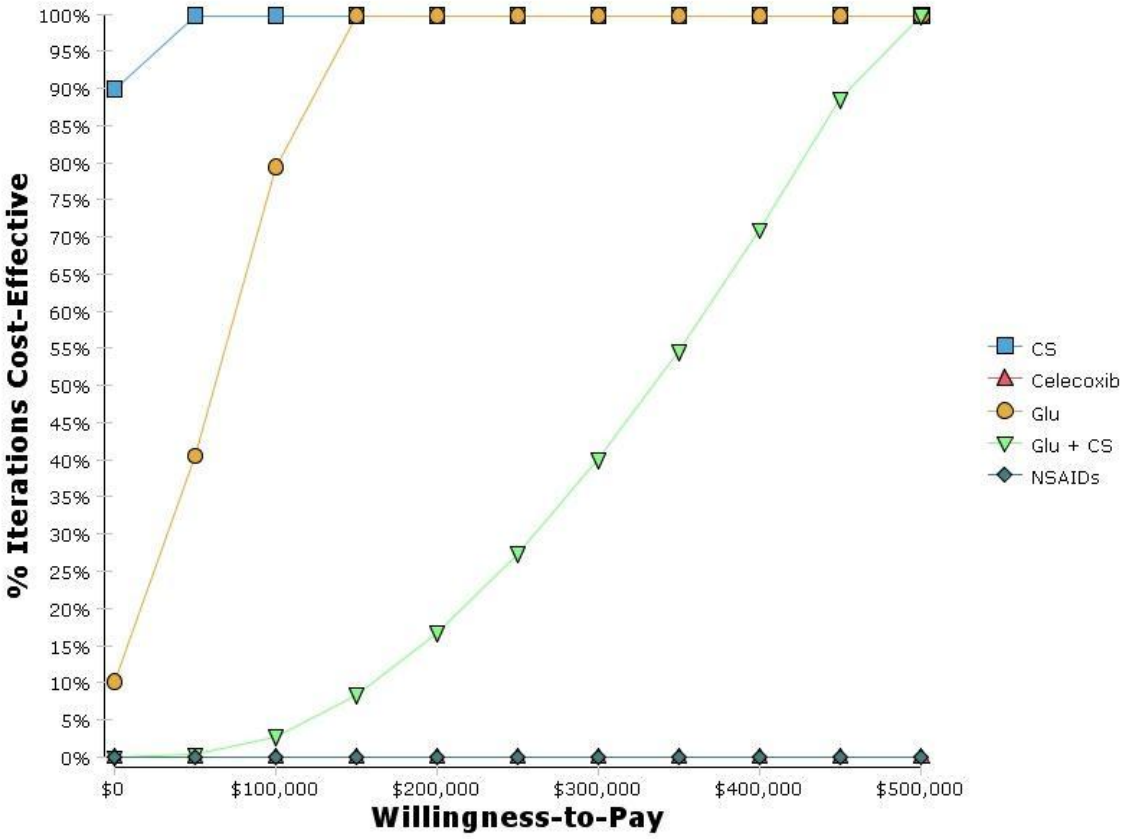


CS=Chondroitin Sulfate; Glu=Glucosamine; Glu + CS=Glucosamine and Chondroitin Sulfate combined therapy; NSAIDs=non-selective Non-Steroidal Anti-Inflammatory Drugs; QALYs=Quality-adjusted life-years

The above scatter plot can be interpreted as follows: the most cost-effective comparator would be one with scatter density towards bottom of the Y-axis (i.e., less expensive) and right hand side from the X-axis (i.e., more effective).

Figure 7 displays the cost-effectiveness acceptability curve for the above described analysis, based on 10,000 simulations and variation of willingness-to-pay from $0 to $500,000 per QALY gained.

Figure 7: Cost-Effectiveness Acceptability Curve, in Overall KOA Patients Group from US Health care Payers' Perspective and 10-year Time-Horizon.



CS=Chondroitin Sulfate; Glu=Glucosamine; Glu + CS=Glucosamine and Chondroitin Sulfate combined therapy; NSAIDs=non-selective Non-Steroidal Anti-Inflammatory Drugs

Cost-Effectiveness of CAM Therapies vs. Conventional Medicines among KOA Patients with Mild Pain

In this sub-group analysis, cost-effectiveness of CAM therapies (i.e., glucosamine, CS, and combination of glucosamine and CS) was compared conventional medicines (i.e., celecoxib and NSAIDs) in the treatment of KOA among those patients that had mild knee pain at the baseline, defined by WOMAC pain sub-scale score of between 150 and 300. The study time-horizon was 10 years and perspective was of the US healthcare payers.

Table 27 displays the base case results for incremental cost-effectiveness of CAM therapies and conventional medicines among the KOA patients group with mild baseline pain from US health care payers' perspective and 10-year time-horizon. In general, CAM therapies were cost-effective than conventional medicines in treating KOA. Specifically, both NSAIDs and celecoxib were dominated by CS in treating KOA from the US health care payers' perspective and 10-year time-horizon. The incremental cost-effectiveness of glucosamine, in comparison to CS, was found to be $86,233.71/QALY gained.

CS alone therapy was used as the reference group in this analysis (reason is described earlier in this chapter) and was found to have the absolute the cost-effectiveness ratio of $1,333.12/QALY gained.

Table 27: Base Case Results for Cost-Effectiveness Analysis, in Mild Pain Only KOA Patients Group from US Health care Payers' Perspective and 10-year Time-Horizon, with Chondroitin Sulfate as the Reference Group.

Study Comparator	Total Cost	Total QALYs gained[┼]	Incremental Cost	Incremental QALYs gained	ICER (Cost/QALY gained)
CS	$7,571	5.6799			
Glucosamine	$8,033	5.6853	$461	0.0053	$86,233
Glucosamine + CS	$9,719	5.6801	$1,686	-0.0052	-$325,005*
Celecoxib	$19,770	4.8560	$11,737	-0.8292	-$14,155*
NSAIDs	$21,301	4.7754	$13,268	-0.9099	-$14,583*

*=Dominated therapies

┼=All QALYs are based on SF-6D based health utilities mapped from SF-36

CS=Chondroitin Sulfate; ICER=Incremental cost-effectiveness ratio; NSAIDs= Non-steroidal anti-inflammatory drugs; QALYs=Quality-adjusted life-years

Sensitivity Analysis

In one-way sensitivity analysis, the following parameters were found to impact the expected value of the cost-effectiveness model: discount rate; utilities of treatment success, no response, and TKR surgery at baseline; transition probability of TKR surgery, response to CS, and response to glucosamine; and cost of TKR surgery, glucosamine, and CS. No other model parameters affect cost-effectiveness ratios.

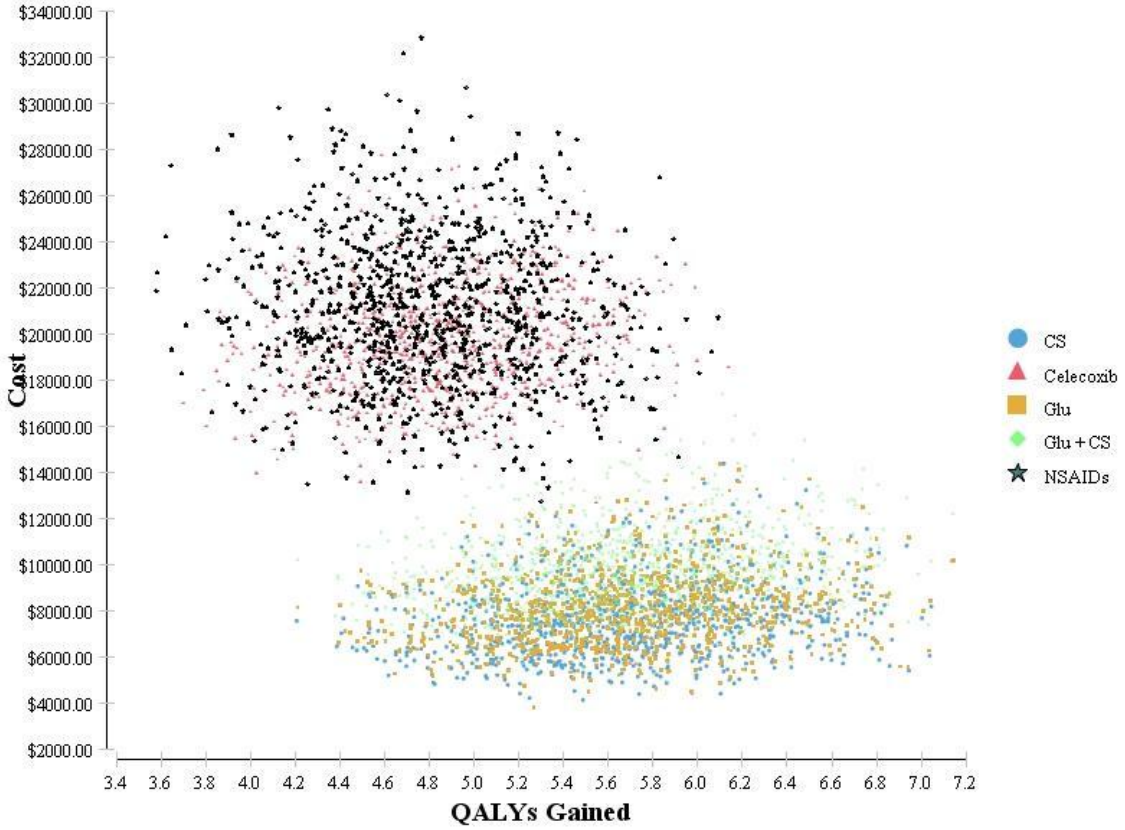
Table 28 displays the detailed results of probabilistic sensitivity analysis on all model inputs and Figure 8 presents its scatter plot based on 10000 second-order Monte Carlo simulations.

Table 28: Probabilistic Sensitivity Analysis Results, in Mild Pain Only KOA Patients Group from US Health care Payers' Perspective and 10-year Time-Horizon.

	Parameters	**CS**	**Glucosamine**	**Glucosamine + CS**	**NSAIDs**	**Celecoxib**
Cost	*Mean*	$7,587	$8,047	$9,740	$21,040	$19,716
	SD	$1,602	$1,608	$1,675	$3,137	$2,302
	Min	$3,174	$3,588	$5,246	$11,169	$12,406
	2.50%	$4,911	$5,349	$6,883	$15,270	$15,543
	10%	$5,644	$6,102	$7,707	$17,084	$16,847
	Median	$7,435	$7,910	$9,599	$20,905	$19,605
	90%	$9,689	$10,154	$11,952	$25,072	$22,701
	97.50%	$11,198	$11,621	$13,390	$27,662	$24,630
	Max	$15,983	$16,349	$18,067	$38,953	$29,745
QALYs gained[┼]	*Mean*	5.7024	5.7078	5.7026	4.8050	4.8785
	SD	0.5134	0.5150	0.5134	0.4381	0.4243
	Min	3.9056	3.9071	3.9048	3.3006	3.3399
	2.50%	4.7095	4.7145	4.7107	3.9712	4.0700
	10%	5.0493	5.0518	5.0505	4.2520	4.3399
	Median	5.6915	5.6972	5.6926	4.7932	4.8685
	90%	6.3780	6.3860	6.3787	5.3782	5.4359
	97.50%	6.7154	6.7200	6.7153	5.6992	5.7162
	Max	7.6477	7.6672	7.6505	6.5334	6.4501

┼=All QALYs are based on SF-6D based health utilities mapped from SF-36
CS=Chondroitin Sulfate; NSAIDs= Non-steroidal anti-inflammatory drugs; QALYs=Quality-adjusted life-years

Figure 8: Scatter Plot for Probabilistic Sensitivity Analysis Based on 10000 Simulations, in Mild Pain Only KOA Patients Group from US Health care Payers' Perspective and 10-year Time-Horizon.

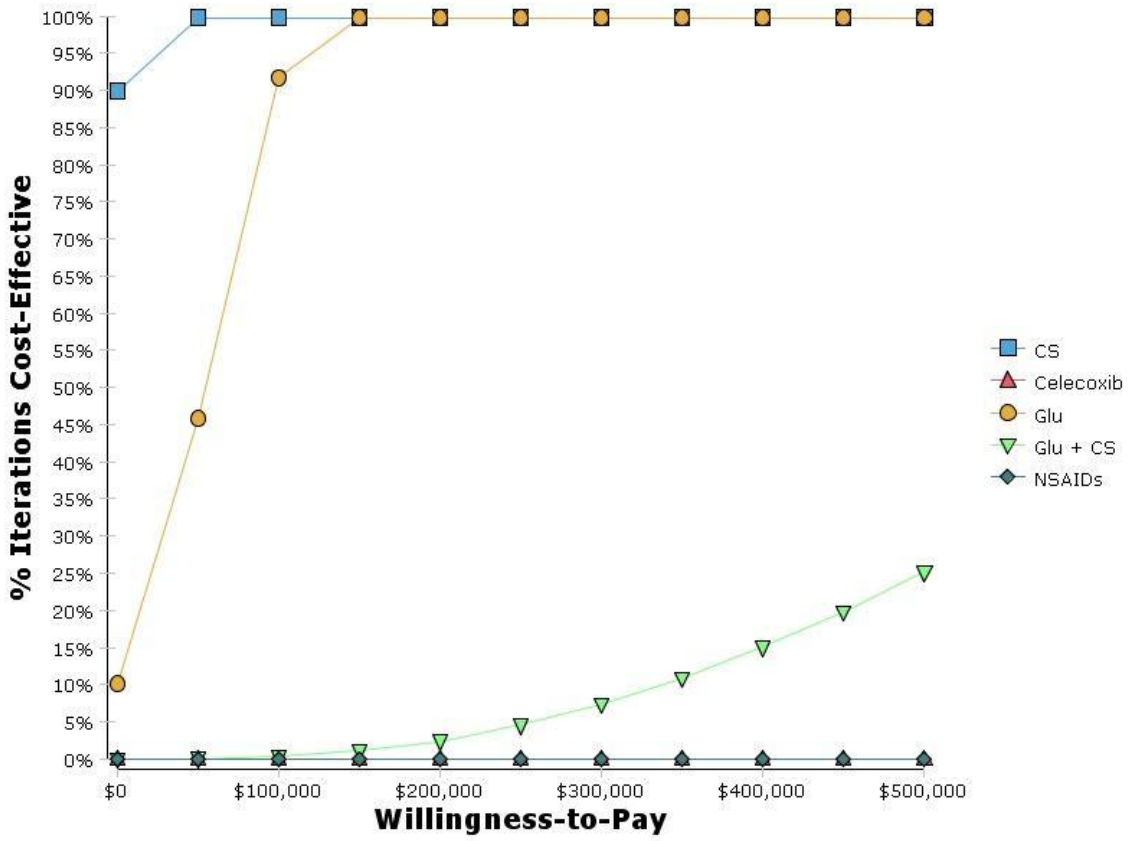


CS=Chondroitin Sulfate; Glu=Glucosamine; Glu + CS=Glucosamine and Chondroitin Sulfate combined therapy; NSAIDs=non-selective Non-Steroidal Anti-Inflammatory Drugs; QALYs=Quality-adjusted life-years

The above scatter plot can be interpreted as follows: the most cost-effective comparator would be one with scatter density towards bottom of the Y-axis (i.e., less expensive) and right hand side from the X-axis (i.e., more effective).

Figure 9 displays the cost-effectiveness acceptability curve for the above described analysis, based on 10,000 simulations and variation of willingness-to-pay from $0 to $500,000 per QALY gained.

Figure 9: Cost-Effectiveness Acceptability Curve, in Mild Pain Only KOA Patients Group from US Health care Payers' Perspective and 10-year Time-Horizon.



CS=Chondroitin Sulfate; Glu=Glucosamine; Glu + CS=Glucosamine and Chondroitin Sulfate combined therapy; NSAIDs=non-selective Non-Steroidal Anti-Inflammatory Drugs

Cost-Effectiveness of CAM Therapies vs. Conventional Medicines among KOA Patients with Moderate to Severe Pain

In this sub-group analysis, cost-effectiveness of CAM therapies (i.e., glucosamine, CS, and combination of glucosamine and CS) was compared conventional medicines (i.e., celecoxib and NSAIDs) in treating KOA among those patients that had moderate to severe knee pain at the baseline defined by WOMAC pain sub-scale score of between 301 and 400. The study time-horizon was 10 years and perspective was of the US healthcare payers'.

Table 29 displays the base case results for incremental cost-effectiveness of CAM therapies and conventional medicines among the KOA patients group with moderate to severe baseline pain from US health care payers' perspective and 10-year time-horizon. In general, CAM therapies were cost-effective than conventional medicines. Specifically, both NSAIDs and celecoxib were dominated by CS in treating KOA from the US health care payers' perspective and 10-year time-horizon. The incremental cost-effectiveness of combination of glucosamine and CS, in comparison to CS, was found to be $73,006.69/QALY gained.

CS alone therapy was used as the reference group in this analysis (reason is described earlier in this chapter) and was found to have the absolute the cost-effectiveness ratio of $1,333.19/QALY gained.

Table 29: Base Case Results for Cost-Effectiveness Analysis, in Moderate to Severe Pain KOA Patients Group from US Health care Payers' Perspective and 10-year Time-Horizon, with Chondroitin Sulfate as the Reference Group.

Study Comparator	Total Cost	Total QALYs gained┼	Incremental Cost	Incremental QALYs gained	ICER (Cost/QALY gained)
CS	$7,572	5.6796			
Glucosamine	$8,033	5.6801	$461	0.0005	$962,943
Glucosamine + CS	$9,719	5.709	$2,147	0.0294	$73,007
Celecoxib	$19,795	4.8545	$10,076	-0.8545	-$11,791*
NSAIDs	$21,363	4.7728	$11,644	-0.9362	-$12437*

*=Dominated therapies

┼=All QALYs are based on SF-6D based health utilities mapped from SF-36

CS=Chondroitin Sulfate; ICER=Incremental cost-effectiveness ratio; NSAIDs= Non-steroidal anti-inflammatory drugs; QALYs=Quality-adjusted life-years

Sensitivity Analysis

In one-way sensitivity analysis, the following parameters were found to impact the expected value of the cost-effectiveness model: discount rate; utilities of treatment success, no response, and TKR surgery at baseline; transition probability of TKR surgery, response to combination therapy of glucosamine and CS; and cost of TKR surgery. No other model parameters affect cost-effectiveness ratios.

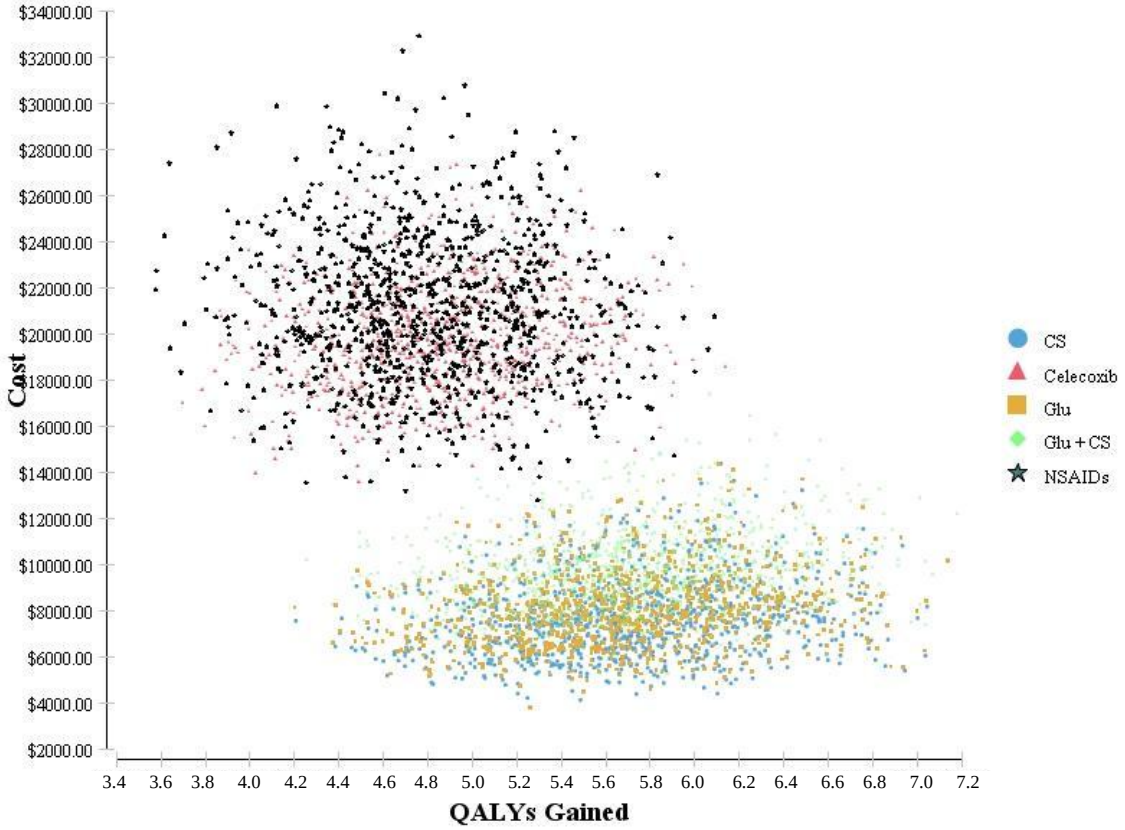
Table 30 displays the detailed results of probabilistic sensitivity analysis on all model inputs and Figure 10 presents its scatter plot based on 10000 second-order Monte Carlo simulations.

Table 30: Probabilistic Sensitivity Analysis Results, in Moderate to Severe Pain KOA Patients Group from US Health care Payers' Perspective and 10-year Time-Horizon.

	Parameters	**CS**	**Glucosamine**	**Glucosamine + CS**	**NSAIDs**	**Celecoxib**
Cost	*Mean*	$7,597	$8,056	$9,749	$21,114	$19,751
	SD	$1,609	$1,614	$1,681	$3,147	$2,313
	Min	$3,175	$3,589	$5,247	$11,188	$11,180
	2.50%	$4,900	$5,350	$6,891	$15,362	$15,555
	10%	$5,644	$6,107	$7,704	$17,162	$16,882
	Median	$7,441	$7,917	$9,607	$20,982	$19,635
	90%	$9,713	$10,179	$11,971	$25,155	$22,745
	97.50%	$11,208	$11,631	$13,398	$27,753	$24,679
	Max	$15,984	$16,350	$18,067	$39,034	$29,809
QALYs gained†	*Mean*	5.7048	5.7053	5.7338	4.8044	4.8791
	SD	0.5122	0.5125	0.5231	0.4375	0.4235
	Min	3.9055	3.9061	3.9111	3.2990	3.3364
	2.50%	4.7201	4.7193	4.7274	3.9709	4.0710
	10%	5.0524	5.0538	5.0633	4.2515	4.3429
	Median	5.6951	5.6967	5.7252	4.7940	4.8693
	90%	6.3778	6.3789	6.4226	5.3748	5.4360
	97.50%	6.7098	6.7155	6.7497	5.6921	5.7137
	Max	7.6467	7.6553	7.7253	6.5288	6.4471

†=All QALYs are based on SF-6D based health utilities mapped from SF-36
CS=Chondroitin Sulfate; NSAIDs= Non-steroidal anti-inflammatory drugs; QALYs=Quality-adjusted life-years

Figure 10: Scatter Plot for Probabilistic Sensitivity Analysis Based on 10000 Simulations, in Moderate to Severe Pain KOA Patients Group from US Health care Payers' Perspective and 10-year Time-Horizon.

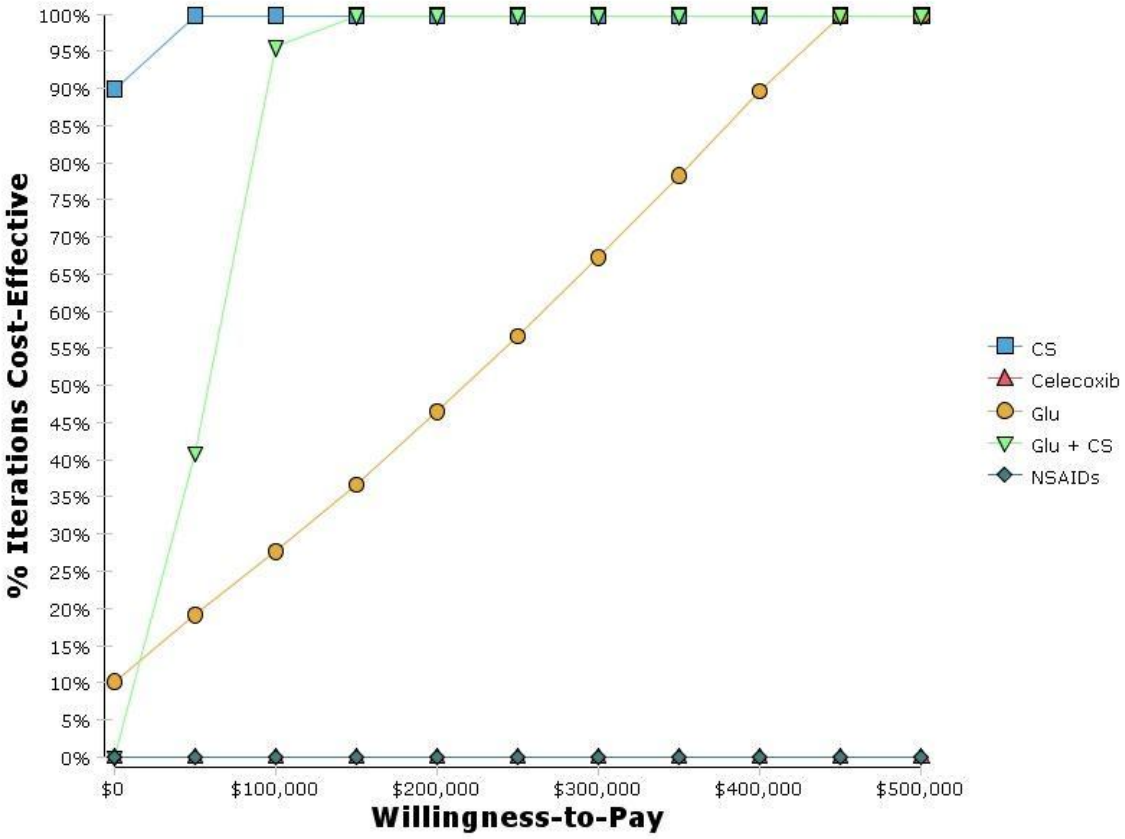


CS=Chondroitin Sulfate; Glu=Glucosamine; Glu + CS=Glucosamine and Chondroitin Sulfate combined therapy; NSAIDs=non-selective Non-Steroidal Anti-Inflammatory Drugs; QALYs=Quality-adjusted life-years

The above scatter plot can be interpreted as follows: the most cost-effective comparator would be one with scatter density towards bottom of the Y-axis (i.e., less expensive) and right hand side from the X-axis (i.e., more effective).

Figure 11 displays the cost-effectiveness acceptability curve for the above described analysis, based on 10,000 simulations and variation of willingness-to-pay from $0 to $500,000 per QALY gained.

Figure 11: Cost-Effectiveness Acceptability Curve, in Moderate to Severe Pain KOA Patients Group from US Health care Payers' Perspective and 10-year Time-Horizon.



CS=Chondroitin Sulfate; Glu=Glucosamine; Glu + CS=Glucosamine and Chondroitin Sulfate combined therapy; NSAIDs=non-selective Non-Steroidal Anti-Inflammatory Drugs

Section 2: Findings for Study Objective 2:

The second objective of our study was to compare the incremental cost-effectiveness of CAM therapies (i.e., glucosamine, CS, and their combination therapy) with celecoxib and placebo in treating KOA from the US health care payers' perspective and 24-week time-horizon. Tables 31 to 36 display results for cost-effectiveness comparison of CAM therapies with celecoxib and placebo among different therapy groups of KOA patients.

Cost-Effectiveness of CAM Therapies vs. Celecoxib among Overall KOA Patients Group

Table 31 displays the base case results for incremental cost-effectiveness of CAM therapies and conventional medicines among the overall KOA patients group (i.e., KOA patients with baseline WOMAC pain sub-scale scores between 150 and 400) from US health care payers' perspective and 24-week time-horizon. Overall, CAM therapies were cost-effective than conventional medicines in treating KOA. Specifically, the incremental cost-effectiveness of glucosamine, in comparison to CS, was found to be $11,215.38/QALY gained; whereas, while placebo was dominated, the cost effectiveness of celecoxib was $106,225.00/QALY gained.

CS alone therapy was used as the reference group in this analysis (reason is described earlier in this chapter) and was found to have the absolute the cost-effectiveness ratio of $167.60/QALY gained.

Table 31: Base Case Results for Cost-Effectiveness Analysis, in Overall KOA Patients Group from US Health care Payers' Perspective and 24-Week Time-Horizon, with Chondroitin Sulfate as the Reference Group.

Study Comparator	Total Cost	Total QALYs gained[┼]	Incremental Cost	Incremental QALYs gained	ICER (Cost/QALY gained)
CS	$114	0.6798			
Glucosamine	$143	0.6824	$29	0.0026	$11,215
Celecoxib	$228	0.6832	$85	0.0008	$106,225
Glucosamine + CS	$250	0.6799	$22	-0.0033	-$6,557*
Placebo	$367	0.6775	$118	-0.0024	-$49,041*

*=Dominated therapies

┼=All QALYs are based on SF-6D based health utilities mapped from SF-36

CS=Chondroitin Sulfate; ICER=Incremental cost-effectiveness ratio; QALYs=Quality-adjusted life-years

Sensitivity Analysis

In one-way sensitivity analysis, the following parameters were found to impact the expected value of the cost-effectiveness model: utilities of response and no response to the treatment at 24-weeks; medications compliance rate; and response rate among compliant patients on celecoxib and glucosamine therapies. No other model parameters affect cost-effectiveness ratios.

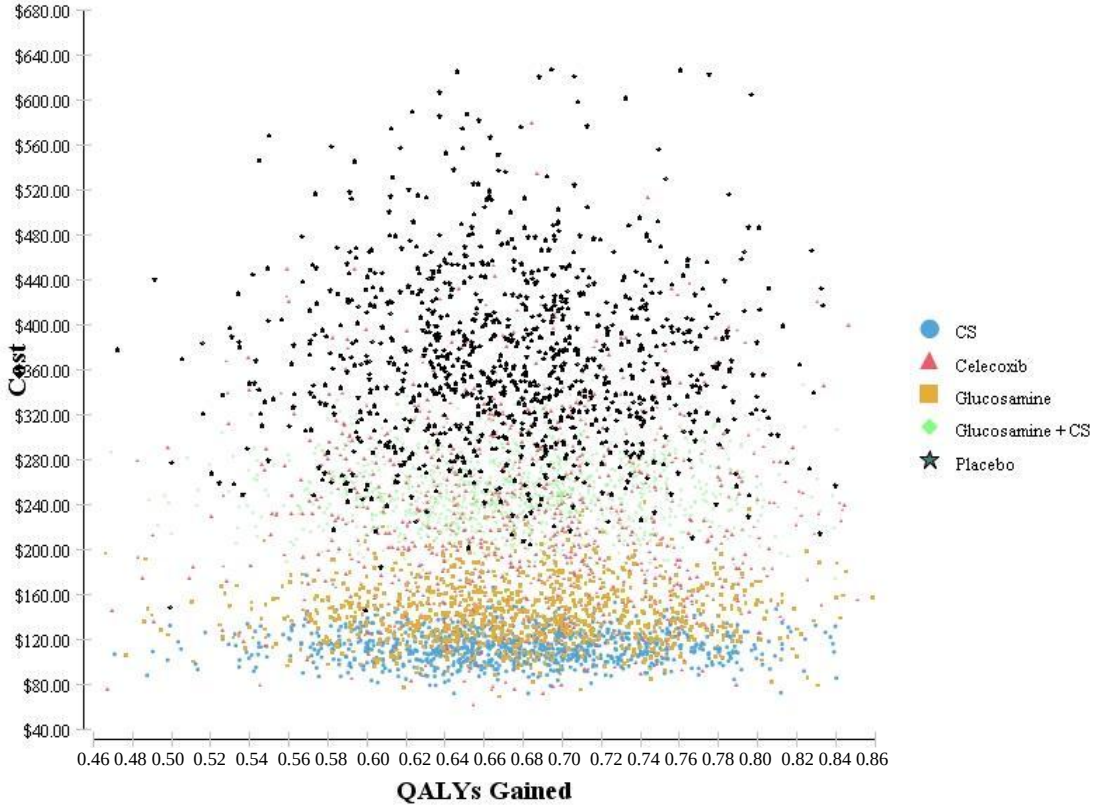
Table 32 displays the detailed results of probabilistic sensitivity analysis on all model inputs and Figure 12 presents its scatter plot based on 10000 second-order Monte Carlo simulations.

Table 32: Probabilistic Sensitivity Analysis Results, in Overall KOA Patients Group from US Health care Payers' Perspective and 24-Week Time-Horizon.

	Parameters	**CS**	**Glucosamine**	**Glucosamine + CS**	**Celecoxib**	**Placebo**
Cost	*Mean*	$114	$143	$250	$229	$366
	SD	$14	$27	$31	$77	$74
	Min	$65	$59	$159	$45	$140
	2.50%	$88	$95	$193	$104	$235
	10%	$96	$110	$211	$138	$275
	Median	$114	$141	$249	$220	$362
	90%	$133	$178	$290	$332	$463
	97.50%	$144	$199	$314	$407	$525
	Max	$178	$275	$397	$598	$749
QALYs gained†	*Mean*	0.6803	0.6828	0.6803	0.6836	0.6779
	SD	0.0643	0.0667	0.0644	0.0673	0.0628
	Min	0.3380	0.2971	0.3336	0.2872	0.3290
	2.50%	0.5472	0.5440	0.5475	0.5433	0.5486
	10%	0.5968	0.5957	0.5966	0.5956	0.5964
	Median	0.6832	0.6859	0.6832	0.6864	0.6805
	90%	0.7620	0.7673	0.7622	0.7686	0.7584
	97.50%	0.7967	0.8032	0.7975	0.8048	0.7927
	Max	0.8802	0.8804	0.8802	0.8808	0.8796

†=All QALYs are based on SF-6D based health utilities mapped from SF-36
CS=Chondroitin Sulfate; QALYs=Quality-adjusted life-years

Figure 12: Scatter Plot for Probabilistic Sensitivity Analysis Based on 10000 Simulations, in Overall KOA Patients Group from US Health care Payers' Perspective and 24-Week Time-Horizon.

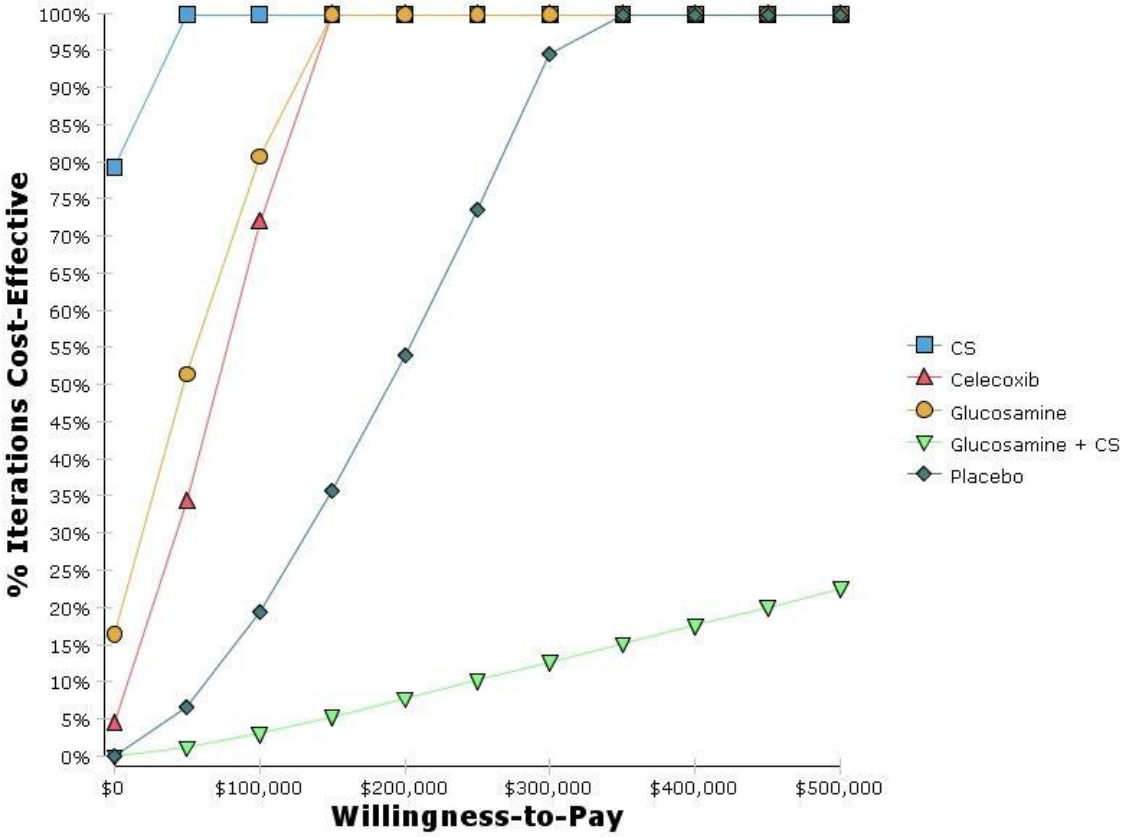


CS=Chondroitin Sulfate; QALYs=Quality-adjusted life-years

The above scatter plot can be interpreted as follows: the most cost-effective comparator would be one with scatter density towards bottom of the Y-axis (i.e., less expensive) and right hand side from the X-axis (i.e., more effective).

Figure 13 displays the cost-effectiveness acceptability curve for the above described analysis, based on 10,000 simulations and variation of willingness-to-pay from $0 to $500,000 per QALY gained.

Figure 13: Cost-Effectiveness Acceptability Curve, in Overall KOA Patients Group from US Health care Payers' Perspective and 24-Week Time-Horizon.



CS=Chondroitin Sulfate

Cost-Effectiveness of CAM Therapies vs. Celecoxib among KOA Patients with Mild Pain

In this sub-group analysis, cost-effectiveness of CAM therapies was compared with celecoxib and placebo in treating KOA among those patients that had mild knee pain at the baseline, defined by WOMAC pain sub-scale score of 150 to 300. The time-horizon was 24-weeks and study perspective was of the US healthcare payers'.

Table 33 displays the base case results for incremental cost-effectiveness of CAM therapies with celecoxib and placebo from US health care payers' perspective and 24-week time-horizon, among the KOA patients group with mild baseline. Overall, CAM therapies were cost-effective than conventional medicines in treating KOA. Specifically, the incremental cost-effectiveness of glucosamine, in comparison to CS, was found to be $24,300.00/QALY gained.

CS alone therapy was used as the reference group in this analysis (reason is described earlier in this chapter) and was found to have the absolute the cost-effectiveness ratio of $167.48/QALY gained.

Table 33: Base Case Results for Cost-Effectiveness Analysis, in Mild Pain Only KOA Patients Group from US Health care Payers' Perspective and 24-Week Time-Horizon, with Chondroitin Sulfate as the Reference Group.

Study Comparator	Total Cost	Total QALYs gained[┼]	Incremental Cost	Incremental QALYs gained	ICER (Cost/QALY gained)
CS	$114	0.6803			
Glucosamine	$143	0.6815	$29	0.0012	$24,300
Celecoxib	$228	0.6832	$85	0.0017	$49,988
Glucosamine + CS	$250	0.6769	$22	-0.0063	-$3,434*
Placebo	$367	0.6787	$118	0.0018	$65,389

*=Dominated therapies

┼=All QALYs are based on SF-6D based health utilities mapped from SF-36

CS=Chondroitin Sulfate; ICER=Incremental cost-effectiveness ratio; QALYs=Quality-adjusted life-years

Sensitivity Analysis

In one-way sensitivity analysis, the following parameters were found to impact the expected value of the cost-effectiveness model: utilities of response and no response to the treatment at 24-weeks; medications compliance rate; and response rate among compliant and non-compliant patients on celecoxib, and among compliant patients on CS and glucosamine. No other model parameters affect cost-effectiveness ratios.

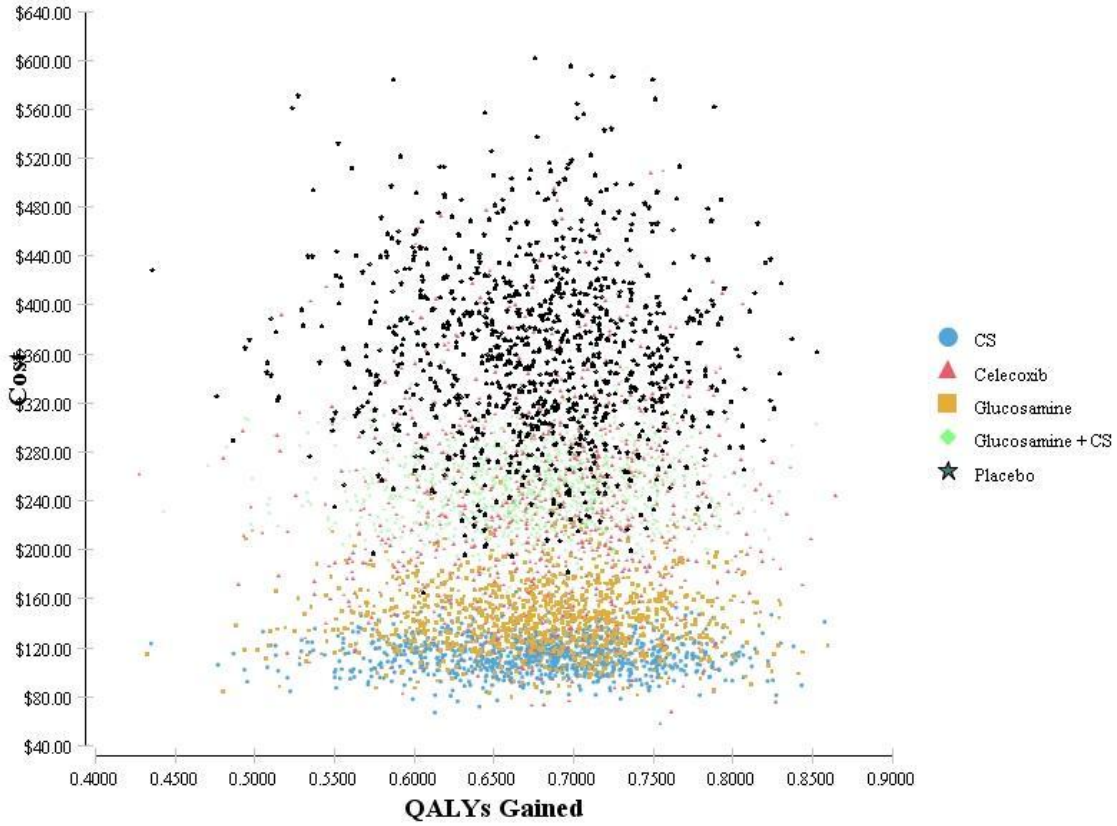
Table 34 displays the detailed results of probabilistic sensitivity analysis on all model inputs and Figure 14 presents its scatter plot based on 10000 second-order Monte Carlo simulations.

Table 34: Probabilistic Sensitivity Analysis Results, in Mild Pain Only KOA Patients Group from US Health care Payers' Perspective and 24-Week Time-Horizon.

	Parameters	**CS**	**Glucosamine**	**Glucosamine + CS**	**Celecoxib**	**Placebo**
Cost	*Mean*	$114	$143	$250	$229	$366
	SD	$14	$27	$31	$77	$74
	Min	$65	$59	$159	$45	$140
	2.50%	$88	$95	$193	$104	$235
	10%	$96	$110	$211	$138	$275
	Median	$114	$141	$249	$220	$362
	90%	$133	$178	$290	$332	$463
	97.50%	$144	$199	$314	$407	$525
	Max	$178	$275	$397	$598	$749
QALYs gained†	*Mean*	0.6803	0.6828	0.6803	0.6836	0.6779
	SD	0.0643	0.0667	0.0644	0.0673	0.0628
	Min	0.3380	0.2971	0.3336	0.2872	0.3290
	2.50%	0.5472	0.5440	0.5475	0.5433	0.5486
	10%	0.5968	0.5957	0.5966	0.5956	0.5964
	Median	0.6832	0.6859	0.6832	0.6864	0.6805
	90%	0.7620	0.7673	0.7622	0.7686	0.7584
	97.50%	0.7967	0.8032	0.7975	0.8048	0.7927
	Max	0.8802	0.8804	0.8802	0.8808	0.8796

†=All QALYs are based on SF-6D based health utilities mapped from SF-36
CS=Chondroitin Sulfate; QALYs=Quality-adjusted life-years

Figure 14: Scatter Plot for Probabilistic Sensitivity Analysis, in Mild Pain Only KOA Patients Group from US Health care Payers' Perspective and 24-Week Time-Horizon.

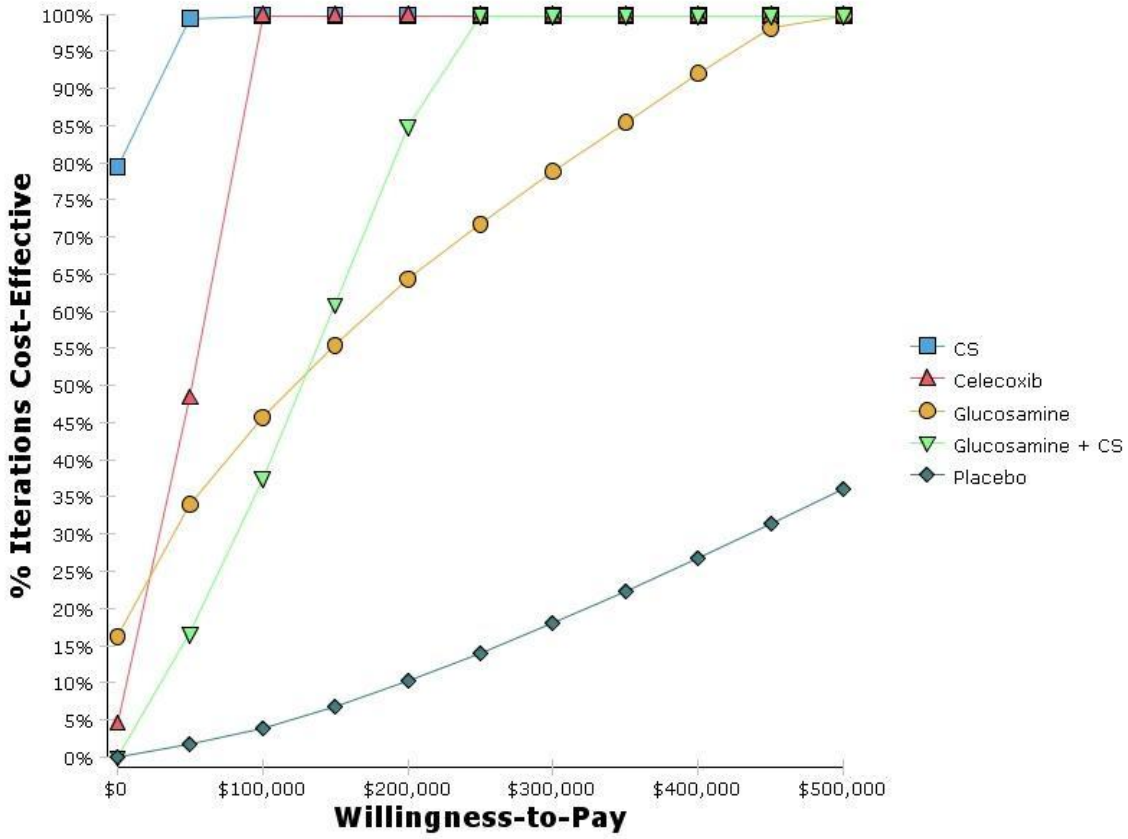


CS=Chondroitin Sulfate; QALYs=Quality-adjusted life-years

The above scatter plot can be interpreted as follows: the most cost-effective comparator would be one with scatter density towards bottom of the Y-axis (i.e., less expensive) and right hand side from the X-axis (i.e., more effective).

Figure 15 displays the cost-effectiveness acceptability curve for the above described analysis, based on 10,000 simulations and variation of willingness-to-pay from $0 to $500,000 per QALY gained.

Figure 15: Cost-Effectiveness Acceptability Curve for Cost-Effectiveness Analysis, in Mild Pain Only KOA Patients Group from US Health care Payers' Perspective and 24-Week Time-Horizon.



CS=Chondroitin Sulfate

Cost-Effectiveness of CAM Therapies vs. Celecoxib among KOA Patients with Moderate to Severe Pain

In this sub-group analysis, cost-effectiveness of CAM therapies was compared with celecoxib and placebo in the treatment of KOA among those patients that had moderate to severe knee pain at the baseline, defined by WOMAC pain sub-scale score of 301 to 400. The time-horizon was 24-weeks and study perspective was of the US healthcare payers'.

Table 35 displays the base case results for incremental cost-effectiveness of CAM therapies with celecoxib and placebo from US health care payers' perspective and 24-week time-horizon, among the KOA patients group with moderate to severe baseline pain. Overall, CAM therapies were cost-effective than conventional medicines in treating KOA. Specifically, the incremental cost-effectiveness of glucosamine, in comparison to CS, was found to be $3,313.63/QALY gained and of combination of glucosamine and CS was $3,278.78/QALY gained.

CS alone therapy was used as the reference group in this analysis (reason is described earlier in this chapter) and was found to have the absolute the cost-effectiveness ratio of $167.17/QALY gained.

Table 35: Base Case Results for Cost-Effectiveness Analysis, in Moderate to Severe Pain KOA Patients Group from US Health care Payers' Perspective and 24-Week Time-Horizon, with Chondroitin Sulfate as the Reference Group.

Study Comparator	Total Cost	Total QALYs gained[┼]	Incremental Cost	Incremental QALYs gained	ICER (Cost/QALY gained)
CS	$114	0.6775			
Glucosamine	$143	0.6863	$29	0.0088	$3,314
Celecoxib	$228	0.6838	$85	-0.0025	-$33,992*
Glucosamine + CS	$250	0.6904	$22	0.0066	$3,279
Placebo	$367	0.6732	$118	-0.0172	-$6,843*

*=Dominated therapies

┼=All QALYs are based on SF-6D based health utilities mapped from SF-36

CS=Chondroitin Sulfate; ICER=Incremental cost-effectiveness ratio; QALYs=Quality-adjusted life-years

Sensitivity Analysis

In one-way sensitivity analysis, the following parameters were found to impact the expected value of the cost-effectiveness model: utilities of response and no response to the treatment at 24-weeks; medications compliance rate; and 24-week cost of treatment with combination therapy of glucosamine and CS. No other model parameters affect cost-effectiveness ratios.

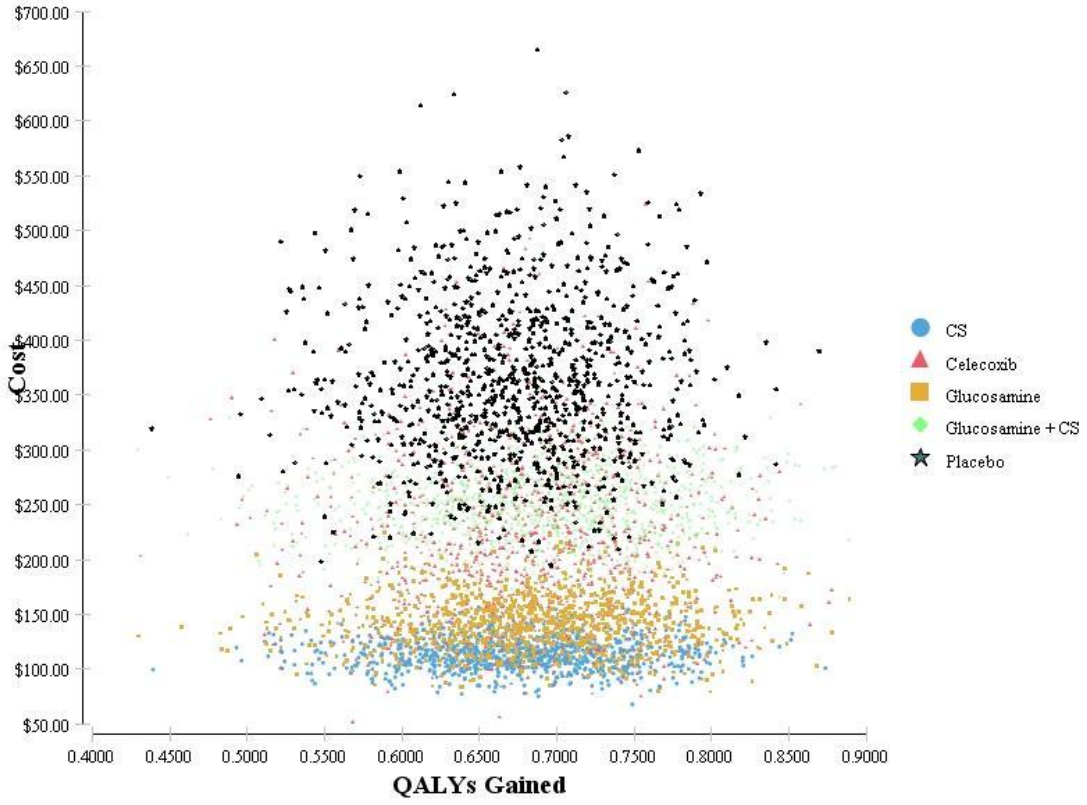
Table 36 displays the detailed results of probabilistic sensitivity analysis on all model inputs and Figure 16 presents its scatter plot based on 10000 second-order Monte Carlo simulations.

Table 36: Probabilistic Sensitivity Analysis Results, in Moderate to Severe Pain KOA Patients Group from US Health care Payers' Perspective and 24-Week Time-Horizon.

	Parameters	**CS**	**Glucosamine**	**Glucosamine + CS**	**Celecoxib**	**Placebo**
Cost	*Mean*	$114	$143	$250	$228	$367
	SD	$14	$27	$31	$77	$74
	Min	$68	$61	$156	$35	$127
	2.50%	$88	$94	$193	$104	$237
	10%	$97	$110	$211	$137	$276
	Median	$114	$141	$249	$219	$362
	90%	$133	$179	$291	$331	$466
	97.50%	$143	$200	$315	$404	$526
	Max	$178	$297	$373	$699	$702
QALYs gained┼	*Mean*	0.6773	0.6862	0.6902	0.6836	0.6730
	SD	0.0625	0.0705	0.0746	0.0677	0.0604
	Min	0.4026	0.3535	0.3546	0.3758	0.4305
	2.50%	0.5482	0.5374	0.5317	0.5419	0.5484
	10%	0.5941	0.5919	0.5911	0.5935	0.5926
	Median	0.6803	0.6896	0.6942	0.6870	0.6758
	90%	0.7552	0.7741	0.7824	0.7683	0.7488
	97.50%	0.7919	0.8138	0.8234	0.8062	0.7853
	Max	0.8890	0.9163	0.9208	0.9007	0.8882

┼=All QALYs are based on SF-6D based health utilities mapped from SF-36
CS=Chondroitin Sulfate; QALYs=Quality-adjusted life-years

Figure 16: Scatter Plot for Probabilistic Sensitivity Analysis, in Moderate to Severe Pain KOA Patients Group from US Health care Payers' Perspective and 24-Week Time-Horizon.

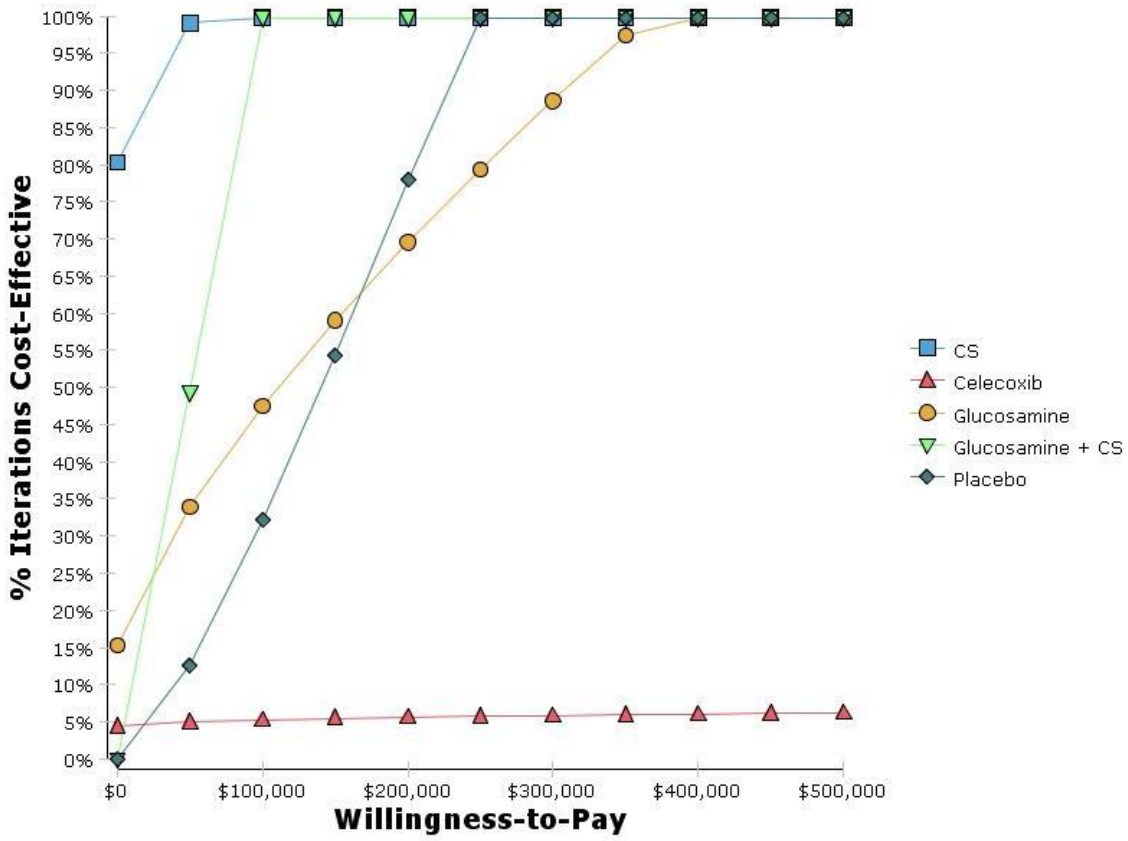


CS=Chondroitin Sulfate; QALYs=Quality-adjusted life-years

The above scatter plot can be interpreted as follows: the most cost-effective comparator would be one with scatter density towards bottom of the Y-axis (i.e., less expensive) and right hand side from the X-axis (i.e., more effective).

Figure 17 displays the cost-effectiveness acceptability curve for the above described analysis, based on 10,000 simulations and variation of willingness-to-pay from $0 to $500,000 per QALY gained.

Figure 17: Cost-Effectiveness Acceptability Curve for Cost-Effectiveness Analysis, in Moderate to Severe Pain KOA Patients Group from US Health care Payers' Perspective and 24-Week Time-Horizon.



CS=Chondroitin Sulfate

Section 3: Findings for Study Objective 3:

The third objective of our study was to compare the incremental cost-effectiveness of CAM therapies (i.e., glucosamine, CS, and their combination therapy) with celecoxib and placebo to treat KOA from the patients' perspective and 24-week time-horizon. Tables 37 to 42 display results for cost-effectiveness comparison of CAM therapies with celecoxib and placebo among different study groups of KOA patients.

Cost-Effectiveness of CAM Therapies vs. Celecoxib among Overall KOA Patients Group

Table 37 displays the base case results for incremental cost-effectiveness of CAM therapies and conventional medicines among the overall KOA patients group (i.e., KOA patients with baseline WOMAC pain sub-scale scores between 150 and 400) from patients' perspective and 24-week time-horizon. Overall, CAM therapies were cost-effective than conventional medicines in treating KOA. Specifically, the incremental cost-effectiveness of glucosamine, in comparison to CS, was found to be $11,215.38/QALY gained; whereas, both placebo and combination therapy of glucosamine and CS were dominated.

CS alone therapy was used as the reference group in this analysis (reason is described earlier in this chapter) and was found to have the absolute the cost-effectiveness ratio of $9,417.63/QALY gained.

Table 37: Base Case Results for Cost-Effectiveness Analysis, in Overall KOA Patients Group from Patients' Perspective and 24-Week Time-Horizon, with Chondroitin Sulfate as the Reference Group.

Study Comparator	Total Cost	Total QALYs gained┼	Incremental Cost	Incremental QALYs gained	ICER (Cost/QALY gained)
CS	$6,402	0.6798			
Glucosamine	$6,431	0.6824	$29	0.0026	$11,215
Celecoxib	$6,516	0.6832	$85	0.0008	$106,225
Glucosamine + CS	$6,538	0.6799	$22	-0.0033	-$6,557*
Placebo	$6,656	0.6775	$118	-0.0024	-$49,041*

*=Dominated therapies

┼=All QALYs are based on SF-6D based health utilities mapped from SF-36

CS=Chondroitin Sulfate; ICER=Incremental cost-effectiveness ratio; QALYs=Quality-adjusted life-years

Sensitivity Analysis

In one-way sensitivity analysis, the following parameters were found to impact the expected value of the cost-effectiveness model: utilities of response and no response to the treatment at 24-weeks; medications compliance rate; indirect healthcare costs for KOA treatment; and response rate among compliant and non-compliant patients on celecoxib and compliant patients on glucosamine and CS alone therapies. No other model parameters affect cost-effectiveness ratios.

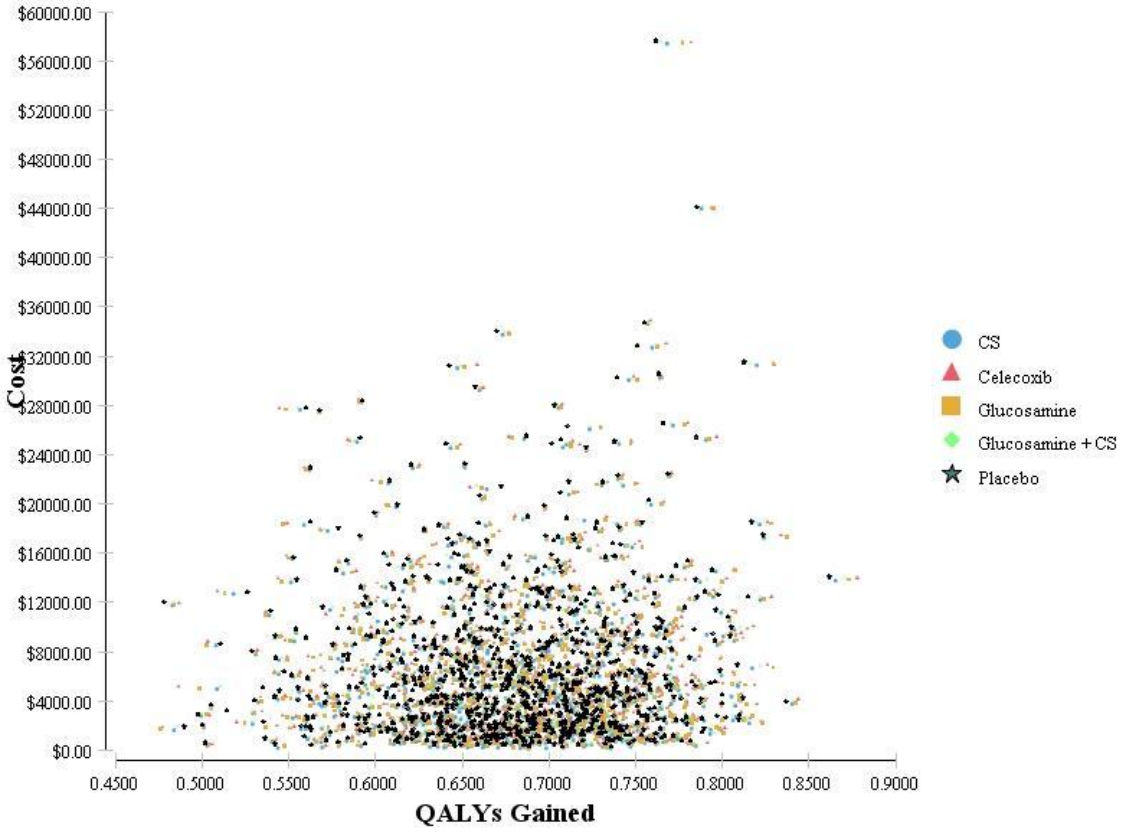
Table 38 displays the detailed results of probabilistic sensitivity analysis on all model inputs and Figure 18 presents its scatter plot based on 10000 second-order Monte Carlo simulations.

Table 38: Probabilistic Sensitivity Analysis Results, in Overall KOA Patients Group from Patients' Perspective and 24-Week Time-Horizon.

	Parameters	CS	Glucosamine	Glucosamine + CS	Celecoxib	Placebo
Cost	*Mean*	$6,443	$6,472	$6,579	$6,558	$6,697
	SD	$5,892	$5,892	$5,892	$5,894	$5,891
	Min	$91	$112	$209	$101	$271
	2.50%	$334	$365	$474	$447	$584
	10%	$946	$969	$1,079	$1,054	$1,200
	Median	$4,674	$4,703	$4,815	$4,803	$4,939
	90%	$14,260	$14,288	$14,397	$14,374	$14,504
	97.50%	$22,261	$22,303	$22,379	$22,361	$22,499
	Max	$56,070	$56,136	$56,241	$56,217	$56,350
QALYs gained┼	*Mean*	0.6808	0.6834	0.6809	0.6841	0.6784
	SD	0.0639	0.0663	0.0639	0.0669	0.0624
	Min	0.4042	0.3990	0.4119	0.4019	0.4087
	2.50%	0.5487	0.5455	0.5486	0.5455	0.5507
	10%	0.5975	0.5971	0.5972	0.5968	0.5970
	Median	0.6836	0.6866	0.6837	0.6874	0.6807
	90%	0.7610	0.7664	0.7608	0.7685	0.7567
	97.50%	0.7981	0.8044	0.7981	0.8051	0.7943
	Max	0.8997	0.9002	0.8997	0.9006	0.8991

┼=All QALYs are based on SF-6D based health utilities mapped from SF-36
CS=Chondroitin Sulfate; QALYs=Quality-adjusted life-years

Figure 18: Scatter Plot for Probabilistic Sensitivity Analysis, in Overall KOA Patients Group from Patients' Perspective and 24-Week Time-Horizon.

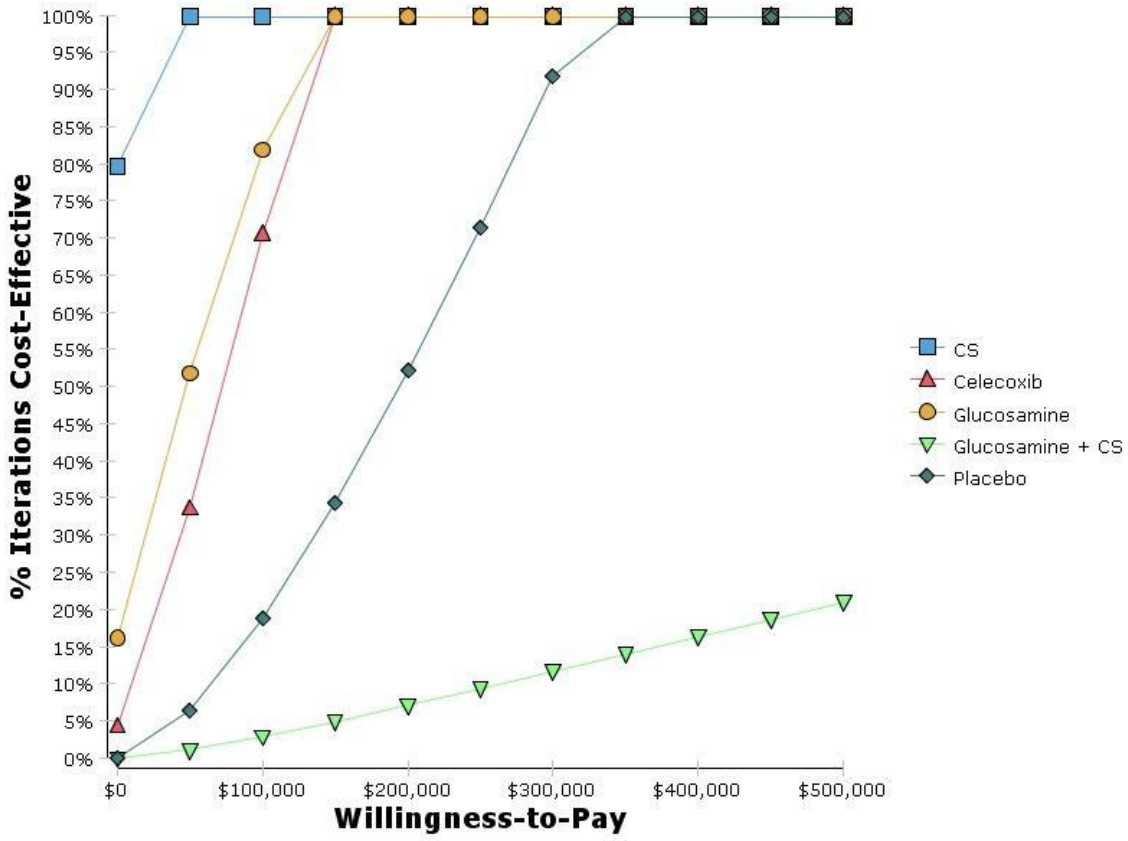


CS=Chondroitin Sulfate; QALYs=Quality-adjusted life-years

The above scatter plot can be interpreted as follows: the most cost-effective comparator would be one with scatter density towards bottom of the Y-axis (i.e., less expensive) and right hand side from the X-axis (i.e., more effective).

Figure 19 displays the cost-effectiveness acceptability curve for the above described analysis, based on 10,000 simulations and variation of willingness-to-pay from $0 to $500,000 per QALY gained.

Figure 19: Cost-Effectiveness Acceptability Curve for Cost-Effectiveness Analysis, in Overall KOA Patients Group from Patients' Perspective and 24-Week Time-Horizon.



CS=Chondroitin Sulfate

Cost-Effectiveness of CAM Therapies vs. Celecoxib among KOA Patients with Mild Pain

In this sub-group analysis, cost-effectiveness of CAM therapies was compared with celecoxib and placebo in the treatment of KOA among those patients that had mild knee pain at the baseline, defined by WOMAC pain sub-scale score of 150 to 300. The time-horizon was 24-weeks and study perspective was of the patients'.

Table 39 displays the base case results for incremental cost-effectiveness of CAM therapies with celecoxib and placebo from patients' perspective and 24-week time-horizon, among the KOA patients group with mild baseline. Overall, CAM therapies were cost-effective than conventional medicines in treating KOA. Specifically, the incremental cost-effectiveness of glucosamine, in comparison to CS, was found to be $24,300.00/QALY gained and of celecoxib was $49,988.24/QALY gained.

CS alone therapy was used as the reference group in this analysis (reason is described earlier in this chapter) and was found to have the absolute the cost-effectiveness ratio of $9,410.71/QALY gained.

Table 39: Base Case Results for Cost-Effectiveness Analysis, in Mild Pain Only KOA Patients Group from Patients' Perspective and 24-Week Time-Horizon, with Chondroitin Sulfate as the Reference Group.

Study Comparator	Total Cost	Total QALYs gained[┼]	Incremental Cost	Incremental QALYs gained	ICER (Cost/QALY gained)
CS	$6,402	0.6803			
Glucosamine	$6,431	0.6815	$29.2	0.0012	$24,300
Celecoxib	$6,516	0.6832	$85.0	0.0017	$49,988
Glucosamine + CS	$6,538	0.6789	$21.6	-0.0063	-$3,434*
Placebo	$6,656	0.6787	$117.7	0.0018	$65,389

*=Dominated therapies

┼=All QALYs are based on SF-6D based health utilities mapped from SF-36

CS=Chondroitin Sulfate; ICER=Incremental cost-effectiveness ratio; QALYs=Quality-adjusted life-years

Sensitivity Analysis

In one-way sensitivity analysis, the following parameters were found to impact the expected value of the cost-effectiveness model: utilities of response and no response to the treatment at 24-weeks; medications compliance rate; indirect healthcare costs of KOA treatment; and response rate among compliant and non-compliant patients on celecoxib, and among compliant patients on CS and glucosamine alone therapies. No other model parameters affect cost-effectiveness ratios.

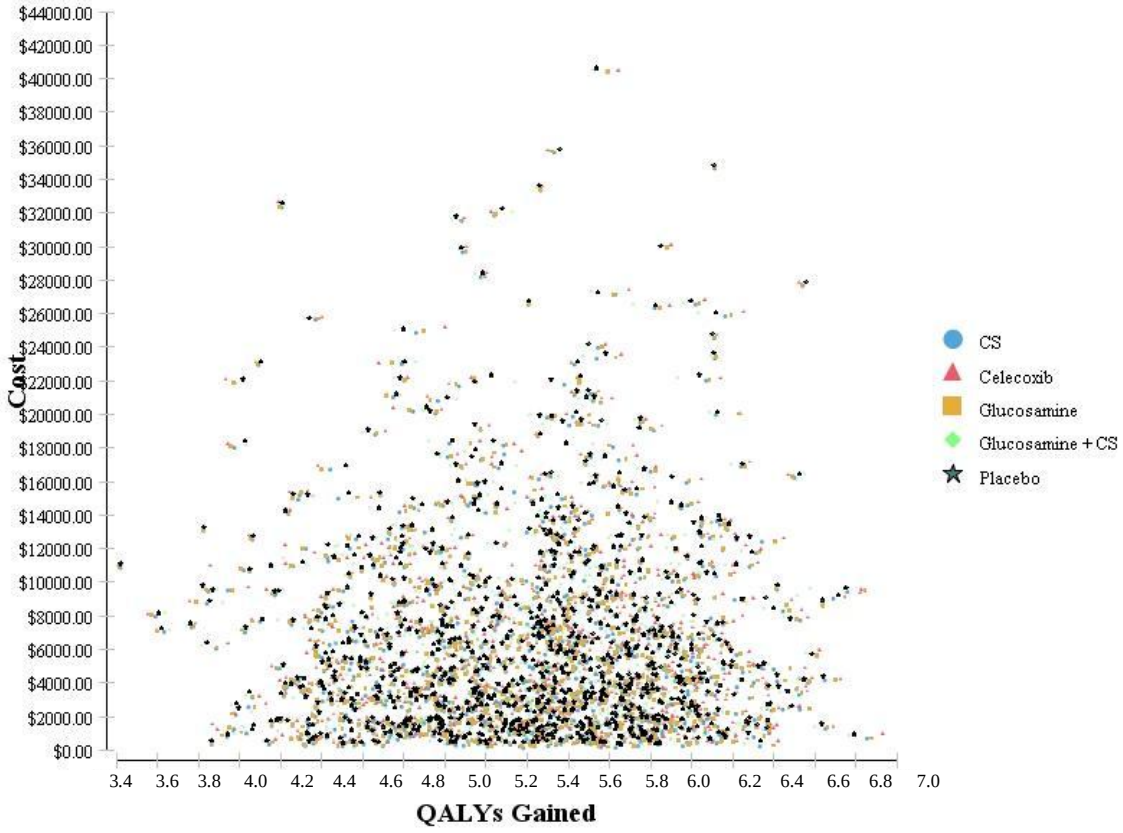
Table 40 displays the detailed results of probabilistic sensitivity analysis on all model inputs and Figure 20 presents its scatter plot based on 10000 second-order Monte Carlo simulations.

Table 40: Probabilistic Sensitivity Analysis Results, in Mild Pain Only KOA Patients Group from Patients' Perspective and 24-Week Time-Horizon.

	Parameters	CS	Glucosamine	Glucosamine + CS	Celecoxib	Placebo
Cost						
	Mean	6,471	6,500	6,606	6,584	6,724
	SD	6,028	6,028	6,028	6,029	6,028
	Min	90	114	212	131	245
	2.50%	325	359	465	436	572
	10%	939	975	1,071	1,042	1,191
	Median	4,616	4,645	4,750	4,725	4,873
	90%	14,341	14,361	14,463	14,436	14,585
	97.50%	22,654	22,698	22,795	22,796	22,839
	Max	51,190	51,214	51,294	51,345	51,304
QALYs gained[┼]						
	Mean	0.6793	0.6805	0.6759	0.6822	0.6777
	SD	0.0650	0.0660	0.0625	0.0674	0.0639
	Min	0.4032	0.4032	0.4016	0.4044	0.4024
	2.50%	0.5470	0.5464	0.5495	0.5453	0.5480
	10%	0.5933	0.5931	0.5934	0.5924	0.5934
	Median	0.6816	0.6829	0.6781	0.6850	0.6801
	90%	0.7610	0.7637	0.7547	0.7670	0.7577
	97.50%	0.7991	0.8026	0.7915	0.8061	0.7953
	Max	0.8873	0.8880	0.8753	0.8915	0.8763

┼=All QALYs are based on SF-6D based health utilities mapped from SF-36
CS=Chondroitin Sulfate; QALYs=Quality-adjusted life-years

Figure 20: Scatter Plot for Probabilistic Sensitivity Analysis, in Mild Pain Only KOA Patients Group from Patients' Perspective and 24-Week Time-Horizon.

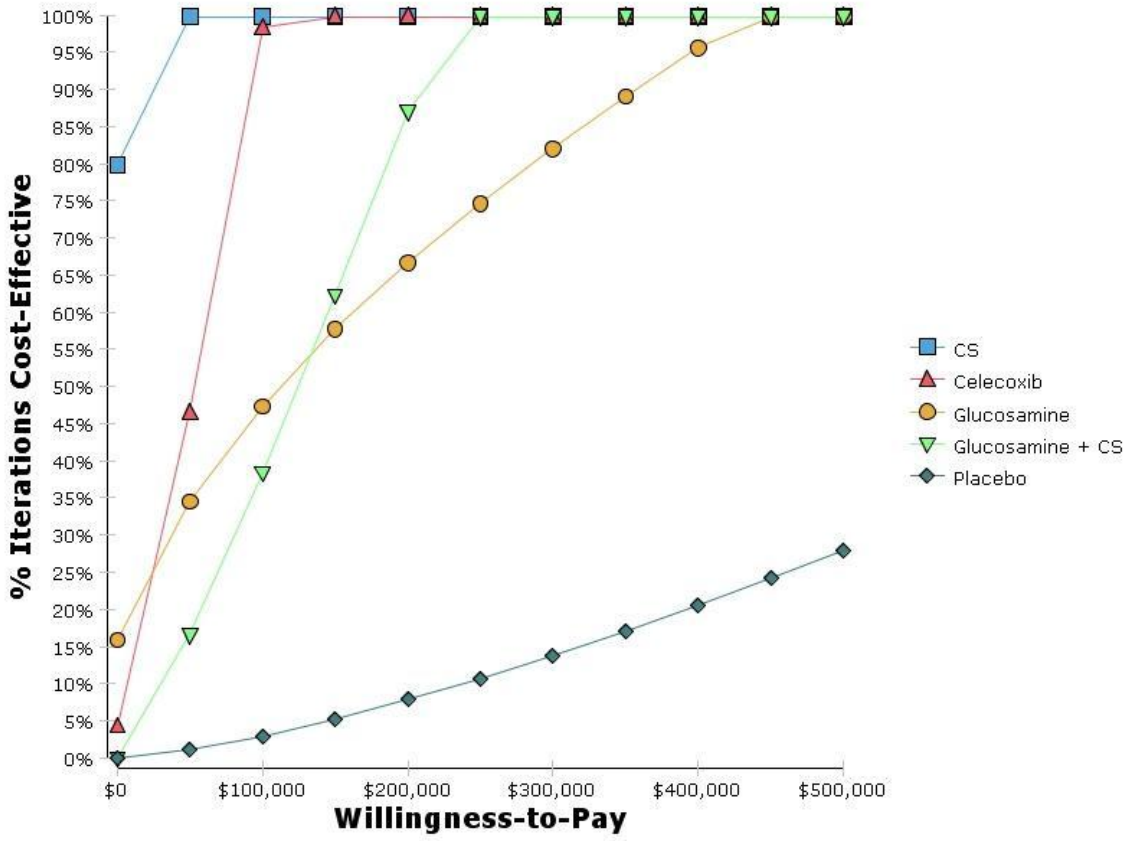


CS=Chondroitin Sulfate; QALYs=Quality-adjusted life-years

The above scatter plot can be interpreted as follows: the most cost-effective comparator would be one with scatter density towards bottom of the Y-axis (i.e., less expensive) and right hand side from the X-axis (i.e., more effective).

Figure 21 displays the cost-effectiveness acceptability curve for the above described analysis, based on 10,000 simulations and variation of willingness-to-pay from $0 to $500,000 per QALY gained.

Figure 21: Cost-Effectiveness Acceptability Curve for Cost-Effectiveness Analysis, in Mild Pain Only KOA Patients Group from Patients' Perspective and 24-Week Time-Horizon.



CS=Chondroitin Sulfate

Cost-Effectiveness of CAM Therapies vs. Celecoxib among KOA Patients with Moderate to Severe Pain

In this sub-group analysis, cost-effectiveness of CAM therapies was compared with celecoxib and placebo in the treatment of KOA among those patients that had moderate to severe knee pain at the baseline, defined by WOMAC pain sub-scale score of 301 to 400. The time-horizon was 24-weeks and study perspective was of the patients.

Table 41 displays the base case results for incremental cost-effectiveness of CAM therapies with celecoxib and placebo from patients' perspective and 24-week time-horizon, among the KOA patients group with moderate to severe baseline pain. Overall, CAM therapies were cost-effective than conventional medicines in treating KOA. Specifically, the incremental cost-effectiveness of glucosamine, in comparison to CS, was found to be $3,313.63/QALY gained and of combination of glucosamine and CS was $3,278.78/QALY gained. On the other hand, both celecoxib and placebo were dominated by CS alone therapy.

CS alone therapy was used as the reference group in this analysis (reason is described earlier in this chapter) and was found to have the absolute the cost-effectiveness ratio of $9,449.60/QALY gained.

Table 41: Base Case Results for Cost-Effectiveness Analysis, in Moderate to Severe Pain KOA Patients Group from Patients' Perspective and 24-Week Time-Horizon, with Chondroitin Sulfate as the Reference Group.

Study Comparator	Total Cost	Total QALYs gained[┼]	Incremental Cost	Incremental QALYs gained	ICER (Cost/QALY gained)
CS	$6,402	0.6775			
Glucosamine	$6,431	0.6863	$29	0.0088	$3,314
Celecoxib	$6,516	0.6838	$85	-0.0025	-$33,992*
Glucosamine + CS	$6,538	0.6904	$22	0.0066	$3,279
Placebo	$6,656	0.6732	$118	-0.0172	-$6,843*

*=Dominated therapies

┼=All QALYs are based on SF-6D based health utilities mapped from SF-36

CS=Chondroitin Sulfate; ICER=Incremental cost-effectiveness ratio; QALYs=Quality-adjusted life-years

Sensitivity Analysis

In one-way sensitivity analysis, the following parameters were found to impact the expected value of the cost-effectiveness model: utilities of response and no response to the treatment at 24-weeks; medications compliance rate; indirect healthcare costs of treating KOA; and response rate among compliant and non-compliant patients on celecoxib and compliant patients on glucosamine and CS alone therapies. No other model parameters affect cost-effectiveness ratios.

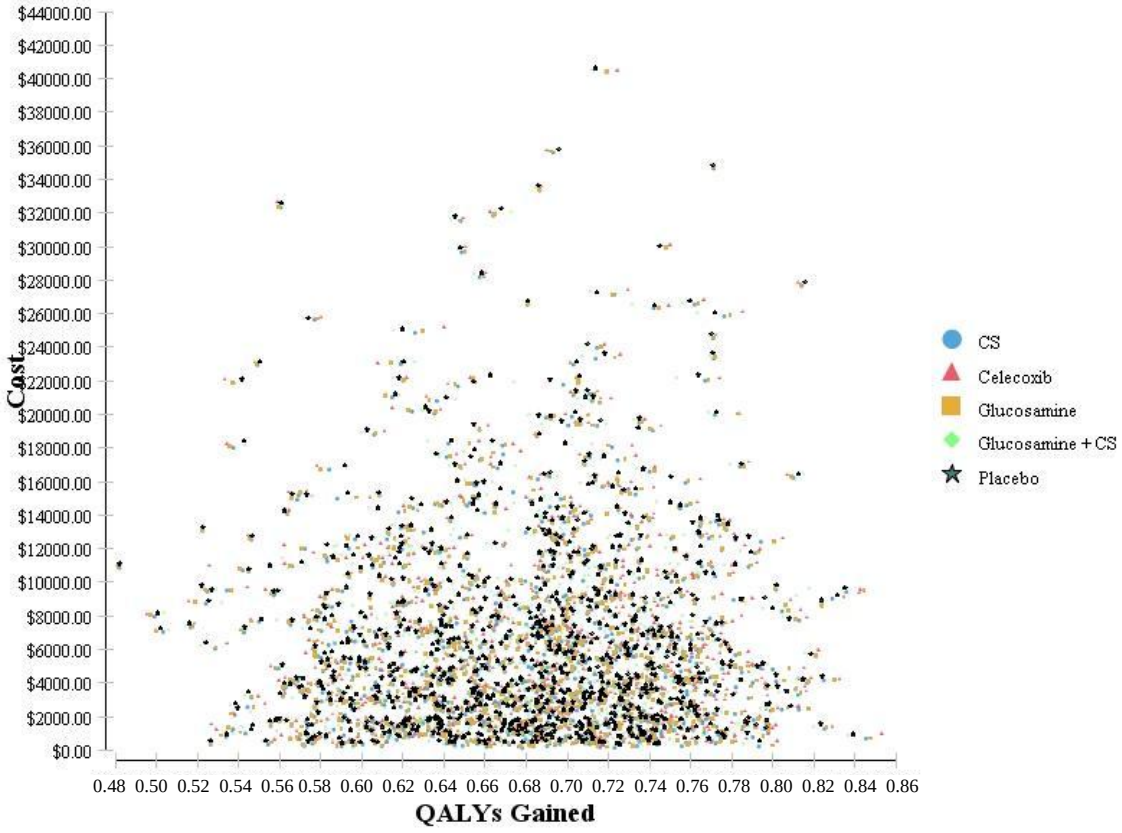
Table 42 displays the detailed results of probabilistic sensitivity analysis on all model inputs and Figure 22 presents its scatter plot based on 10000 second-order Monte Carlo simulations.

Table 42: Probabilistic Sensitivity Analysis Results, in Moderate to Severe Pain KOA Patients Group from Patients' Perspective and 24-Week Time-Horizon.

	Parameters	**CS**	**Glucosamine**	**Glucosamine + CS**	**Celecoxib**	**Placebo**
Cost	*Mean*	$114	$143	$250	$230	$369
	SD	$14	$27	$32	$78	$74
	Min	$67	$52	$154	$39	$143
	2.50%	$88	$95	$191	$101	$240
	10%	$97	$110	$210	$137	$278
	Median	$114	$141	$249	$221	$363
	90%	$132	$179	$291	$332	$467
	97.50%	$144	$201	$315	$404	$526
	Max	$174	$281	$382	$717	$761
QALYs gained┼	*Mean*	0.6775	0.6861	0.6900	0.6836	0.6733
	SD	0.0627	0.0709	0.0750	0.0680	0.0605
	Min	0.4358	0.4100	0.4101	0.4262	0.4461
	2.50%	0.5484	0.5395	0.5343	0.5425	0.5504
	10%	0.5954	0.5933	0.5910	0.5943	0.5939
	Median	0.6799	0.6897	0.6946	0.6868	0.6750
	90%	0.7567	0.7753	0.7846	0.7692	0.7503
	97.50%	0.7935	0.8148	0.8239	0.8069	0.7854
	Max	0.8660	0.9038	0.8935	0.8905	0.8623

┼=All QALYs are based on SF-6D based health utilities mapped from SF-36
CS=Chondroitin Sulfate; QALYs=Quality-adjusted life-years

Figure 22: Scatter Plot for Probabilistic Sensitivity Analysis, in Moderate to Severe Pain KOA Patients Group from Patients' Perspective and 24-Week Time-Horizon.

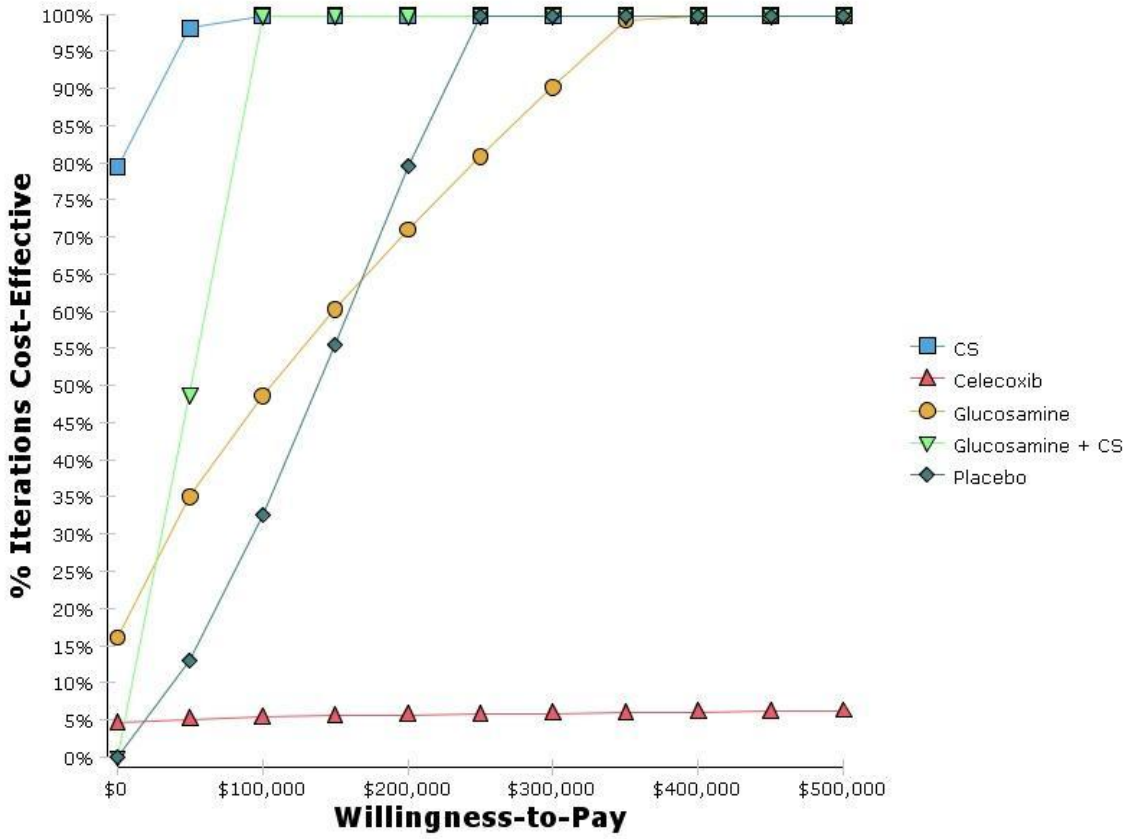


CS=Chondroitin Sulfate; QALYs=Quality-adjusted life-years

The above scatter plot can be interpreted as follows: the most cost-effective comparator would be one with scatter density towards bottom of the Y-axis (i.e., less expensive) and right hand side from the X-axis (i.e., more effective).

Figure 23 displays the cost-effectiveness acceptability curve for the above described analysis, based on 10,000 simulations and variation of willingness-to-pay from $0 to $500,000 per QALY gained.

Figure 23: Cost-Effectiveness Acceptability Curve for Cost-Effectiveness Analysis, in Moderate to Severe Pain KOA Patients Group from Patients' Perspective and 24-Week Time-Horizon.



CS=Chondroitin Sulfate

Section 4: Findings for Study Objective 4:

The fourth objective of our study was to compare the incremental cost-effectiveness of CAM therapies (i.e., glucosamine, CS, and their combination therapy) with celecoxib and placebo in treating KOA from the US health care payers' perspective and 2-year time-horizon. Tables 43 to 48 display results for cost-effectiveness comparison of CAM therapies with celecoxib and placebo among different study groups of KOA patients.

Cost-Effectiveness of CAM Therapies vs. Celecoxib among Overall KOA Patients Group

Table 43 displays the base case results for incremental cost-effectiveness of CAM therapies and conventional medicines among the overall KOA patients group (i.e., KOA patients with baseline WOMAC pain sub-scale scores between 150 and 400) from US health care payers' perspective and 2-year time-horizon. Overall, CAM therapies were cost-effective than conventional medicines in treating KOA. Specifically, the incremental cost-effectiveness of glucosamine, in comparison to CS, was found to be $11,810.64/QALY gained; whereas, all other therapies were dominated.

CS alone therapy was used as the reference group in this analysis (reason is described earlier in this chapter) and was found to have the absolute the cost-effectiveness ratio of $669.23/QALY gained.

Table 43: Base Case Results for Cost-Effectiveness Analysis, in Overall KOA Patients Group from US Health care Payers' Perspective and 2-Year Time-Horizon, with Chondroitin Sulfate as the Reference Group.

Study Comparator	Total Cost	Total QALYs gained[┼]	Incremental Cost	Incremental QALYs gained	ICER (Cost/QALY gained)
CS	$434	0.6482			
Glucosamine	$545	0.6576	$111	0.0094	$11,811
Placebo	$699	0.6492	$155	-0.0084	-$18,406*
Celecoxib	$868	0.6488	$169	-0.0004	-$422,325*
Glucosamine + CS	$951	0.642	$82	-0.0068	-$12,116*

*=Dominated therapies

┼=All QALYs are based on SF-6D based health utilities mapped from SF-36

CS=Chondroitin Sulfate; ICER=Incremental cost-effectiveness ratio; QALYs=Quality-adjusted life-years

Sensitivity Analysis

In one-way sensitivity analysis, the following parameters were found to impact the expected value of the cost-effectiveness model: utilities of response and no response to the treatment at 2-years; medications compliance rate; discount rate; and response rate among compliant and non-compliant patients on glucosamine. No other model parameters affect cost-effectiveness ratios.

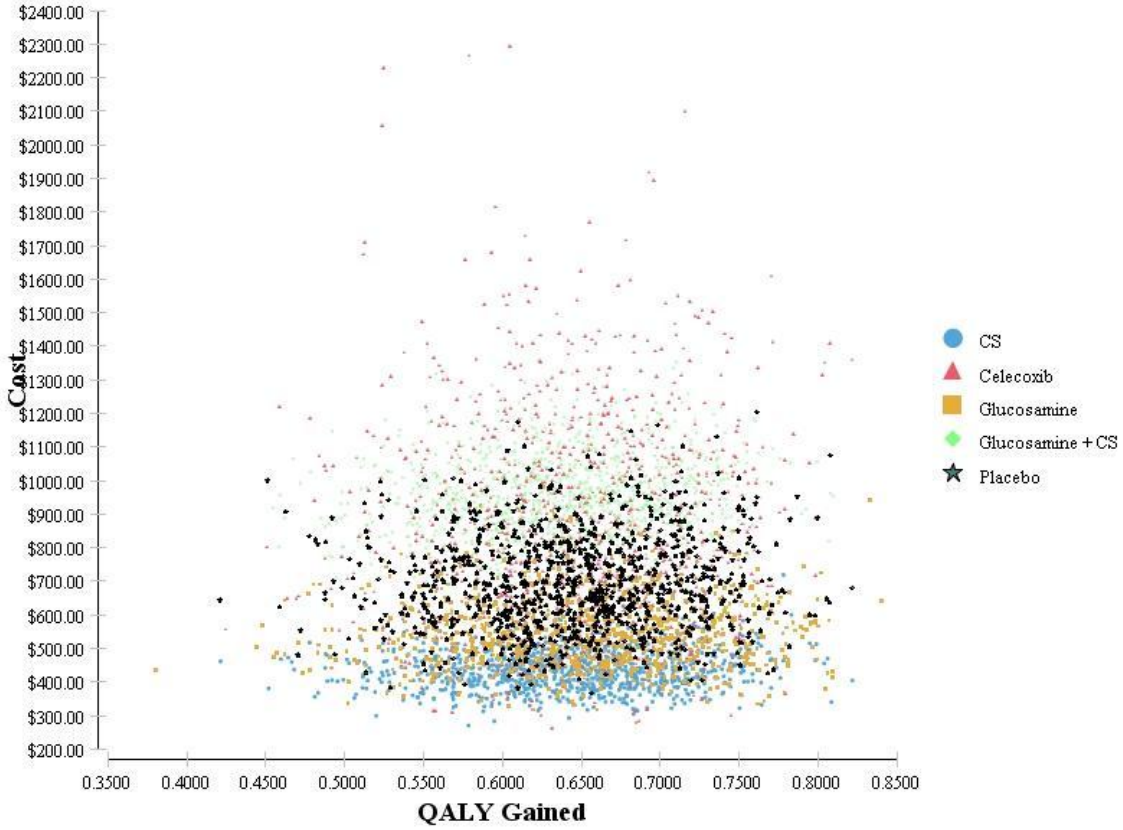
Table 44 displays the detailed results of probabilistic sensitivity analysis on all model inputs and Figure 24 presents its scatter plot based on 10000 second-order Monte Carlo simulations.

Table 44: Probabilistic Sensitivity Analysis Results, in Overall KOA Patients Group from US Health care Payers' Perspective and 2-Year Time-Horizon.

	Parameters	**CS**	**Glucosamine**	**Glucosamine + CS**	**Celecoxib**	**Placebo**
Cost	*Mean*	$434	$545	$951	$866	$699
	SD	$56	$103	$122	$294	$143
	Min	$263	$191	$542	$153	$315
	2.50%	$331	$366	$731	$393	$452
	10%	$364	$417	$798	$515	$523
	Median	$432	$539	$946	$834	$689
	90%	$506	$681	$1,112	$1,259	$889
	97.50%	$550	$761	$1,208	$1,530	$1,007
	Max	$719	$1,137	$1,429	$2,302	$699
QALYs gained†	*Mean*	0.6485	0.6578	0.6424	1324.98	0.6495
	SD	0.0620	0.0681	0.0599	0.6491	0.0623
	Min	0.3963	0.3784	0.3964	0.0622	0.3963
	2.50%	0.5226	0.5187	0.5217	0.3963	0.5226
	10%	0.5680	0.5684	0.5650	0.5226	0.5682
	Median	0.6502	0.6604	0.6437	0.5680	0.6513
	90%	0.7270	0.7439	0.7193	0.6508	0.7284
	97.50%	0.7627	0.7815	0.7528	0.7274	0.7643
	Max	0.8646	0.8737	0.8650	0.7638	0.8647

┼=All QALYs are based on SF-6D based health utilities mapped from SF-36
CS=Chondroitin Sulfate; QALYs=Quality-adjusted life-years

Figure 24: Scatter Plot for Probabilistic Sensitivity Analysis Based on 10000 Simulations, in Overall KOA Patients Group from US Health care Payers' Perspective and 2-Year Time-Horizon.

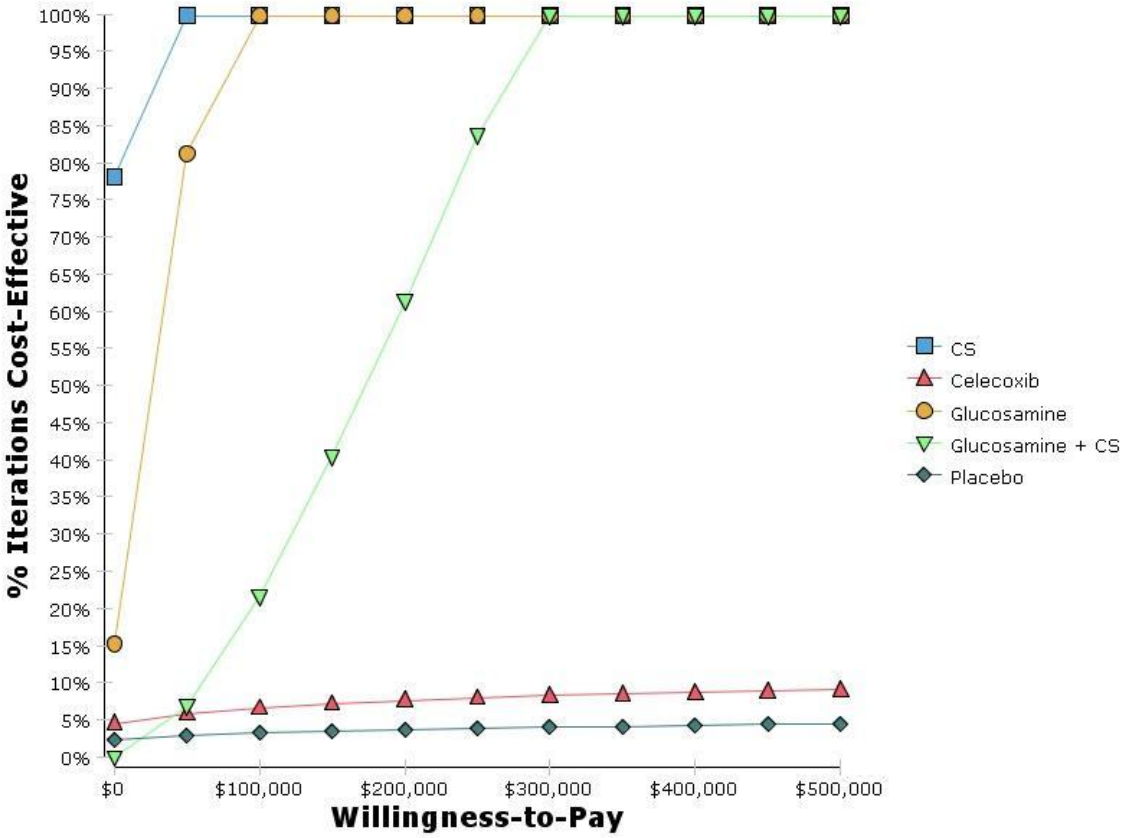


CS=Chondroitin Sulfate; QALYs=Quality-adjusted life-years

The above scatter plot can be interpreted as follows: the most cost-effective comparator would be one with scatter density towards bottom of the Y-axis (i.e., less expensive) and right hand side from the X-axis (i.e., more effective).

Figure 25 displays the cost-effectiveness acceptability curve for the above described analysis, based on 10,000 simulations and variation of willingness-to-pay from $0 to $500,000 per QALY gained.

Figure 25: Cost-Effectiveness Acceptability Curve, in Overall KOA Patients Group from US Health care Payers' Perspective and 2-Year Time-Horizon.



CS=Chondroitin Sulfate

Cost-Effectiveness of CAM Therapies vs. Celecoxib among KOA Patients with Mild Pain

In this sub-group analysis, cost-effectiveness of CAM therapies was compared with celecoxib and placebo in the treatment of KOA among those patients that had mild knee pain at the baseline defined by WOMAC pain sub-scale score of 150 to 300. The time-horizon was 2-years and study perspective was of the US healthcare payers'.

Table 45 displays the base case results for incremental cost-effectiveness of CAM therapies with celecoxib and placebo from US health care payers' perspective and 2-year time-horizon, among the KOA patients group with mild baseline. Overall, CAM therapies were cost-effective than conventional medicines in treating KOA. Specifically, the incremental cost-effectiveness of glucosamine, in comparison to CS, was found to be $9,570.69/QALY gained.

CS alone therapy was used as the reference group in this analysis (reason is described earlier in this chapter) and was found to have the absolute the cost-effectiveness ratio of $668.51/QALY gained.

Table 45: Base Case Results for Cost-Effectiveness Analysis, in Mild Pain Only KOA Patients Group from US Health care Payers' Perspective and 2-Year Time-Horizon, with Chondroitin Sulfate as the Reference Group.

Study Comparator	Total Cost	Total QALYs gained[┼]	Incremental Cost	Incremental QALYs gained	ICER (Cost/QALY gained)
CS	$434	0.6489			
Glucosamine	$545	0.6605	$111	0.0116	$9,571
Placebo	$699	0.6476	$155	-0.0129	-$11985*
Celecoxib	$868	0.6482	$169	0.0006	$281,550
Glucosamine + CS	$951	0.6421	$82	-0.0061	-$13506*

*=Dominated therapies

┼=All QALYs are based on SF-6D based health utilities mapped from SF-36

CS=Chondroitin Sulfate; ICER=Incremental cost-effectiveness ratio; QALYs=Quality-adjusted life-years

Sensitivity Analysis

In one-way sensitivity analysis, the following parameters were found to impact the expected value of the cost-effectiveness model: utilities of response and no response to the treatment at 2-years; medications compliance rate; discount rate; response rate among compliant and non-compliant patients on glucosamine; and 2-years cost of glucosamine therapy. No other model parameters affect cost-effectiveness ratios.

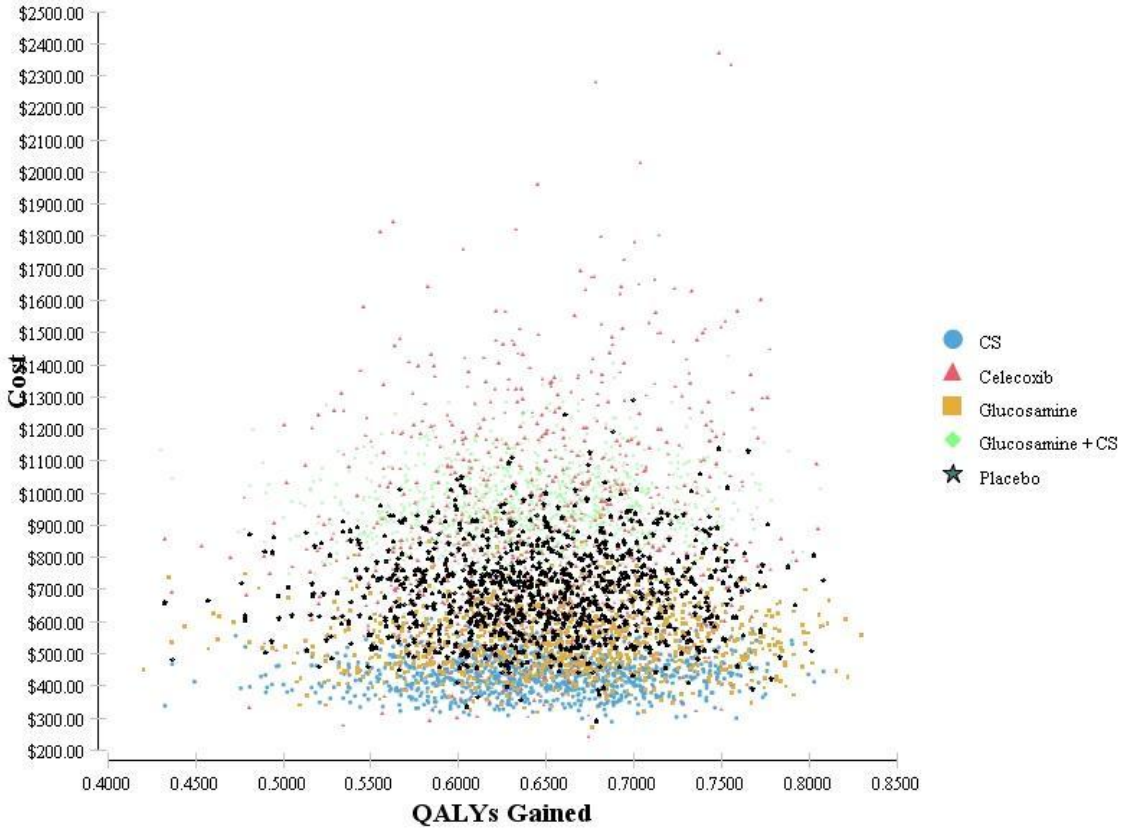
Table 46 displays the detailed results of probabilistic sensitivity analysis on all model inputs and Figure 26 presents its scatter plot based on 10000 second-order Monte Carlo simulations.

Table 46: Probabilistic Sensitivity Analysis Results, in Mild Pain Only KOA Patients Group from US Health care Payers' Perspective and 2-Year Time-Horizon.

	Parameters	**CS**	**Glucosamine**	**Glucosamine + CS**	**Celecoxib**	**Placebo**
Cost	*Mean*	$433	$545	$951	$870	$697
	SD	$56	$102	$122	$298	$144
	Min	$260	$188	$551	$117	$249
	2.50%	$331	$364	$731	$387	$445
	10%	$363	$421	$799	$518	$521
	Median	$430	$540	$944	$837	$687
	90%	$506	$678	$1,113	$1,270	$886
	97.50%	$550	$763	$1,208	$1,553	$1,005
	Max	$717	$1,113	$1,483	$2,365	$1,353
QALYs gained†	*Mean*	0.6493	0.6609	0.6425	0.6486	0.6480
	SD	0.0619	0.0703	0.0596	0.0616	0.0612
	Min	0.3987	0.3774	0.4089	0.3998	0.3996
	2.50%	0.5200	0.5121	0.5208	0.5200	0.5198
	10%	0.5681	0.5693	0.5648	0.5680	0.5677
	Median	0.6514	0.6642	0.6440	0.6509	0.6501
	90%	0.7275	0.7496	0.7177	0.7263	0.7253
	97.50%	0.7642	0.7875	0.7561	0.7638	0.7625
	Max	0.8457	0.8726	0.8409	0.8460	0.8439

┼=All QALYs are based on SF-6D based health utilities mapped from SF-36
CS=Chondroitin Sulfate; QALYs=Quality-adjusted life-years

Figure 26: Scatter Plot for Probabilistic Sensitivity Analysis, in Mild Pain Only KOA Patients Group from US Health care Payers' Perspective and 2-Year Time-Horizon.

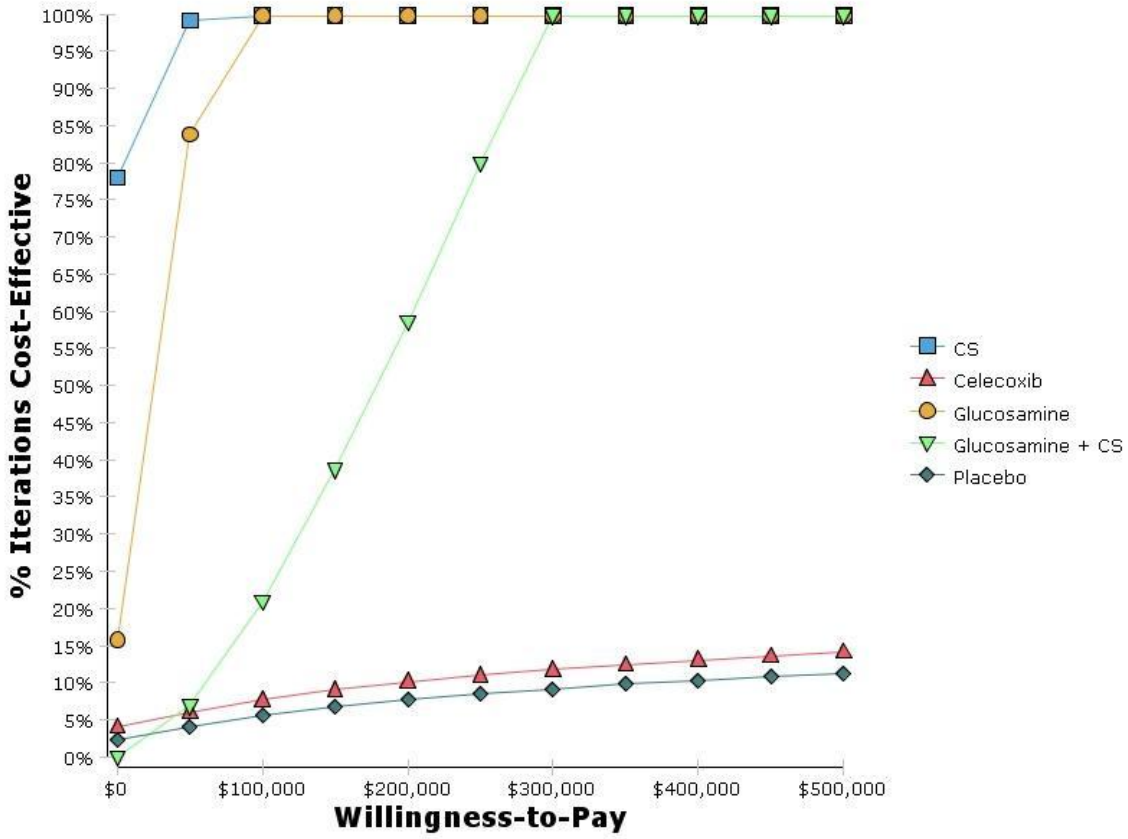


CS=Chondroitin Sulfate; QALYs=Quality-adjusted life-years

The above scatter plot can be interpreted as follows: the most cost-effective comparator would be one with scatter density towards bottom of the Y-axis (i.e., less expensive) and right hand side from the X-axis (i.e., more effective).

Figure 27 displays the cost-effectiveness acceptability curve for the above described analysis, based on 10,000 simulations and variation of willingness-to-pay from $0 to $500,000 per QALY gained.

Figure 27: Cost-Effectiveness Acceptability Curve for Cost-Effectiveness Analysis, in Mild Pain Only KOA Patients Group from US Health care Payers' Perspective and 2-Year Time-Horizon.



CS=Chondroitin Sulfate

Cost-Effectiveness of CAM Therapies vs. Celecoxib among KOA Patients with Moderate to Severe Pain

In this sub-group analysis, cost-effectiveness of CAM therapies was compared with celecoxib and placebo in the treatment of KOA among those patients that had moderate to severe knee pain at the baseline defined by WOMAC pain sub-scale score of 301 to 400. The time-horizon was 2-year and study perspective was of the US healthcare payers'.

Table 47 displays the base case results for incremental cost-effectiveness of CAM therapies with celecoxib and placebo from US health care payers' perspective and 2-year time-horizon, among the KOA patients group with moderate to severe baseline pain. Overall, with CS as the reference group, the incremental cost-effectiveness of placebo therapy was found to be $12368.80/QALY gained.

CS alone therapy was used as the reference group in this analysis (reason is described earlier in this chapter) and was found to have the absolute the cost-effectiveness ratio of $672.14/QALY gained.

Table 47: Base Case Results for Cost-Effectiveness Analysis, in Moderate to Severe Pain KOA Patients Group from US Health care Payers' Perspective and 2-Year Time-Horizon, with Chondroitin Sulfate as the Reference Group.

Study Comparator	Total Cost	Total QALYs gained[┼]	Incremental Cost	Incremental QALYs gained	ICER (Cost/QALY gained)
CS	$434	0.6454			
Glucosamine	$545	0.6458	$111	0.0004	$277,550
Placebo	$699	0.6583	$155	0.0125	$12,369
Celecoxib	$868	0.6557	$169	-0.0026	-$64973*
Glucosamine + CS	$951	0.6423	$82	-0.0134	-$6148*

*=Dominated therapies

┼=All QALYs are based on SF-6D based health utilities mapped from SF-36

CS=Chondroitin Sulfate; ICER=Incremental cost-effectiveness ratio; QALYs=Quality-adjusted life-years

Sensitivity Analysis

In one-way sensitivity analysis, the following parameters were found to impact the expected value of the cost-effectiveness model: utilities of response and no response to the treatment at 24-weeks; discount rate; medications compliance rate; 2-year cost of treatment with placebo; and response rate among compliant patients on combination of glucosamine and CS. No other model parameters affect cost-effectiveness ratios.

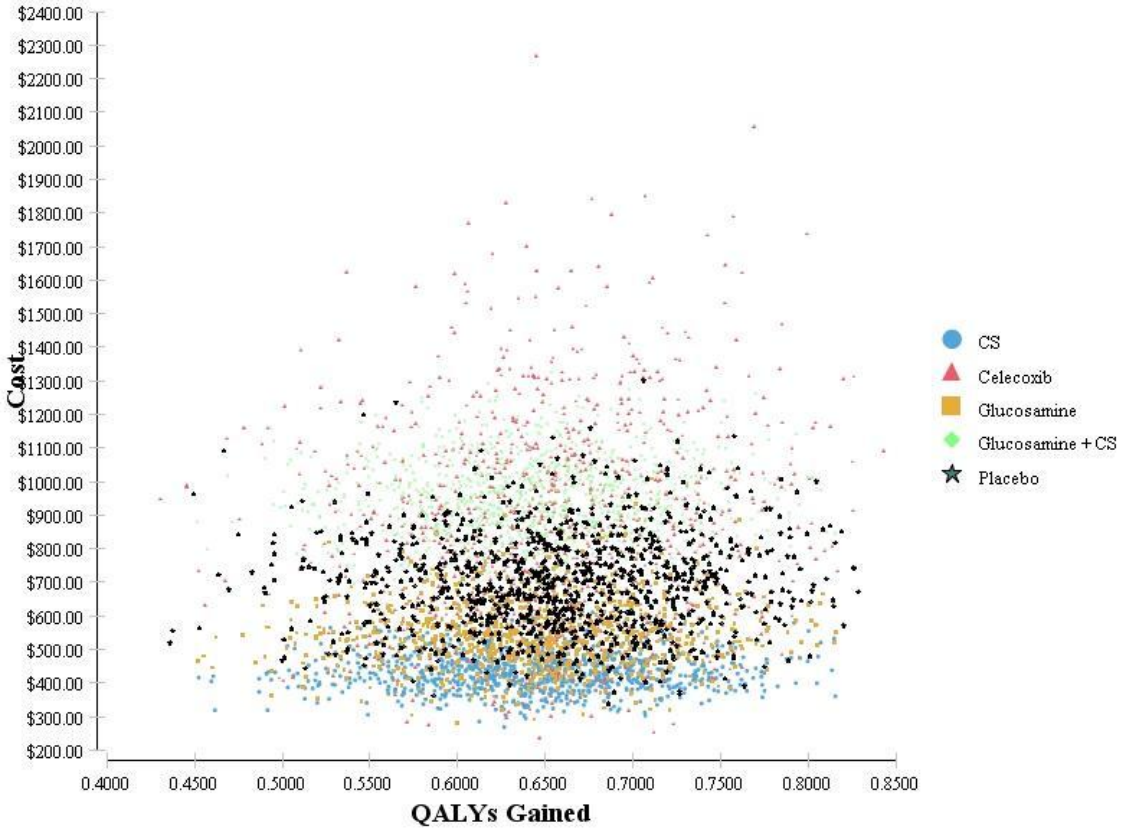
Table 48 displays the detailed results of probabilistic sensitivity analysis on all model inputs and Figure 28 presents its scatter plot based on 10000 second-order Monte Carlo simulations.

Table 48: Probabilistic Sensitivity Analysis Results, in Moderate to Severe Pain KOA Patients Group from US Health care Payers' Perspective and 2-Year Time-Horizon.

	Parameters	**CS**	**Glucosamine**	**Glucosamine + CS**	**Celecoxib**	**Placebo**
Cost	*Mean*	$434	$545	$949	$874	$698
	SD	$55	$104	$122	$294	$143
	Min	$267	$234	$469	$190	$289
	2.50%	$333	$365	$723	$398	$446
	10%	$365	$416	$796	$521	$523
	Median	$432	$539	$944	$843	$687
	90%	$507	$682	$1,106	$1,272	$887
	97.50%	$550	$764	$1,201	$1,540	$1,007
	Max	$681	$1,013	$1,498	$2,313	$1,379
QALYs gained┼	*Mean*	0.6458	0.6462	0.6426	0.6561	0.6586
	SD	0.0610	0.0616	0.0602	0.0678	0.0687
	Min	0.4005	0.4001	0.4023	0.3964	0.3877
	2.50%	0.5218	0.5216	0.5205	0.5183	0.5143
	10%	0.5665	0.5662	0.5648	0.5675	0.5681
	Median	0.6473	0.6479	0.6443	0.6581	0.6612
	90%	0.7229	0.7244	0.7192	0.7414	0.7447
	97.50%	0.7606	0.7615	0.7556	0.7822	0.7849
	Max	0.8411	0.8448	0.8393	0.8734	0.8607

┼=All QALYs are based on SF-6D based health utilities mapped from SF-36
CS=Chondroitin Sulfate; QALYs=Quality-adjusted life-years

Figure 28: Scatter Plot for Probabilistic Sensitivity Analysis, in Moderate to Severe Pain KOA Patients Group from US Health care Payers' Perspective and 2-Year Time-Horizon.

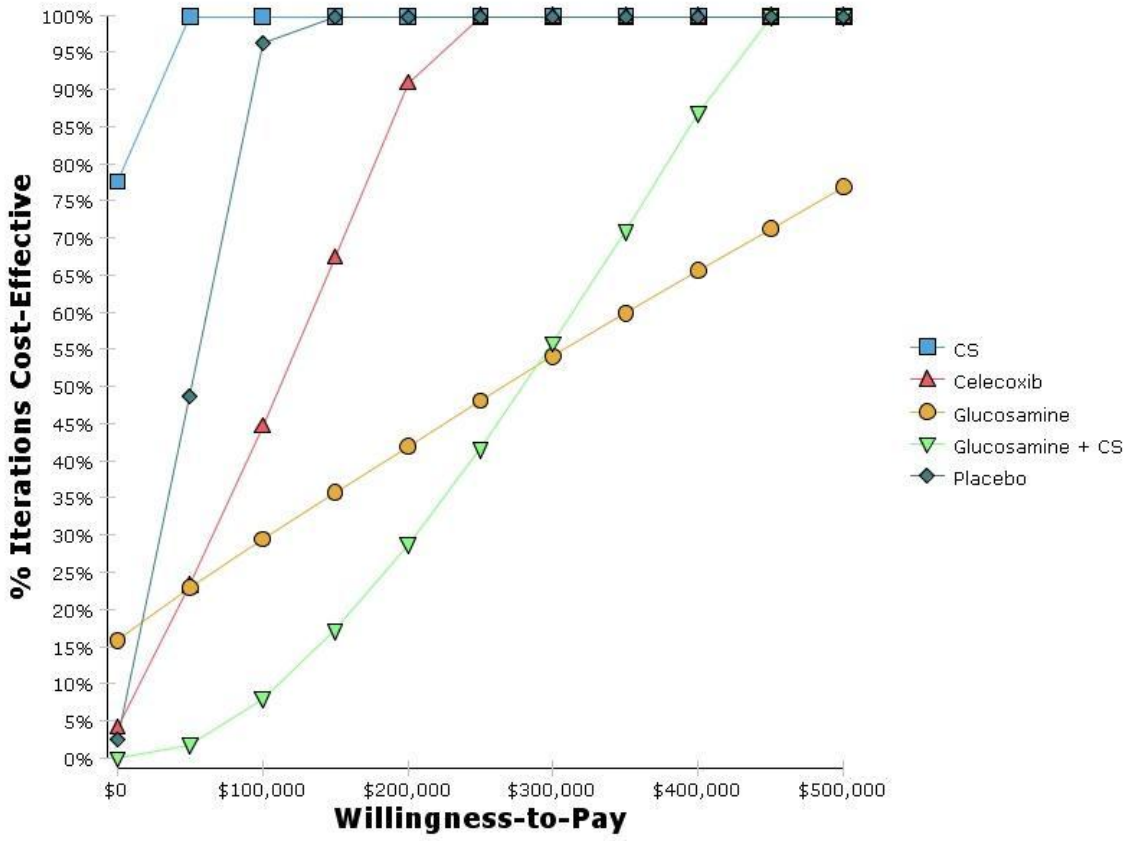


CS=Chondroitin Sulfate; QALYs=Quality-adjusted life-years

The above scatter plot can be interpreted as follows: the most cost-effective comparator would be one with scatter density towards bottom of the Y-axis (i.e., less expensive) and right hand side from the X-axis (i.e., more effective).

Figure 29 displays the cost-effectiveness acceptability curve for the above described analysis, based on 10,000 simulations and variation of willingness-to-pay from $0 to $500,000 per QALY gained.

Figure 29: Cost-Effectiveness Acceptability Curve for Cost-Effectiveness Analysis, in Moderate to Severe Pain KOA Patients Group from US Health care Payers' Perspective and 2-Year Time-Horizon.



CS=Chondroitin Sulfate

Section 5: Findings for Study Objective 5:

The fifth objective of our study was to compare the incremental cost-effectiveness of CAM therapies (i.e., glucosamine, CS, and their combination therapy) with celecoxib and placebo to treat KOA from patients' perspective and 2-year time-horizon. Tables 49 to 54 display results for cost-effectiveness comparison of CAM therapies with celecoxib and placebo among different study groups of KOA patients.

Cost-Effectiveness of CAM Therapies vs. Celecoxib among Overall KOA Patients Group

Table 49 displays the base case results for incremental cost-effectiveness of CAM therapies and conventional medicines among the overall KOA patients group (i.e., KOA patients with baseline WOMAC pain sub-scale scores between 150 and 400) patients' perspective and 2-year time-horizon. Overall, CAM therapies were cost-effective than conventional medicines in treating KOA. Specifically, the incremental cost-effectiveness of glucosamine, in comparison to CS, was found to be $11,810.64/QALY gained; whereas, while all other therapies were dominated.

CS alone therapy was used as the reference group in this analysis (reason is described earlier in this chapter) and was found to have the absolute the cost-effectiveness ratio of $40,681.17/QALY gained.

Table 49: Base Case Results for Cost-Effectiveness Analysis, in Overall KOA Patients Group from Patients' Perspective and 2-Year Time-Horizon, with Chondroitin Sulfate as the Reference Group.

Study Comparator	Total Cost	Total QALYs gained[┼]	Incremental Cost	Incremental QALYs gained	ICER (Cost/QALY gained)
CS	$26,370	0.6482			
Glucosamine	$26,481	0.6576	$111	0.0094	$11,811
Placebo	$26,635	0.6492	$155	-0.0084	-$18,406*
Celecoxib	$26,804	0.6488	$169	-0.0004	-$422,325*
Glucosamine + CS	$26,886	0.642	$82	-0.0068	-$12,116*

*=Dominated therapies

┼=All QALYs are based on SF-6D based health utilities mapped from SF-36

CS=Chondroitin Sulfate; ICER=Incremental cost-effectiveness ratio; QALYs=Quality-adjusted life-years

Sensitivity Analysis

In one-way sensitivity analysis, the following parameters were found to impact the expected value of the cost-effectiveness model: utilities of response and no response to the treatment at 2-years; medications compliance rate; discount rate; response rate among compliant and non-compliant patients on glucosamine; and 2-year cost of treatment with glucosamine and indirect health care costs. No other model parameters affect cost-effectiveness ratios.

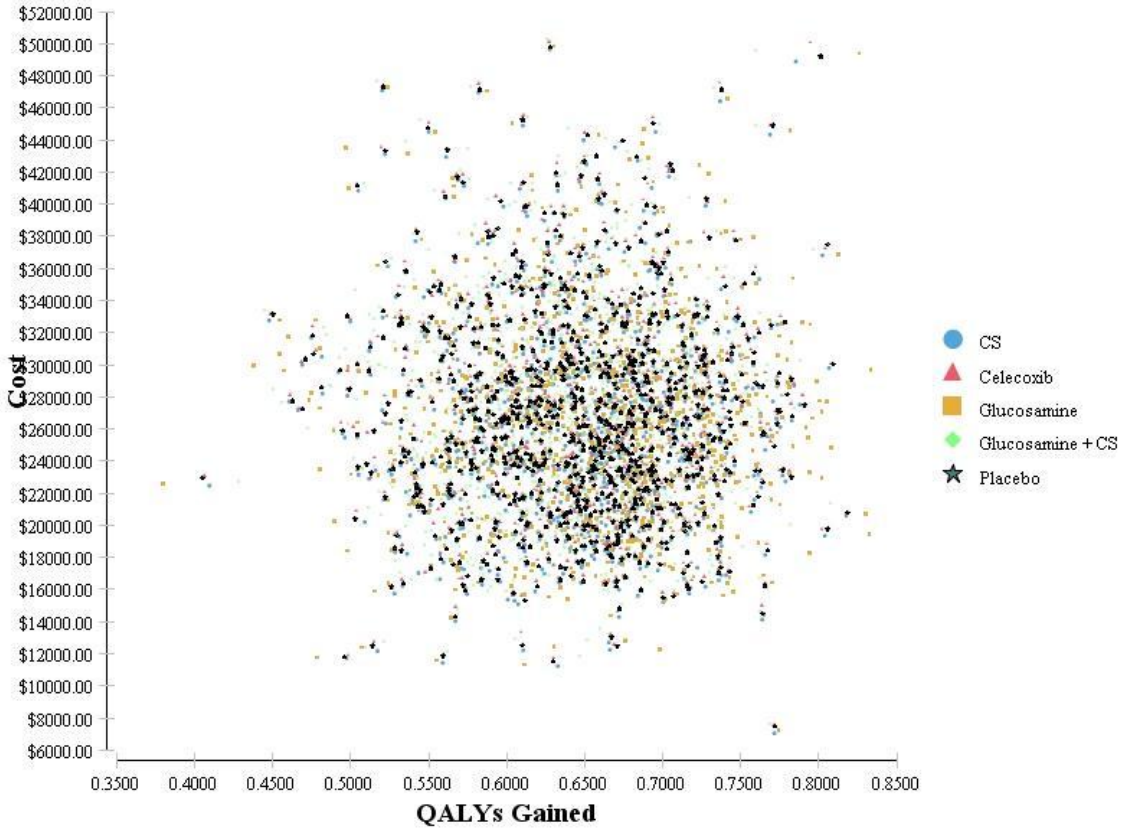
Table 50 displays the detailed results of probabilistic sensitivity analysis on all model inputs and Figure 30 presents its scatter plot based on 10000 second-order Monte Carlo simulations.

Table 50: Probabilistic Sensitivity Analysis Results, in Overall KOA Patients Group from Patients' Perspective and 2-Year Time-Horizon.

	Parameters	**CS**	**Glucosamine**	**Glucosamine + CS**	**Celecoxib**	**Placebo**
Cost	*Mean*	$26,461	$26,570	$26,979	$26,894	$26,728
	SD	$6,147	$6,149	$6,149	$6,156	$6,151
	Min	$7,047	$7,192	$7,611	$7,482	$7,497
	2.50%	$15,811	$15,990	$16,327	$16,232	$16,144
	10%	$18,822	$18,956	$19,353	$19,308	$19,100
	Median	$25,965	$26,067	$26,491	$26,402	$26,232
	90%	$34,622	$34,761	$35,172	$35,105	$34,905
	97.50%	$39,779	$39,873	$40,281	$40,132	$40,004
	Max	$57,455	$57,365	$57,851	$58,291	$57,269
QALYs gained┼	*Mean*	0.6487	0.6582	0.6425	0.6493	0.6497
	SD	0.0624	0.0686	0.0604	0.0627	0.0629
	Min	0.4036	0.3804	0.4009	0.4031	0.4034
	2.50%	0.5218	0.5175	0.5185	0.5214	0.5214
	10%	0.5664	0.5660	0.5634	0.5670	0.5670
	Median	0.6510	0.6624	0.6447	0.6518	0.6521
	90%	0.7271	0.7441	0.7184	0.7278	0.7285
	97.50%	0.7644	0.7830	0.7557	0.7658	0.7665
	Max	0.8635	0.8711	0.8588	0.8643	0.8646

┼=All QALYs are based on SF-6D based health utilities mapped from SF-36
CS=Chondroitin Sulfate; QALYs=Quality-adjusted life-years

Figure 30: Scatter Plot for Probabilistic Sensitivity Analysis Based on 10000 Simulations, in Overall KOA Patients Group from Patients' Perspective and 2-Year Time-Horizon.

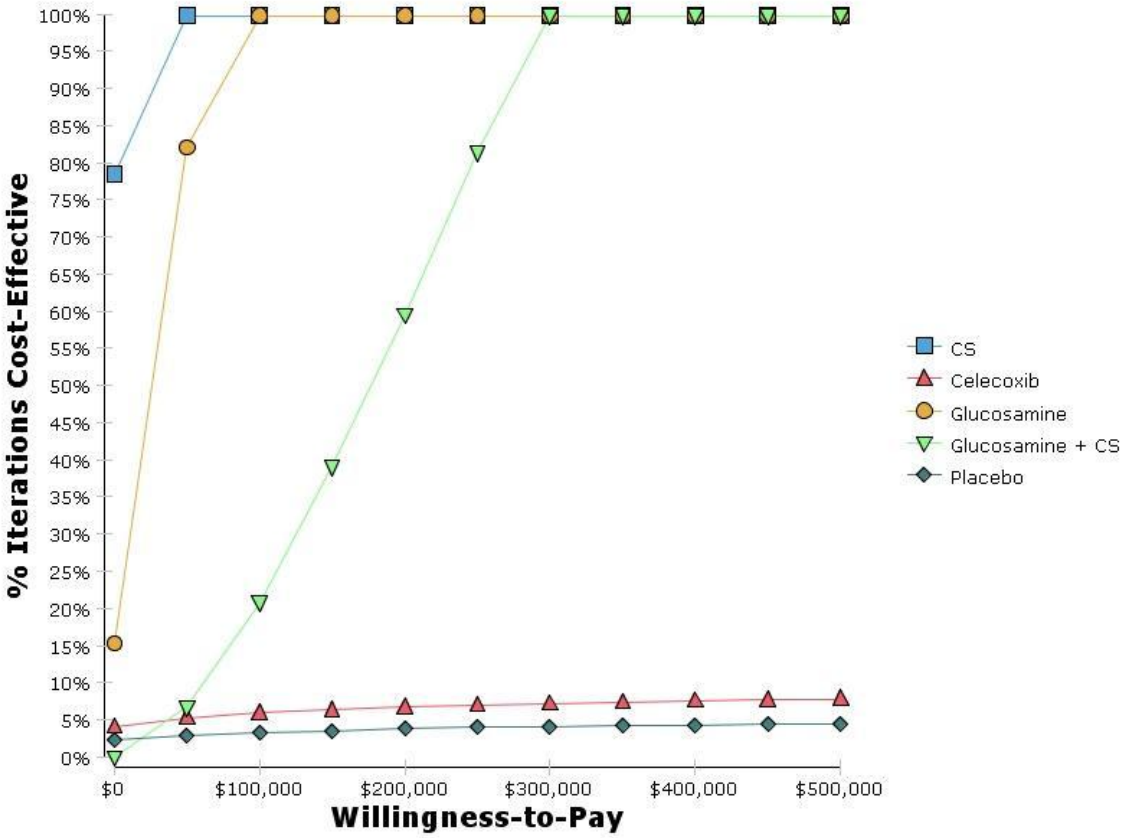


CS=Chondroitin Sulfate; QALYs=Quality-adjusted life-years

The above scatter plot can be interpreted as follows: the most cost-effective comparator would be one with scatter density towards bottom of the Y-axis (i.e., less expensive) and right hand side from the X-axis (i.e., more effective).

Figure 31 displays the cost-effectiveness acceptability curve for the above described analysis, based on 10,000 simulations and variation of willingness-to-pay from $0 to $500,000 per QALY gained.

Figure 31: Cost-Effectiveness Acceptability Curve, in Overall KOA Patients Group from Patients' Perspective and 2-Year Time-Horizon.



CS=Chondroitin Sulfate

Cost-Effectiveness of CAM Therapies vs. Celecoxib among KOA Patients with Mild Pain

In this sub-group analysis, cost-effectiveness of CAM therapies was compared with celecoxib and placebo in the treatment of KOA among those patients that had mild knee pain at the baseline defined by WOMAC pain sub-scale score of 150 to 300. The time-horizon was 2-years and study perspective was of the patients'.

Table 51 displays the base case results for incremental cost-effectiveness of CAM therapies with celecoxib and placebo from patients' perspective and 2-year time-horizon, among the KOA patients group with mild baseline. Overall, CAM therapies were cost-effective than conventional medicines in treating KOA. Specifically, the incremental cost-effectiveness of glucosamine, in comparison to CS, was found to be $9,570.69/QALY gained.

CS alone therapy was used as the reference group in this analysis (reason is described earlier in this chapter) and was found to have the absolute the cost-effectiveness ratio of $40,783.97/QALY gained.

Table 51: Base Case Results for Cost-Effectiveness Analysis, in Mild Pain Only KOA Patients Group from Patients' Perspective and 2-Year Time-Horizon, with Chondroitin Sulfate as the Reference Group.

Study Comparator	Total Cost	Total QALYs gained[┼]	Incremental Cost	Incremental QALYs gained	ICER (Cost/QALY gained)
CS	$26,465	0.6489			
Glucosamine	$26,576	0.6605	$111	0.0116	$9,571
Placebo	$26,730	0.6476	$155	-0.0129	-$11,986*
Celecoxib	$26,899	0.6482	$169	0.0006	$281,533
Glucosamine + CS	$26,982	0.6421	$82	-0.0061	-$13,506*

*=Dominated therapies

┼=All QALYs are based on SF-6D based health utilities mapped from SF-36

CS=Chondroitin Sulfate; ICER=Incremental cost-effectiveness ratio; QALYs=Quality-adjusted life-years

Sensitivity Analysis

In one-way sensitivity analysis, the following parameters were found to impact the expected value of the cost-effectiveness model: utilities of response and no response to the treatment at 2-years; medications compliance rate; discount rate; response rate among compliant and non-compliant patients on glucosamine; and 2-years cost of glucosamine therapy and indirect health care costs. No other model parameters affect cost-effectiveness ratios.

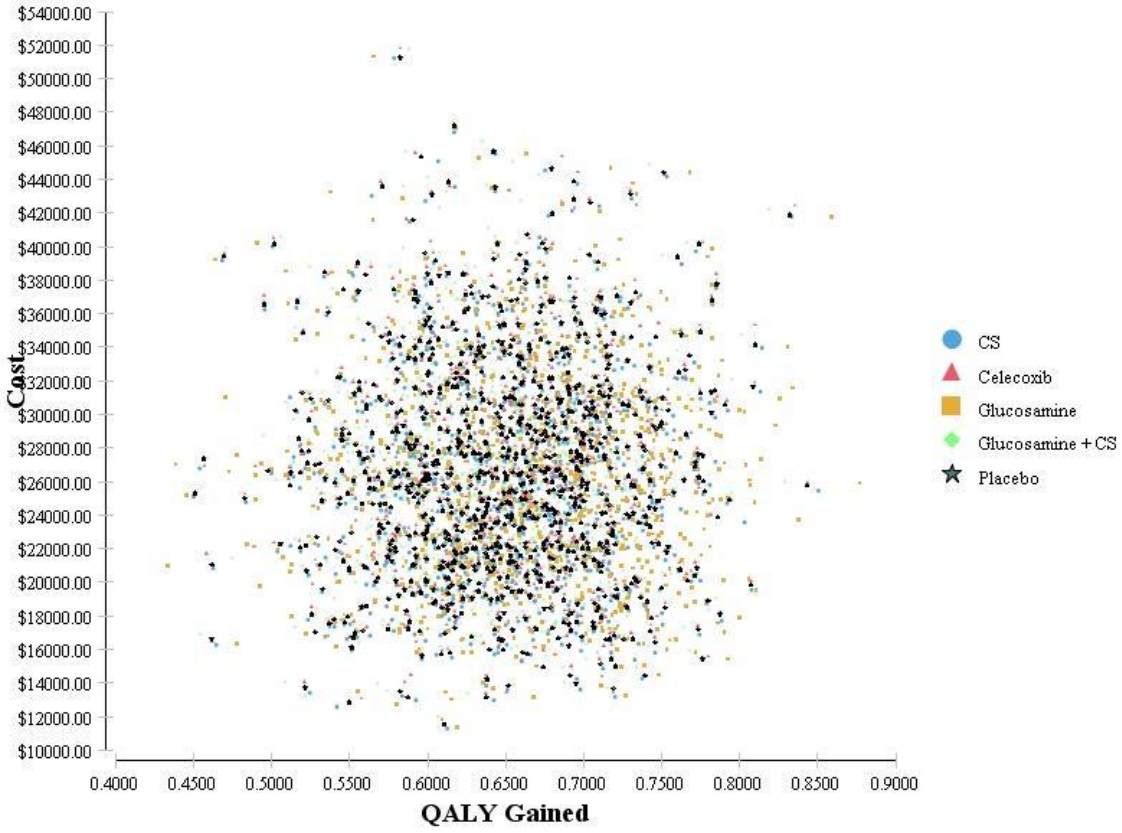
Table 52 displays the detailed results of probabilistic sensitivity analysis on all model inputs and Figure 32 presents its scatter plot based on 10000 second-order Monte Carlo simulations.

Table 52: Probabilistic Sensitivity Analysis Results, in Mild Pain Only KOA Patients Group from Patients' Perspective and 2-Year Time-Horizon.

	Parameters	**CS**	**Glucosamine**	**Glucosamine + CS**	**Celecoxib**	**Placebo**
Cost	*Mean*	$26,495	$26,604	$27,011	$26,929	$26,761
	SD	$6,099	$6,099	$6,103	$6,111	$6,102
	Min	$9,019	$9,117	$9,524	$9,286	$9,546
	2.50%	$16,014	$16,119	$16,514	$16,424	$16,243
	10%	$19,169	$19,276	$19,672	$19,595	$19,421
	Median	$26,034	$26,147	$26,524	$26,444	$26,284
	90%	$34,510	$34,601	$35,006	$34,916	$34,779
	97.50%	$39,997	$40,149	$40,514	$40,450	$40,289
	Max	$57,950	$58,024	$58,282	$58,364	$58,237
QALYs gained┼	*Mean*	0.6500	0.6616	0.6431	0.6493	0.6486
	SD	0.0625	0.0708	0.0601	0.0621	0.0617
	Min	0.4209	0.3852	0.4072	0.4215	0.4210
	2.50%	0.5228	0.5158	0.5219	0.5223	0.5226
	10%	0.5674	0.5670	0.5650	0.5673	0.5670
	Median	0.6521	0.6650	0.6451	0.6513	0.6507
	90%	0.7294	0.7511	0.7195	0.7284	0.7272
	97.50%	0.7666	0.7897	0.7569	0.7655	0.7643
	Max	0.8584	0.8853	0.8418	0.8580	0.8567

┼=All QALYs are based on SF-6D based health utilities mapped from SF-36
CS=Chondroitin Sulfate; QALYs=Quality-adjusted life-years

Figure 32: Scatter Plot for Probabilistic Sensitivity Analysis, in Mild Pain Only KOA Patients Group from Patients' Perspective and 2-Year Time-Horizon.

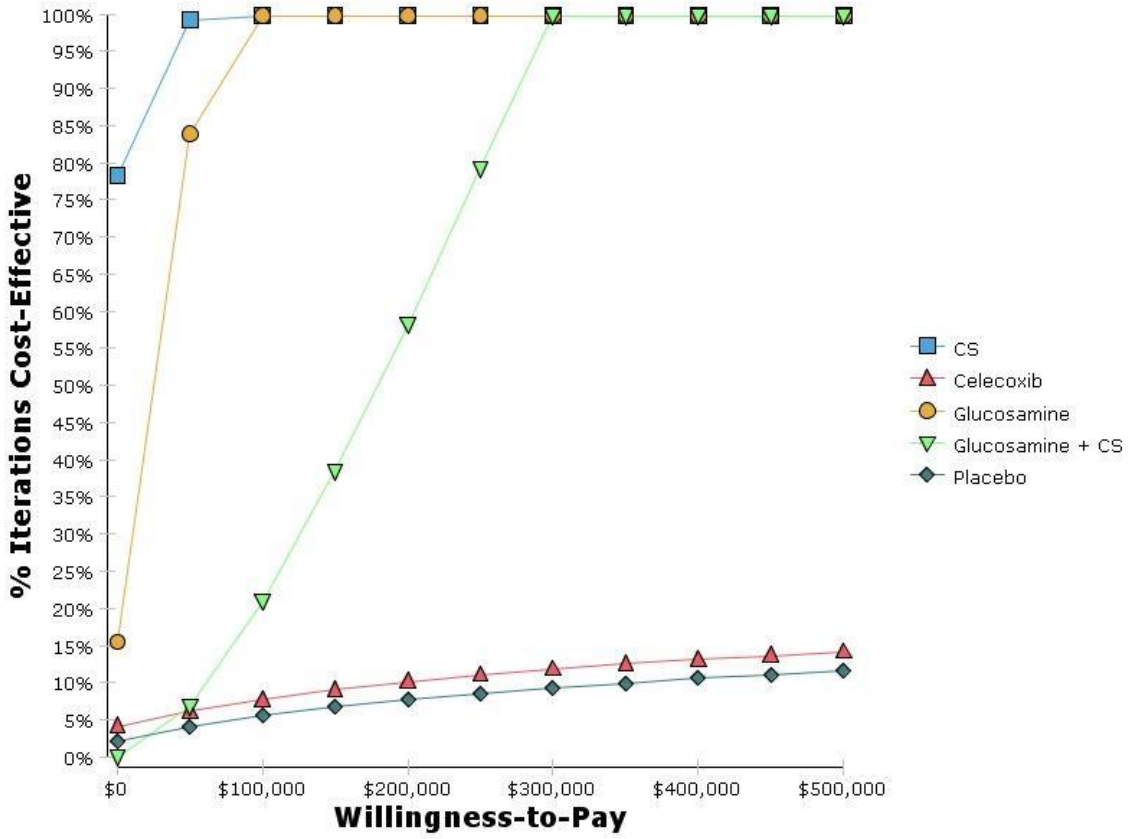


CS=Chondroitin Sulfate; QALYs=Quality-adjusted life-years

The above scatter plot can be interpreted as follows: the most cost-effective comparator would be one with scatter density towards bottom of the Y-axis (i.e., less expensive) and right hand side from the X-axis (i.e., more effective).

Figure 33 displays the cost-effectiveness acceptability curve for the above described analysis, based on 10,000 simulations and variation of willingness-to-pay from $0 to $500,000 per QALY gained.

Figure 33: Cost-Effectiveness Acceptability Curve for Cost-Effectiveness Analysis, in Mild Pain Only KOA Patients Group from Patients' Perspective and 2-Year Time-Horizon.



CS=Chondroitin Sulfate

Cost-Effectiveness of CAM Therapies vs. Celecoxib among KOA Patients with Moderate to Severe Pain

In this sub-group analysis, cost-effectiveness of CAM therapies was compared with celecoxib and placebo in the treatment of KOA among those patients that had moderate to severe knee pain at the baseline defined by WOMAC pain sub-scale score of 301 to 400. The time-horizon was 2-year and study perspective was of the patients'.

Table 53 displays the base case results for incremental cost-effectiveness of CAM therapies with celecoxib and placebo from patients' perspective and 2-year time-horizon, among the KOA patients group with moderate to severe baseline pain. Overall, with CS as the reference group, the incremental cost-effectiveness ratio of placebo was $12,257.03/QALY gained. While celecoxib and combination therapy of glucosamine and CS were dominated by CS alone therapy, the incremental cost-effectiveness of glucosamine alone therapy was $281,984.30/QALY gained.

CS alone therapy was used as the reference group in this analysis (reason is described earlier in this chapter) and was found to have the absolute the cost-effectiveness ratio of $40,891.35/QALY gained.

Table 53: Base Case Results for Cost-Effectiveness Analysis, in Moderate to Severe Pain KOA Patients Group from Patients' Perspective and 2-Year Time-Horizon, with Chondroitin Sulfate as the Reference Group.

Study Comparator	Total Cost	Total QALYs gained[┼]	Incremental Cost	Incremental QALYs gained	ICER (Cost/QALY gained)
CS	$26,417	0.646032			
Glucosamine	$26,528	0.646426	$111	0.0004	$281,984
Placebo	$26,683	0.65904	$155	0.0126	$12,257
Celecoxib	$26,852	0.65631	$169	-0.0027	-$61,865*
Glucosamine + CS	$26,934	0.642957	$82	-0.0134	-$6,170*

*=Dominated therapies

┼=All QALYs are based on SF-6D based health utilities mapped from SF-36

CS=Chondroitin Sulfate; ICER=Incremental cost-effectiveness ratio; QALYs=Quality-adjusted life-years

Sensitivity Analysis

In one-way sensitivity analysis, the following parameters were found to impact the expected value of the cost-effectiveness model: utilities of response and no response to the treatment at 2-years; medications compliance rate; discount rate; response rate among compliant and non-compliant patients on glucosamine; and 2-years cost of glucosamine therapy. No other model parameters affect cost-effectiveness ratios.

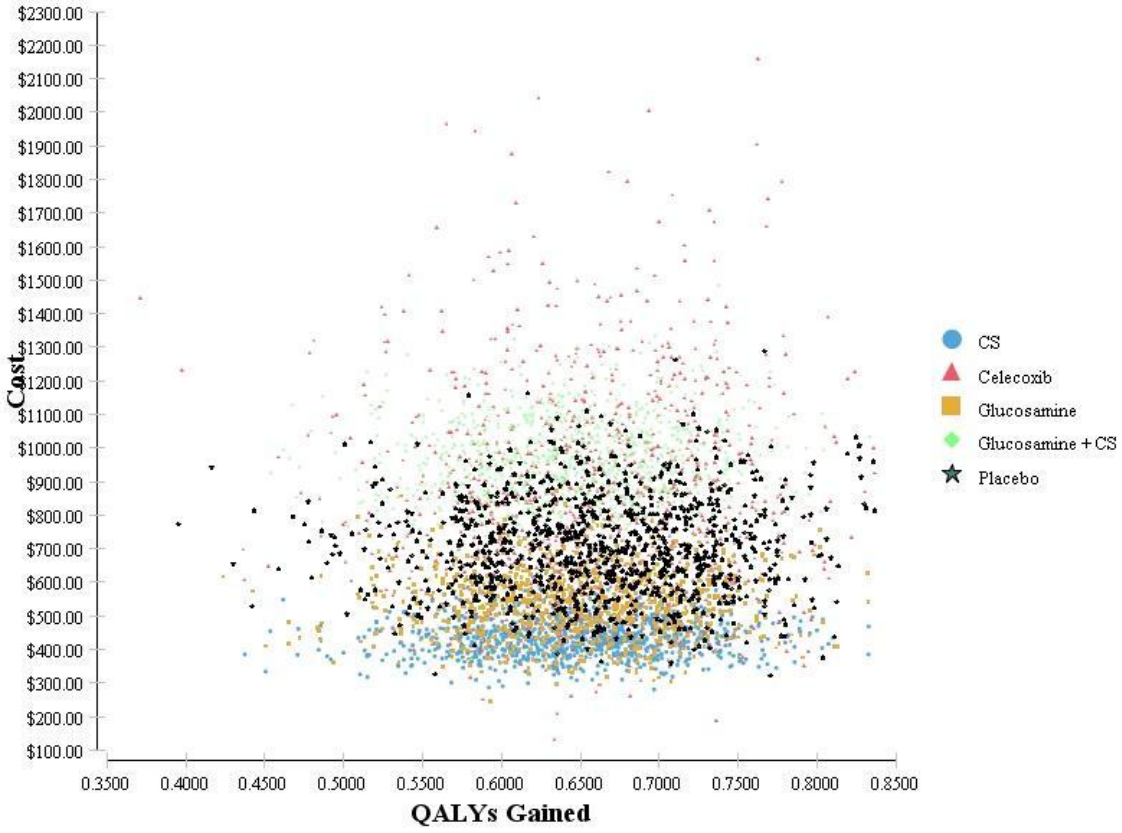
Table 54 displays the detailed results of probabilistic sensitivity analysis on all model inputs and Figure 34 presents its scatter plot based on 10000 second-order Monte Carlo simulations.

Table 54: Probabilistic Sensitivity Analysis Results, in Moderate to Severe Pain KOA Patients Group from Patients' Perspective and 2-Year Time-Horizon.

	Parameters	**CS**	**Glucosamine**	**Glucosamine + CS**	**Celecoxib**	**Placebo**
Cost	*Mean*	$434	$545	$949	$873	$702
	SD	$56	$103	$122	$292	$146
	Min	$253	$245	$541	$121	$252
	2.50%	$333	$363	$725	$397	$447
	10%	$366	$417	$800	$526	$521
	Median	$432	$538	$942	$839	$692
	90%	$507	$681	$1,108	$1,255	$894
	97.50%	$551	$762	$1,204	$1,532	$1,013
	Max	$646	$1,042	$1,682	$2,183	$1,385
QALYs gained†	*Mean*	0.6460	0.6464	0.6430	0.6563	0.6590
	SD	0.0612	0.0617	0.0602	0.0683	0.0694
	Min	0.3967	0.3960	0.3998	0.3714	0.3868
	2.50%	0.5222	0.5208	0.5214	0.5156	0.5156
	10%	0.5664	0.5660	0.5643	0.5669	0.5676
	Median	0.6476	0.6478	0.6440	0.6583	0.6619
	90%	0.7238	0.7250	0.7191	0.7413	0.7459
	97.50%	0.7608	0.7621	0.7564	0.7835	0.7851
	Max	0.8525	0.8528	0.8531	0.8697	0.8696

┼=All QALYs are based on SF-6D based health utilities mapped from SF-36
CS=Chondroitin Sulfate; QALYs=Quality-adjusted life-years

Figure 34: Scatter Plot for Probabilistic Sensitivity Analysis, in Moderate to Severe Pain KOA Patients Group from Patients' Perspective and 2-Year Time-Horizon.

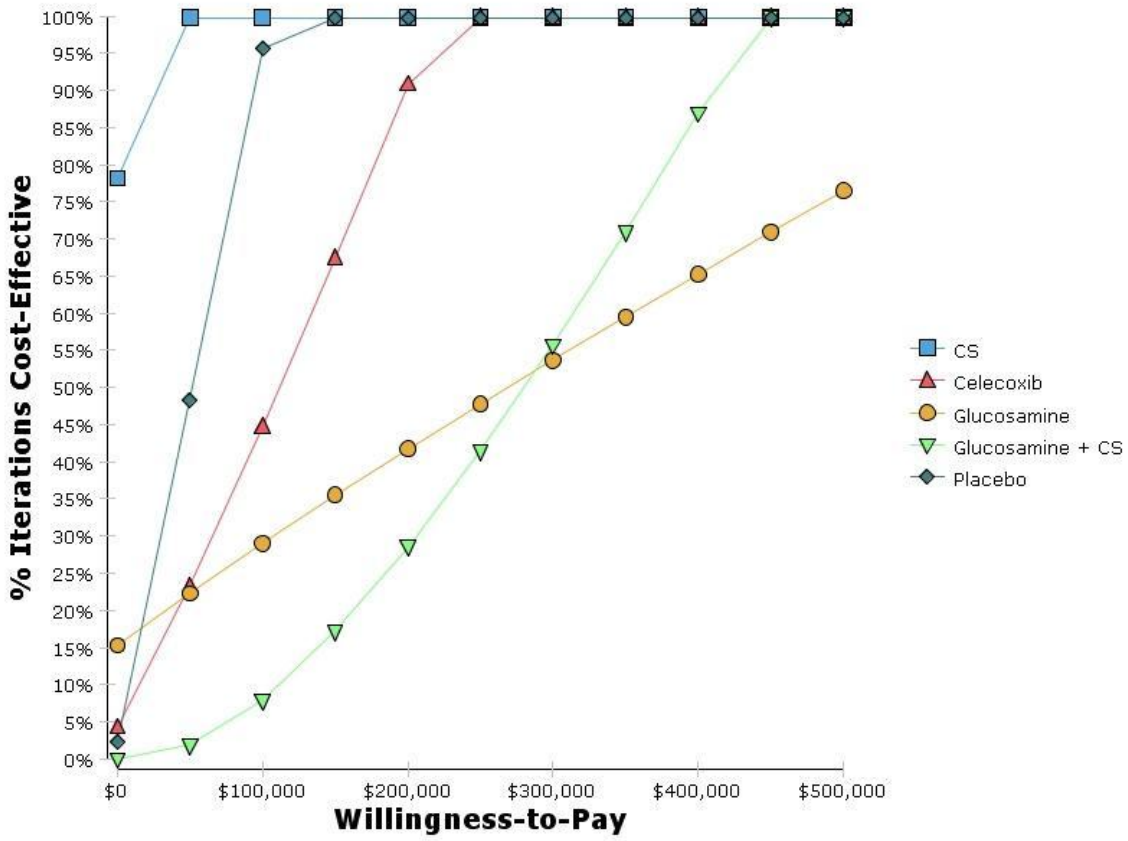


CS=Chondroitin Sulfate; QALYs=Quality-adjusted life-years

The above scatter plot can be interpreted as follows: the most cost-effective comparator would be one with scatter density towards bottom of the Y-axis (i.e., less expensive) and right hand side from the X-axis (i.e., more effective).

Figure 35 displays the cost-effectiveness acceptability curve for the above described analysis, based on 10,000 simulations and variation of willingness-to-pay from $0 to $500,000 per QALY gained.

Figure 35: Cost-Effectiveness Acceptability Curve for Cost-Effectiveness Analysis, in Moderate to Severe Pain KOA Patients Group from Patients' Perspective and 2-Year Time-Horizon.



CS=Chondroitin Sulfate

Structural Sensitivity Analysis

As described in the methods section, structural sensitivity analysis was performed on the 10-year Markov model to account for the robustness of assumption of no risk of adverse events associated with CAM therapies.

Structural Sensitivity Analysis of Cost-Effectiveness of CAM Therapies vs. Conventional Medicines among Overall KOA Patients Group

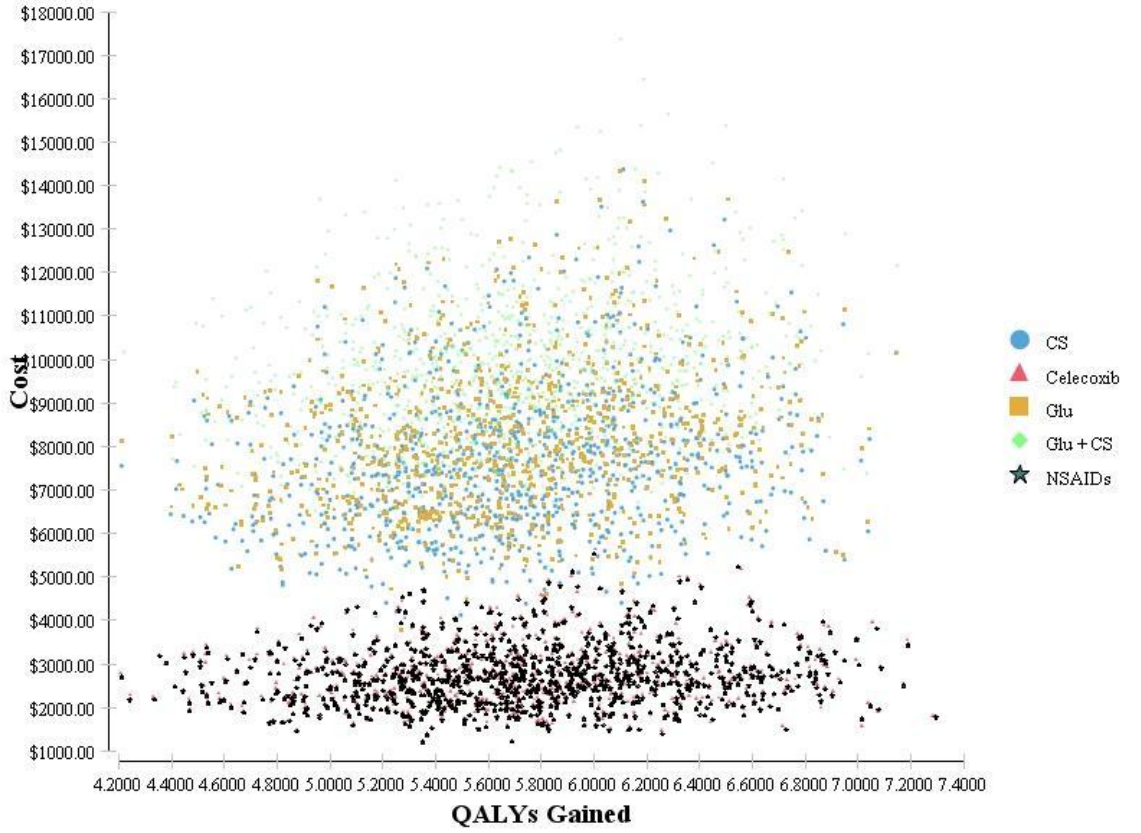
Table 55 displays the detailed results of probabilistic sensitivity analysis on all model inputs and Figure 36 presents its scatter plot based on 10000 second-order Monte Carlo simulations.

Table 55: Probabilistic Sensitivity Analysis Results, in Overall KOA Patients Group from Healthcare Payers Perspective and 10-Year Time-Horizon.

	Parameters	CS	Glucosamine	Glucosamine + CS	Celecoxib	NSAIDs
Cost	*Mean*	$7,598	$8,057	$9,749	$2,696	$2,696
	SD	$1,607	$1,613	$1,680	$665	$665
	Min	$3,175	$3,589	$5,247	$975	$967
	2.50%	$4,913	$5,352	$6,884	$1,585	$1,582
	10%	$5,649	$6,115	$7,708	$1,893	$1,894
	Median	$7,441	$7,917	$9,609	$2,631	$2,630
	90%	$9,706	$10,169	$11,963	$3,572	$3,570
	97.50%	$11,210	$11,628	$13,398	$4,185	$4,194
	Max	$15,984	$16,350	$18,067	$6,363	$6,366
QALYs gained†	*Mean*	5.71	5.71	5.71	5.75	5.75
	SD	0.51	0.51	0.51	0.55	0.55
	Min	3.91	3.91	3.91	3.88	3.89
	2.50%	4.72	4.72	4.72	4.67	4.67
	10%	5.05	5.05	5.05	5.04	5.04
	Median	5.70	5.70	5.70	5.75	5.75
	90%	6.38	6.39	6.39	6.48	6.48
	97.50%	6.71	6.72	6.72	6.82	6.82
	Max	7.66	7.67	7.67	7.86	7.86

†=All QALYs are based on SF-6D based health utilities mapped from SF-36
CS=Chondroitin Sulfate; QALYs=Quality-adjusted life-years

Figure 36: Scatter Plot for Probabilistic Sensitivity Analysis, in Overall KOA Patients Group from Healthcare Payers Perspective and 10-Year Time-Horizon.

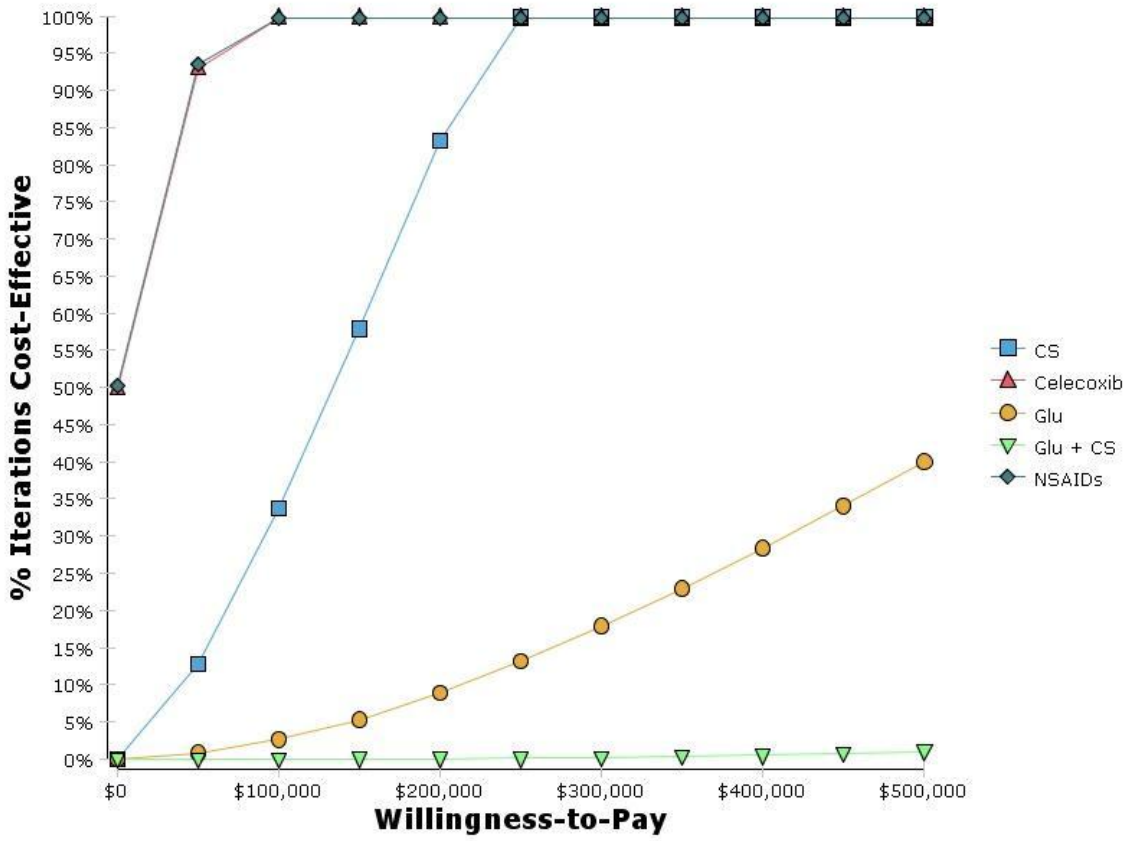


CS=Chondroitin Sulfate; QALYs=Quality-adjusted life-years

The above scatter plot can be interpreted as follows: the most cost-effective comparator would be one with scatter density towards bottom of the Y-axis (i.e., less expensive) and right hand side from the X-axis (i.e., more effective).

Figure 37 displays the cost-effectiveness acceptability curve for the above described analysis, based on 10,000 simulations and variation of willingness-to-pay from $0 to $500,000 per QALY gained.

Figure 37: Cost-Effectiveness Acceptability Curve for Cost-Effectiveness Analysis, in Overall KOA Patients Group from Healthcare Payer's Perspective and 10-Year Time-Horizon.



CS=Chondroitin Sulfate

Structural Sensitivity Analysis of Cost-Effectiveness of CAM Therapies vs. Conventional Medicines among Moderate to Severe KOA Patients Group

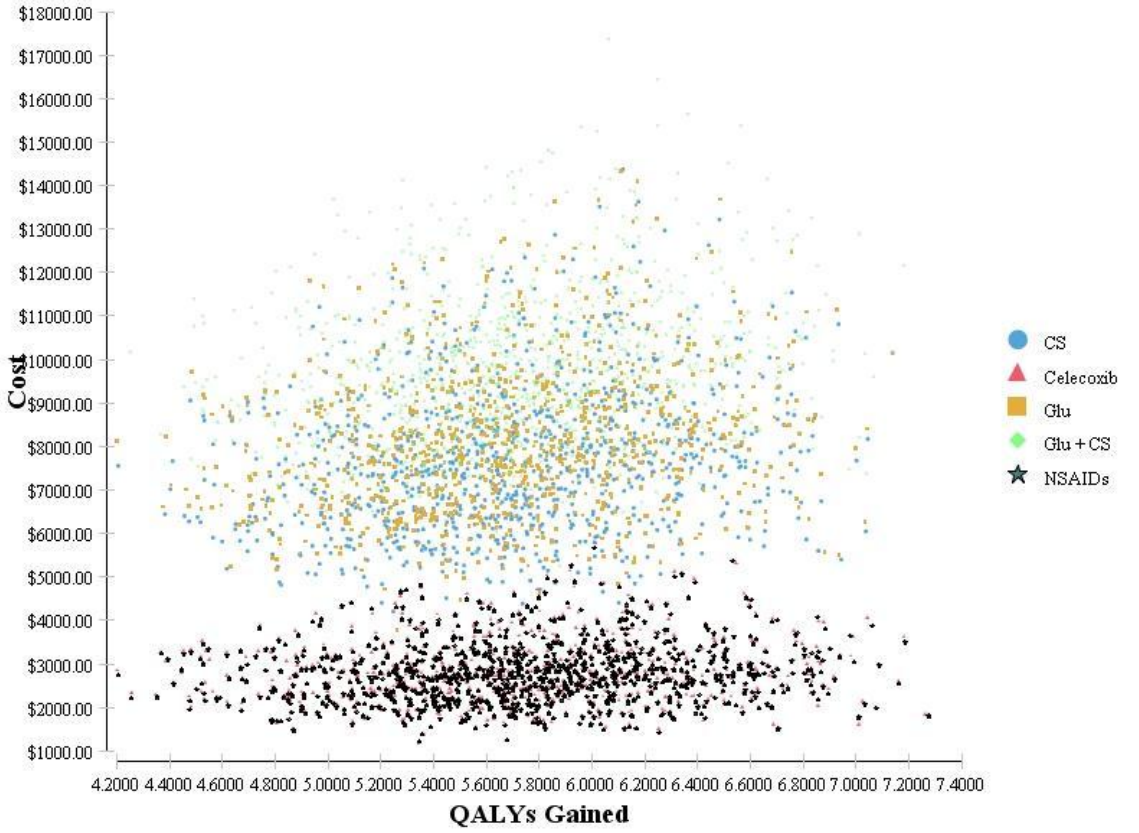
Table 56 displays the detailed results of probabilistic sensitivity analysis on all model inputs and Figure 38 presents its scatter plot based on 10000 second-order Monte Carlo simulations.

Table 56: Probabilistic Sensitivity Analysis Results, in Moderate to Severe Pain KOA Patients Group from Healthcare Payers Perspective and 10-Year Time-Horizon.

	Parameters	CS	Glucosamine	Glucosamine + CS	Celecoxib	NSAIDs
Cost	*Mean*	$7,597	$8,056	$9,749	$2,755	$2,755
	SD	$1,609	$1,614	$1,681	$683	$683
	Min	$3,175	$3,589	$5,247	$991	$984
	2.50%	$4,900	$5,350	$6,891	$1,616	$1,612
	10%	$5,644	$6,107	$7,704	$1,932	$1,933
	Median	$7,441	$7,917	$9,607	$2,689	$2,689
	90%	$9,713	$10,179	$11,971	$3,654	$3,651
	97.50%	$11,208	$11,631	$13,398	$4,277	$4,290
	Max	$15,984	$16,350	$18,067	$6,525	$6,517
QALYs gained[┼]	*Mean*	5.70	5.71	5.73	5.75	5.75
	SD	0.51	0.51	0.52	0.55	0.55
	Min	3.91	3.91	3.91	3.89	3.90
	2.50%	4.72	4.72	4.73	4.68	4.68
	10%	5.05	5.05	5.06	5.05	5.05
	Median	5.70	5.70	5.73	5.75	5.75
	90%	6.38	6.38	6.42	6.48	6.47
	97.50%	6.71	6.72	6.75	6.82	6.82
	Max	7.65	7.66	7.73	7.85	7.84

┼=All QALYs are based on SF-6D based health utilities mapped from SF-36
CS=Chondroitin Sulfate; QALYs=Quality-adjusted life-years

Figure 38: Scatter Plot for Probabilistic Sensitivity Analysis, in Moderate to Severe Pain KOA Patients Group from Healthcare Payers Perspective and 10-Year Time-Horizon.

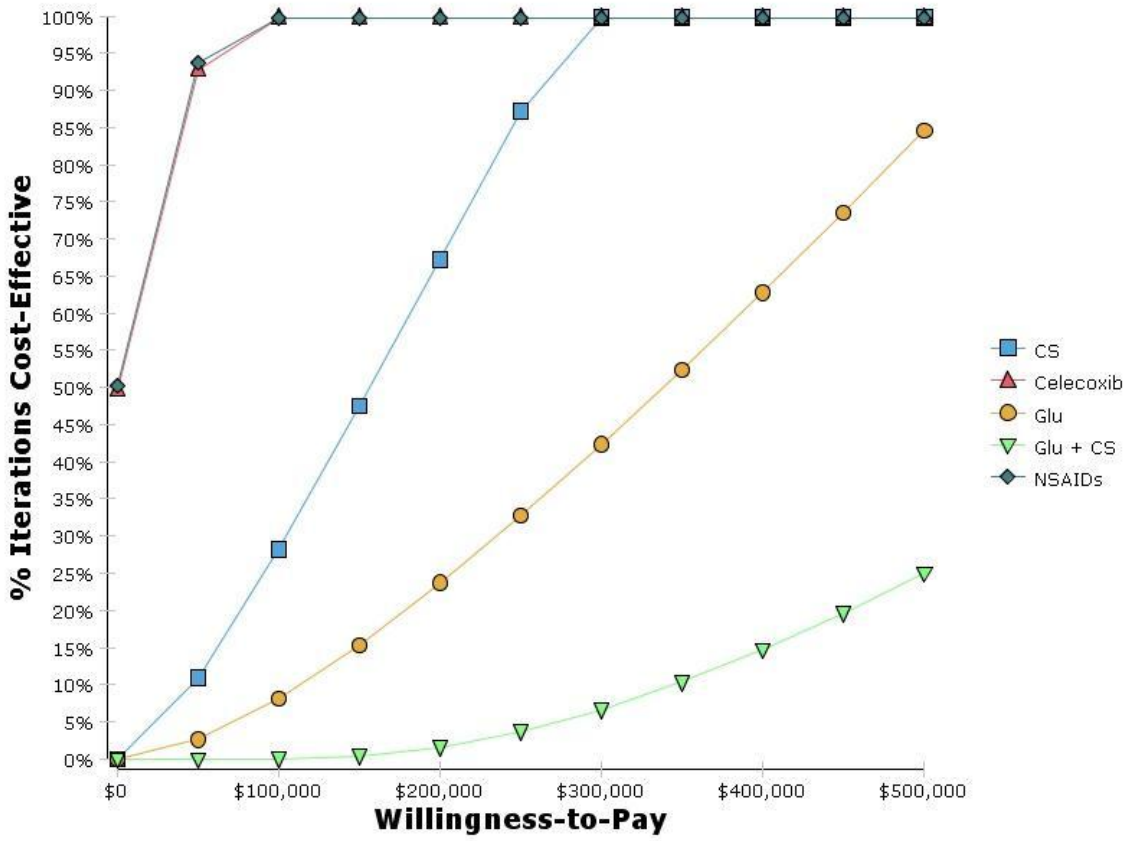


CS=Chondroitin Sulfate; QALYs=Quality-adjusted life-years

The above scatter plot can be interpreted as follows: the most cost-effective comparator would be one with scatter density towards bottom of the Y-axis (i.e., less expensive) and right hand side from the X-axis (i.e., more effective).

Figure 39 displays the cost-effectiveness acceptability curve for the above described analysis, based on 10,000 simulations and variation of willingness-to-pay from $0 to $500,000 per QALY gained.

Figure 39: Cost-Effectiveness Acceptability Curve for Cost-Effectiveness Analysis, in Moderate to Severe Pain KOA Patients Group from Healthcare Payer's Perspective and 10-Year Time-Horizon.



CS=Chondroitin Sulfate

Structural Sensitivity Analysis of Cost-Effectiveness of CAM Therapies vs. Conventional Medicines among Mild Pain Only KOA Patients Group

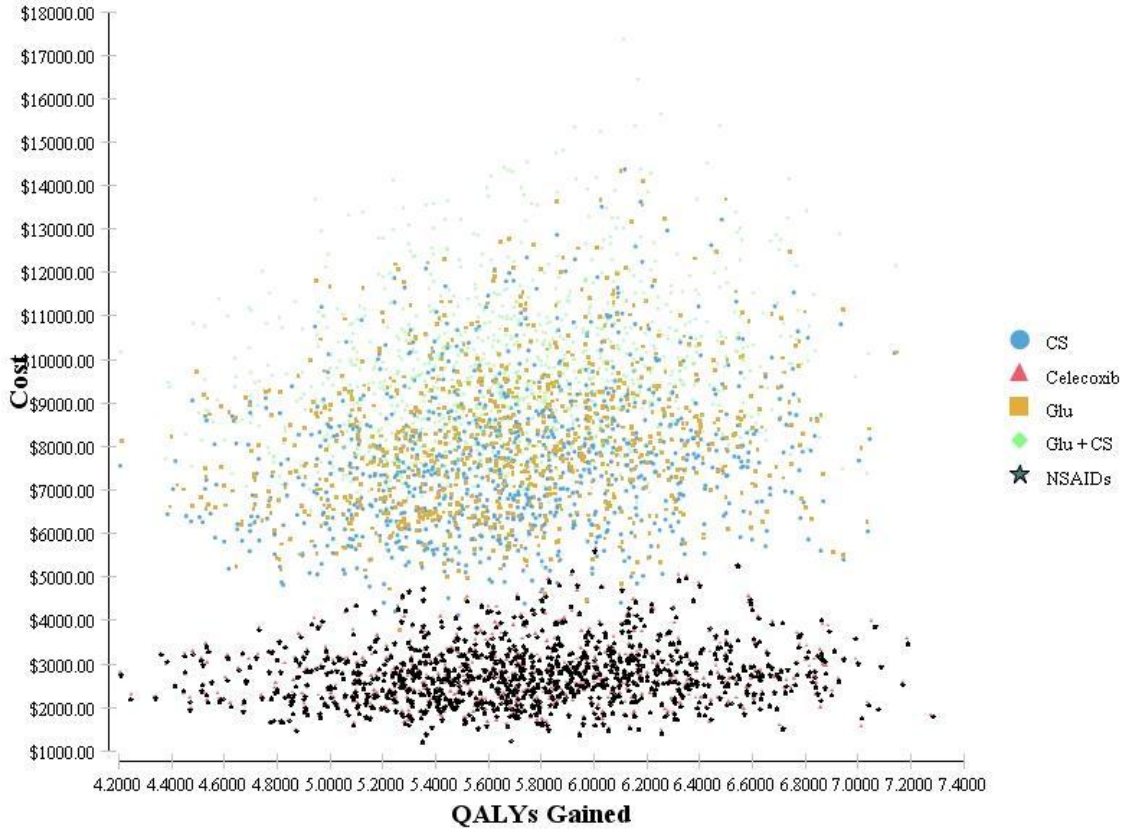
Table 57 displays the detailed results of probabilistic sensitivity analysis on all model inputs and Figure 40 presents its scatter plot based on 10000 second-order Monte Carlo simulations.

Table 57: Probabilistic Sensitivity Analysis Results, in Mild Pain Only KOA Patients Group from Healthcare Payers Perspective and 10-Year Time-Horizon.

	Parameters	CS	Glucosamine	Glucosamine + CS	Celecoxib	NSAIDs
Cost	*Mean*	$7,588	$8,048	$9,740	$2,710	$2,710
	SD	$1,602	$1,608	$1,675	$668	$668
	Min	$3,175	$3,589	$5,247	$979	$972
	2.50%	$4,912	$5,350	$6,884	$1,595	$1,593
	10%	$5,644	$6,102	$7,707	$1,903	$1,906
	Median	$7,436	$7,911	$9,599	$2,646	$2,646
	90%	$9,690	$10,155	$11,953	$3,588	$3,584
	97.50%	$11,199	$11,621	$13,391	$4,204	$4,218
	Max	$15,984	$16,350	$18,067	$6,401	$6,413
QALYs gained[┼]	*Mean*	5.70	5.71	5.70	5.75	5.75
	SD	0.51	0.51	0.51	0.55	0.55
	Min	3.91	3.91	3.90	3.89	3.89
	2.50%	4.71	4.71	4.71	4.67	4.67
	10%	5.05	5.05	5.05	5.04	5.04
	Median	5.69	5.70	5.69	5.75	5.75
	90%	6.38	6.39	6.38	6.48	6.48
	97.50%	6.72	6.72	6.72	6.83	6.83
	Max	7.65	7.67	7.65	7.86	7.85

┼=All QALYs are based on SF-6D based health utilities mapped from SF-36
CS=Chondroitin Sulfate; QALYs=Quality-adjusted life-years

Figure 40: Scatter Plot for Probabilistic Sensitivity Analysis, in Mild Pain Only KOA Patients Group from Healthcare Payers Perspective and 10-Year Time-Horizon.

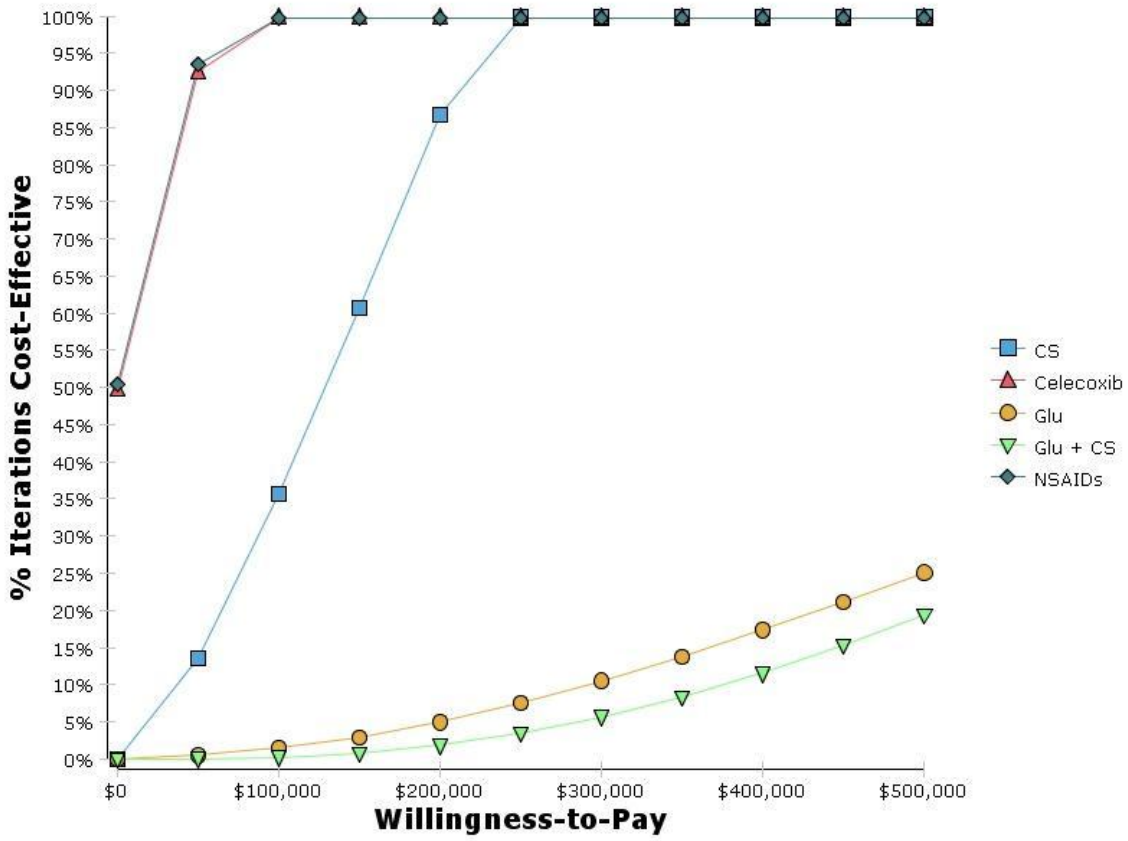


CS=Chondroitin Sulfate; QALYs=Quality-adjusted life-years

The above scatter plot can be interpreted as follows: the most cost-effective comparator would be one with scatter density towards bottom of the Y-axis (i.e., less expensive) and right hand side from the X-axis (i.e., more effective).

Figure 41 displays the cost-effectiveness acceptability curve for the above described analysis, based on 10,000 simulations and variation of willingness-to-pay from $0 to $500,000 per QALY gained.

Figure 41: Cost-Effectiveness Acceptability Curve for Cost-Effectiveness Analysis, in Mild Pain Only KOA Patients Group from Healthcare Payer's Perspective and 10-Year Time-Horizon.



CS=Chondroitin Sulfate

Summary of Findings

Overall, CS was found to be the most cost-effective option to treat KOA patients, among all three groups (i.e., overall, mild pain only, and moderate to severe pain). Other CAM therapy based strategies, i.e. glucosamine alone or in combination with CS, were also found to be cost-effective in general. Celecoxib was cost-effective among the mild pain only group of KOA patients from a 24-week time-horizon and both health care payers' and patient's perspectives, compared to CS as the reference.

CHAPTER 5: DISCUSSION

This chapter is divided into six main sections. In the first section, we begin by providing the interpretation of the findings of our study. This section is followed by discussion on the role of adverse events as a driver of the cost-effectiveness ratios and QALYs gained as an outcome measure. In the next section, our findings are compared with the previous literature in the successive section. Proceeding forward in this chapter, in the next two sections, we discuss implications of our study findings and areas for future research related to our study. This chapter then ends by discussing the strengths and limitations of our study in penultimate section trailed by conclusion of our study.

Interpretation of Study Findings

In this section we discuss findings of our study for all five objectives and identify different cost-effective therapies in treating KOA for different scenarios of time-horizons and study perspectives. Specifically, we provide details of cost-effectiveness of all study comparators analyzed in this study, at time-horizons of 10 years, 2 years, and 24 weeks and from the perspectives of patients and healthcare payers. Table 55 summarizes cost-effectiveness of various study comparators during different conditions, as mentioned previously.

Table 58: Summary of Cost-Effectiveness Findings with Chondroitin Sulfate as the Reference Group.

Time Horizon	ICER For Study Comparators* (Cost/QALY gained)				
	Glu	**Glu + CS**	**Celecoxib**	**NSAIDs**	**Placebo**
10 Years (objective 1)					
Overall Group	$120367[§]	$3250047	Dominated	Dominated	NA
Mild Pain Group	$86233[†]	Dominated	Dominated	Dominated	NA
Moderate to Severe Pain Group	$962943	$73006[†]	Dominated	Dominated	NA
24 Weeks					
Healthcare Payers' Perspective *(objective 2)*					
Overall Group	$11215[‡]	Dominated	$106225	NA	Dominated
Mild Pain Group	$24300[‡]	Dominated	$49988[‡]	NA	Dominated
Moderate to Severe Pain Group	$3313[‡]	$3278[‡]	Dominated	NA	Dominated
Patients' Perspective *(objective 3)*					
Overall Group	$11215[‡]	Dominated	$106225	NA	Dominated
Mild Pain Group	$24300[‡]	Dominated	$49988[‡]	NA	Dominated
Moderate to Severe Pain Group	$3313[‡]	$3278[‡]	Dominated	NA	Dominated
2 Years					
Healthcare Payers' Perspective *(objective 4)*					
Overall Group	$11810[‡§]	Dominated	Dominated	NA	Dominated
Mild Pain Group	$9570[‡]	Dominated	281550[‡]	NA	Dominated
Moderate to Severe Pain Group	$277550	Dominated	Dominated	NA	$12368[‡]
Patients' Perspective *(objective 5)*					
Overall Group	$11810[‡]	Dominated	Dominated	NA	Dominated
Mild Pain Group	$9570[‡]	Dominated	281533[‡]	NA	Dominated
Moderate to Severe Pain Group	$281984	Dominated	Dominated	NA	$12257[‡]

*=Chondroitin Sulfate is used as the reference group for incremental cost-effectiveness ratios.
┼=Cost-effective at ICER threshold of $100,000/QALY gained.
‡=Cost-effective at ICER of $50,000/QALY gained.
§=Cost-effectiveness ratio of the overall pain group from 10-years horizon is substantially higher than 2-years and 24-weeks as the former is the cumulative of annual cost-effectiveness ratios from year 1 to 10 after discounting at 3%

CS=Chondroitin Sulfate; Glu=Glucosamine; NA=Not applicable; NSAIDs= Non-Steroidal Anti-Inflammatory Drugs; ICER=Incremental cost-effectiveness ratio

For Objective 1

The first objective was to compare cost-effectiveness of CAM therapies with conventional medicines for the treatment of KOA from the US health care payers' perspective and 10-year time-horizon.

Overall KOA Group

For base case analysis, from US healthcare payers' perspective and 10-year time-horizon, neither glucosamine (alone or in combination with CS) nor conventional medicines were incrementally cost-effective. Only CS alone therapy was found to be cost-effective at the ICER threshold of $100,000/QALY. All these results were robust to the modeling parameters in the probabilistic sensitivity analysis (Figure 6).

KOA Patients with Mild Knee Pain

For base case analysis, we found that CS alone therapy had the lowest cost/QALY gained and glucosamine alone therapy was incrementally cost-effective at the societal acceptability of $100,000/QALY. All other study comparators were dominated by CS alone therapy in this study group. All findings were reaffirmed in the probabilistic sensitivity analysis (Figure 8).

KOA Patients with Moderate to Severe Pain

For base case analysis, we found that CS alone therapy had the lowest cost/QALY gained and its combination therapy with glucosamine was the only incrementally cost-effective comparator at the threshold of $100,000/QALY gained. All findings were robust in the probabilistic sensitivity analysis (Figure 10).

For Objective 2

The second objective was to compare the cost-effectiveness of CAM therapies with celecoxib and placebo for the treatment of KOA from the US health care payers' perspective and 24-week time-horizon.

Overall KOA Group

For base case analysis, we found that CS alone therapy had the lowest cost/QALY gained, with glucosamine alone therapy being incrementally cost-effective at the threshold of $100,000/QALY gained. No other therapy was incrementally cost-effective compared to CS alone therapy. These results of the base case analysis were reaffirmed in the probabilistic sensitivity analysis (Figure 12).

KOA Patients with Mild Knee Pain

For base case analysis, we found that CS alone therapy had the lowest cost/QALY gained and only the combination therapy of glucosamine and CS was incrementally cost-effective at the threshold of $100,000/QALY gained. In probabilistic sensitivity analysis as well, while CS was found to be the most cost-effective option (distribution towards bottom right corner in scatterplot in Figure 14), combination therapy of glucosamine and CS was incrementally cost-effective.

KOA Patients with Moderate to Severe Pain

For base case analysis, we found that all three CAM therapies based treatment strategies were cost-effective at the ICER threshold of $100,000/QALY gained. Specifically, the CS alone therapy had the lowest cost/QALY gained and both

glucosamine alone and combination of glucosamine and CS were incrementally cost-effective at the threshold of $100,000/QALY gained, with cost-effectiveness ratios of $3,313.63/QALY and $3,278.78/QALY gained, respectively. On the other hand, both celecoxib and placebo therapies were dominated by CS alone therapy in this group of KOA patients. All findings were robust to the probabilistic sensitivity analysis (Figure 16).

For Objective 3

The third objective was to compare the cost-effectiveness of CAM therapies with celecoxib and placebo for treatment of KOA from the US patients' perspective and 24-week time-horizon.

Overall KOA Group

For base case analysis, we found that CS alone therapy had the lowest cost/QALY gained; whereas, only glucosamine therapy was incrementally cost-effective at the threshold of $100,000/QALY gained. In probabilistic sensitivity analysis, CS alone therapy was the most cost-effective option followed by glucosamine and celecoxib (as it can be seen from the respective scatter distributions in Figure 18)—affirming the results of base case analysis.

KOA Patients with Mild Knee Pain

For base case analysis, we found that CS alone therapy was the mocst cost-effective; both glucosamine alone and celecoxib therapies were incrementally cost-effective at the threshold of $100,000/QALY gained with respective cost-effectiveness

ratios being $24,300.00/QALY and $49,988.24/QALY gained. In probabilistic sensitivity analysis as well, similar to the overall group of KOA patients, CS alone was the most cost-effective therapy followed by glucosamine alone and celecoxib therapies (Figure 20).

KOA Patients with Moderate to Severe Pain

For base case analysis, we found that CS alone therapy had the lowest cost/QALY gained. Therapies of glucosamine alone and its combination with CS were incrementally cost-effective at the threshold of $100,000/QALY gained. In probabilistic sensitivity analysis, on the other hand, combination therapy of glucosamine and CS was found to be incrementally cost-effective based on 10,000 second order Monte Carlo simulations, as is displayed in Figure 22.

For Objective 4

The fourth objective was to compare the cost-effectiveness of CAM therapies with celecoxib and placebo for treatment of KOA from the US health care payers' perspective and 2-year time-horizon.

Overall KOA Group

For base case analysis, we found that CS alone therapy had the lowest cost/QALY gained, whereas only glucosamine alone therapy was incrementally cost-effective at the threshold of $100,000/QALY gained. These findings were robust to the modeling parameters, as found through the probabilistic sensitivity analysis (Figure 24).

KOA Patients with Mild Knee Pain

Similar to overall KOA group, for base case analysis, we found that CS alone therapy had the lowest cost/QALY gained and only glucosamine alone therapy was incrementally cost-effective at the threshold of $100,000/QALY gained. In probabilistic sensitivity analysis as well, the distribution density of CS alone therapy towards bottom right hand side of the scatterplot in Figure 26 demonstrates it to be the most cost-effective option.

KOA Patients with Moderate to Severe Pain

For the base case analysis, we found that CS alone therapy had the lowest cost/QALY gained. Interestingly, placebo therapy was incrementally cost-effective at the threshold of $100,000/QALY gained.

Nonetheless, these findings provide only the economic perspective and not the ethical perspective for practicing medicine. The use of placebo in the real-world clinical settings to treat patients is deemed unethical and all patients shall be treated with the best available standard of care.[284] All findings were robust to the modeling parameters, as found in the probabilistic sensitivity analysis (Figure 28).

For Objective 5

The fifth objective was to compare the cost-effectiveness of CAM therapies with celecoxib and placebo for treatment of KOA from the US patients' perspective and 2-year time-horizon.

Overall KOA Group

For base case analysis, we found that CS alone therapy had the lowest cost/QALY gained and only glucosamine alone therapy was found to be incrementally cost-effective at the threshold of $100,000/QALY gained. In probabilistic sensitivity analysis, based on 10,000 second order Monte Carlo simulations, as can be seen from scatterplot in Figure 30, CS alone therapy was the most cost-effective option—affirming the results of base case analysis.

KOA Patients with Mild Knee Pain

Similar to the above findings, for base case analysis, we found that CS alone therapy had the lowest cost/QALY gained and only glucosamine alone therapy was incrementally cost-effective at $100,000/QALY gained threshold. In probabilistic sensitivity analysis as well, similar to the overall KOA patient group, CS alone therapy was found to be the most cost-effective option, followed by glucosamine alone therapy (Figure 32).

KOA Patients with Moderate to Severe Pain

For base case analysis, we found that CS alone therapy had the lowest cost/QALY gained. Interestingly, placebo therapy was incrementally cost-effective at the threshold of $100,000/QALY gained. These findings were robust to the modeling parameters as found in the probabilistic sensitivity analysis results (Figure 34).

Adverse Events as a Driver of Cost-Effectiveness Ratios

Risks of serious cardiovascular and GI adverse events associated with NSAIDs and celecoxib were accounted for in the cost-effectiveness analysis while comparing the CAM therapies and conventional medicines from the 10-year time-horizon. As described earlier, we found that neither of the NSAIDs or celecoxib were incrementally cost-effective compared to CS in the base case analysis. However, in the structural sensitivity analysis when the risk of serious adverse events associated with conventional medicines was excluded, we found that both NSAIDs and celecoxib are highly cost-effective compared to the CAM therapies (Figures 51 to 56). These findings were valid for all types of KOA patient population (i.e., overall, mild, and moderate groups), indicating that the risk of serious adverse events modeled to be associated with conventional medicines was a key driver of the cost-effectiveness ratios in our study.

The risk of adverse events associated with CAM therapies was not modeled in our study due to a lack of strong scientific evidence for the same. We conducted both primary and secondary research to find any data on the adverse events potentially associated with the CAM therapies. In the primary analysis we searched the FAERS database to identify safety signals associated with glucosamine and/or CS through the standard Research on Adverse Drug evens And Reports (RADAR) methodology. No new safety signals associated with glucosamine and/or CS were found, potentially because of the voluntary nature of reporting of adverse events to this database. In the secondary analysis, we reviewed the findings of two recently published meta-analyses that were based on the previously conducted clinical trials of glucosamine and CS.[25, 29] Similar to our primary analysis, we did not find any significant ($p<0.05$) risk of adverse events associated with

CAM therapies from these reviews. To the best of our knowledge, there is no other published study (interventional or observational) that has examined the safety or efficacy of glucosamine and/or CS. Based on these data, we conclude a scarcity of evidence for the safety of CAM therapies.

Recent efforts by the FDA to facilitate the reporting of adverse events associated with dietary supplements like CAM therapies are intended to broaden the knowledge of safety of these agents. In one such instance, starting January 13th, 2014, the FDA's Center for Food Safety and Applied Nutrition accepts online submission of voluntary and mandatory dietary supplements adverse events reports through forms 3500A and 3500, respectively. Previously, only paper versions of these forms were available to report adverse events associated with dietary supplements to the FDA. Future research examining these data may be of high scientific importance.

Comparison with Previous Literature

Only one published cost-effectiveness analysis has previously compared CAM therapies with conventional medicines in treating KOA.[58,59] In this study, cost-effectiveness of glucosamine was compared with paracetamol (acetaminophen) and placebo to treat KOA from 6-month time-horizon and health care payers' perspective. The primary outcome measure of effectiveness used in this study was QALY gained. Only direct healthcare costs were included in the analysis, in accordance to the health care payers' perspective. The incremental cost-effectiveness ratios were estimated utilizing data from a closed out clinical trial.[68] This study concluded glucosamine to be highly cost-effective in treating KOA; glucosamine dominated the paracetamol strategy and was found to have incremental cost-effectiveness ratio of €4,285/QALY (2009) gained in comparison to placebo.

The findings of our study are in congruence with the above described cost-effectiveness analysis. Specifically, we found CS to be the most cost-effective option in all analyses and glucosamine to have a low incremental cost-effectiveness ratio in both 24-week and 2-year time-horizon analysis, from health care payers' as well as patients' perspectives. From 10-year time-horizon and health care payers' perspective, glucosamine alone therapy was cost-effective only among KOA patients that had mild knee pain at baseline. In moderate to severe baseline knee pain group, however, the combination of glucosamine and CS was incrementally cost-effective at $100,000/QALY gained threshold, but glucosamine alone was not

Our study has several strengths in comparison to this previously published cost-effectiveness analysis. First, while Scholtissen et al. conducted their study from only 6-month time-horizon, our study is conducted from 6-month (24-week), 2-year, and 10-year time-horizons to comprehensively compare cost-effectiveness of CAM therapies with conventional medicines in treating KOA. Second, we examined the cost-effectiveness of glucosamine and CS alone as well as combination therapies in our study; whereas Scholtissen et al. examined only glucosamine alone therapy. Third, for the 10 year time horizon we included two conventional medicines in our analysis, i.e. celecoxib and NSAIDs, in comparison to only acetaminophen in the previous study. Fourth, we included risks of several GI and cardiovascular adverse events associated with conventional medicines in our study—since the comparator was paracetamol no such inclusion was made in the previous study. Inclusion of such adverse events in our analysis more closely replicates the clinical scenario of treating KOA with conventional medicines. Fifth, our estimates of efficacies of the therapies were based on a much larger sample size from the GAIT study (n=1,583), in comparison to the estimates used in the previously published cost-effectiveness analysis study that were based on only 318 participants,[68] leading to narrower confidence intervals of modeling parameters. Sixth, the primary focus of our study is on the US population, in comparison to Spanish population focus of the Scholtissen et al. study; therefore, our results may be more helpful for health care decision-making in the US.

Study Implications

The primary aim of conducting any cost-effectiveness analysis study is usually exploring the optimal ways for allocation of resources. In the light of currently available data, our results justify use of glucosamine and CS as therapies to treat KOA among the US population, as we found CAM therapies to be cost-effective compared to conventional medicines for the treatment of this pathology in general. Specifically, among the overall group of KOA patients, glucosamine and CS alone therapies were the most cost-effective. These CAM therapies were also found to be cost-effective from 10-year and 2-year time-horizons among the KOA patients that had mild knee pain at the baseline.

Comparison with GAIT findings[24, 33]

We found celecoxib to be cost-effective in patients with only mild pain from 24-week time-horizon and both health care payers' and patient's perspective, at the ICER of $50,000/QALY gained compared to CS. In congruence to these findings, celecoxib was reported to be the only significantly better strategy than placebo in treating KOA in the GAIT study. However in contrast with GAIT, the glucosamine, CS, or combination treatments were no better than placebo.

Similarly, among patients with moderate to severe pain, the GAIT study found the combination therapy of glucosamine and CS and celecoxib were significantly better placebo in treating KOA at 24 weeks. In our study as well, among moderate to severe pain group, this CAM combination therapy was highly cost-effective in treating KOA from both health care payers' and patient's perspectives, with an ICER of $3,278/QALY

gained compared to CS alone. Moreover, this combination CAM therapy was not-statistically significant different from placebo in GAIT study in both the overall and mild only pain groups; in our study as well, this combination therapy was dominated (or had extremely high ICER) compared to CS in these groups.

The higher incremental cost-effectiveness of conventional medicines, in comparison to CAM therapies, was primarily driven by their higher drug utilization costs (for celecoxib) and the associated risks of serious cardiovascular and GI adverse events that lead to both higher costs and lower number of QALYs gained (for celecoxib and NSAIDs). The currently available evidence suggests no risk of serious adverse events associated with glucosamine and CS therapies (please refer to the materials and methods chapter for more details); however, establishment of such relationships in future may decrease the cost-effectiveness of CAM therapies.

The findings of our study would be most valuable after more evidence on clinical efficacy of glucosamine and CS for treating KOA were obtained. As described in the introduction chapter, a recent meta-analysis of 10 clinical trials reported no significant differences in joint pain reduction or joint space width narrowing benefits between placebo and glucosamine, CS, or combination therapy of glucosamine and CS among the KOA patients.[25] On the other hand, this meta-analysis is widely criticized for using artificially back transforming effect sizes of the included studies to obtain pooled estimates meta-analysis.[26, 27] Furthermore, this study is criticized for not studying the effect of CAM therapies on TKR surgery rates: a follow-up study of one of the clinical trials included in this meta-analysis reported glucosamine group of KOA having a significant risk reduction in TKR surgery (5-year relative risk=0.43; 95% CI=0.2-0.92),

in comparison to placebo group.[28] This, translating into per patient per month (PPPM) cost saving of $35.44 to the health plan among the KOA patients.[216] Moreover, a similar meta-analysis study reported effect size of 0.35 (95% CI=0.14 to 0.56) in favor of glucosamine for treating KOA.[29] Since the conducted probabilistic sensitivity analysis accounts for a wide variation in all our model inputs, including the efficacy of glucosamine and TKR surgery rates, we do not expect these differences to impact our findings substantially.

QALYs as an Outcome Measure

Amount of QALYs gained by KOA patients varied by treatment strategies and time-horizon for the analysis (Table 59). A recent systematic review of SF-6D based QALYs gained reported 0.033 (95% CI=0.029 to 0.037) as the minimal important difference (MID) in QALYs gained.[285] On this basis, only MID found in our study was in the 10-year time-horizon model. In this model, CAM therapies of CS and glucosamine, alone as well as together, had meaningfully more QALYs gained than conventional medicines.

Table 59: QALYs gained in Different Cost-Effectiveness Models.

Time Horizon	QALYs gained					
	CS	**Glu**	**Glu + CS**	**Celecoxib**	**NSAIDs**	**Placebo**
10 Years (objective 1)						
Overall Group	5.6833	5.6872	5.6877	4.8567	4.7765	n/a
Mild Pain Group	5.6799	5.6853	5.6801	4.8560	4.7754	n/a
Moderate to Severe Pain Group	5.6796	5.6801	5.709	4.8545	4.7728	n/a
24 Weeks						
Healthcare Payers' Perspective *(objective 2)*						
Overall Group	0.6798	0.6824	0.6799	0.6832	n/a	0.6775
Mild Pain Group	0.6803	0.6815	0.6769	0.6832	n/a	0.6787
Moderate to Severe Pain Group	0.6775	0.6863	0.6904	0.6838	n/a	0.6732
Patients' Perspective *(objective 3)*						
Overall Group	0.6798	0.6824	0.6799	0.6832	n/a	0.6775
Mild Pain Group	0.6803	0.6815	0.6769	0.6832	n/a	0.6787
Moderate to Severe Pain	0.6775	0.6863	0.6904	0.6838	n/a	0.6732

Time Horizon	QALYs gained					
	CS	**Glu**	**Glu + CS**	**Celecoxib**	**NSAIDs**	**Placebo**
Group						
2 Years						
Healthcare Payers' Perspective *(objective 4)*						
Overall Group	0.6482	0.6576	0.6420	0.6488	n/a	0.6492
Mild Pain Group	0.6489	0.6605	0.6421	0.6482	n/a	0.6476
Moderate to Severe Pain Group	0.6454	0.6458	0.6423	0.6557	n/a	0.6583
Patients' Perspective *(objective 5)*						
Overall Group	0.6482	0.6576	0.6420	0.6488	n/a	0.6492
Mild Pain Group	0.6489	0.6605	0.6421	0.6482	n/a	0.6476
Moderate to Severe Pain Group	0.6454	0.6458	0.6423	0.6557	n/a	0.6583

CS=Chondroitin Sulfate; Glu=Glucosamine; NA=Not applicable; NSAIDs= Non-Steroidal Anti-Inflammatory Drugs

It is noteworthy that different PRO instruments used to measure health utilities values in order to estimate QALYs may yield different results.[286, 287] For example, Raisch et al compared health utilities estimated using the SF-6D, Health Utilities Index, Mark II and Mark III (HUI2 and HUI3) and the feeling thermometer (FT) among type 2 diabetes participants in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial.[283] Poor agreement between different instruments were reported except for two: the intra-correlation cofficients were 0.245 for FT/SF-6D, 0.313 for HUI3/SF-6D, 0.437 for HUI2/SF-6D, 0.338 for FT/HUI2, 0.337 for FT/HUI3 and 0.751 for HUI2/HUI3 ($P <$ 0.001 for all).

Areas for Future Research

The sub-sections below discuss several areas for future research that may help in informing health care decision-making processes related to KOA treatment, in the US as well as internationally.

Societal Perspective

Some stakeholders recommend using a societal perspective for base case analysis such as The US Panel on Cost-Effectiveness in Health and Medicine. Future cost-effectiveness analyses conducted from societal perspective to compare cost-effectiveness of CAM therapies with conventional medicines may be helpful to the decision-makers, because of inclusion of KOA treatment costs to the society in the analysis as well as utilization of societal health utility values rather than of the patients. The SF-6D is derived from a British societal perspective, so it could vary from QALY measures using a US societal perspective.

We chose health care payers' and patients' perspectives for the purpose of our study for the following reasons: (1) All published health utility data currently available for modeling inputs required to conduct cost-effectiveness analysis like ours are based on KOA patients rather than societal sample; therefore, using such data for societal perspective analysis may yield biased estimates of cost-effectiveness ratios, (2) In the US, health insurance providers (government and commercial), followed by out-of-pocket payments by patients, are the two largest sources of financing health care services.[288] As a result, it is important to analyze cost-effectiveness from the perspectives of these stakeholders.

Analysis in other countries

The ISPOR Good Research Practices Task Force Report on transferability of health economic evaluations across international jurisdictions (i.e., across different countries) suggests several reasons for why the cost-effectiveness of health technologies may vary from place to place.[289] These reasons include differences in the incidence and severity of the disease in question, the availability of health care resources, clinical practice patterns, and relative prices of health care.[290]

The primary focus of our study was on the US population. Further, only one previously published cost-effectiveness analysis has compared CAM therapies with conventional medicines in treating KOA—this study was focused on Spanish market. Therefore, future studies focusing on other population groups such as in Europe and Japan are required to help in informing the clinical decision-making processes in these respective places.

Inclusion of Other Study Comparators

For our analysis, as CAM therapies, we examined glucosamine and CS alone and as combination. In addition to these agents, several other types of CAM therapies are currently available and used in treating KOA. These other CAM therapies include acupuncture as well as dietary supplements such as methylsulfonylmethane, ridedronate, and diacerein. Similarly, for conventional medicines, we examined only celecoxib (a selective COX-2 inhibitor) and NSAIDs; whereas several other agents such as corticosteroids, hyaluronate injections, and acetaminophen are currently used to treat KOA. Future cost-effectiveness studies comparing these agents could be beneficial in informing decision-making process for clinicians.

Different Therapeutic Doses of Glucosamine and/or CS

Currently, both glucosamine and CS, alone and in combination, do not have an approved dosage in the US, as these agents are treated as dietary supplements and are not approved by the US FDA. Previously conducted clinical trials have used different doses of CS (ranged from 800 mg/day to 1200 mg/day) and glucosamine (ranged from 1200 mg/day to 1500 mg/day).[21, 24, 69, 86-98, 105-110]

The drug clinical efficacy data utilized in our study were based on the GAIT clinical trial in which participants were daily given 1500 mg of glucosamine, 1200 mg of CS, or their combination. Since, as described before, there is no currently approved dose for glucosamine or CS, future cost-effectiveness studies conducted utilizing clinical efficacy data based on different doses of these agents than ours may be helpful.

Long Term Clinical Data on Glucosamine and/or CS

Further research is required to examine the long-term clinical efficacy and safety of CAM therapies such as glucosamine and CS, alone or in combination, to treat KOA. The currently available longest duration trials for glucosamine and CS alone therapies are of 162 weeks and 104 weeks durations, respectively.[33, 91, 93, 108] Based on these trials, as well as other similar studies, as described in the literature review chapter of this manuscript, the effectiveness of glucosamine and CS in treating KOA is currently not well-established. Therefore, future research examining long-term efficacies and safety of CAM therapies in treating KOA may be of scientific importance.

Study Limitations

Although our study is the first to compare cost-effectiveness of glucosamine and CS with conventional medicines in treating KOA, it has several limitations. First, sampling uncertainty may exist in our study results. This is because the clinical efficacy estimates used in our study for CAM therapies as well as conventional medicines were primarily obtained from the GAIT study in which a single sample was drawn from the KOA patients population. This issue was addressed in our study by reporting the 95% confidence intervals around point estimates for average costs and QALYs gained for all study comparators and by representing the cost-effectiveness results on acceptability curves.

Second, risks of adverse events associated with studied therapies were not modeled in the decision-trees. This was done because the primary data source to populate decision-tree models in our study was GAIT in which the reported adverse events were mild and similar across all study groups.[33, 174] Exclusion of adverse events from the decision-tree model may lead to overestimation of the cost-effectiveness of drug therapies, especially for celecoxib which has risks of serious GI and cardiovascular events.[8] In the GAIT study, at 24-week follow-up, only three adverse events were deemed to be associated with the drugs by the study investigators. These serious adverse events were: heart failure (in a patient receiving combination of glucosamine and CS), stroke (in a patient receiving celecoxib), and chest pain (in a patient receiving glucosamine). Due to the uncommon nature of these events we do not estimate these to impact our results. Further, no other data is currently available to associate glucosamine and/or CS with cardiovascular events. Similarly, there were no serious GI adverse events

or deaths reported at the 24-week follow-up. In the 2-year GAIT follow-up study, a total of five serious adverse events were associated with the studied therapies. These events were myocardial infarction (in a patient receiving the glucosamine/CS combination), coronary angioplasty (in placebo group), and hip arthroplasty, cerebrovascular accident and abdominal wall abscess (in celecoxib group).

Third, the time-horizon of our study does not include life-time of the patients, but extends only to 10-years. This time-period is enough to capture intervention outcomes for both symptom-modifying and structure-modifying KOA clinical trial studies.[291] Nonetheless, some organizations recommend life-time of the patients as the time-horizon for "reference case" evaluation in cost-effectiveness analyses.[34] Extrapolating time-horizon of our study to life-time of the patients may have introduced regression to the mean as a source of bias in the magnitude of drugs' efficacies due to the natural course of KOA.[33, 292] The possibility of the effect of regression to the mean was also reported in the GAIT 2-year follow-up study as well as in a meta-analysis comparing the efficacy of glucosamine, CS, their combination, and celecoxib.[25, 33] Thus, one may get different results by extending the study time-horizon to the life-time of the patients.

Fourth, the GAIT participants had relatively mild knee pain at baseline. This factor is different from some other KOA clinical trials in which a criterion for entry in the study was a disease flare after the discontinuation of NSAIDs.[293, 294] For this reason, one may argue that the GAIT study may have underestimated clinical efficacies of the therapies under study; this, in turn, may have led to biased estimates of cost-effectiveness in our study (i.e., parameter uncertainty). To account for this, we conducted cost-effectiveness analysis stratifying KOA patients by their baseline knee pain levels into

mild pain and moderate to severe pain groups. The cost-effectiveness analysis results from these subgroups were similar to the overall GAIT study population (i.e., overall KOA group), indicating the robustness of our findings to the severity of baseline pain level. Further, this robustness of our study findings was confirmed in the one-way and probabilistic sensitivity analyses.

Fifth, cost of physicians' office visit is included in both CAM therapies and conventional medicines groups. One may argue that patients on conventional medicines would incur more physicians' office visits in order to obtain prescriptions for celecoxib or NSAIDs. Nonetheless, from the published literature, we did not find any evidence of differences in the number of physicians' office visits between KOA patients on CAM therapies and conventional medicines. Resultantly, assumption of equal number of physicians' office visit in these two groups of KOA patients was made for the purpose of our study. If at all, this assumption would bias cost-effectiveness ratios against CAM therapies, because, *ceteris paribus*, KOA patients on CAM therapies would visit physicians' less as they do not need any prescriptions.

Sixth, our Markov cohort model does not account for the risk of revision TKR surgery, which has both substantial costs and quality-of-life burden.[216, 224, 272, 273] In the US, 52.2% of males and 50.6% who are diagnosed with primary KOA would undergo TKR surgery during their life-time.[3] Currently, an estimated 3,471,300 KOA patients aged over 50 years live with an intact TKR in the US, with annual revision TKR rates of only 1.9% in adults aged less than 65 years and 1.0% in older ones.[283] Therefore, we do not expect substantial changes in cost-effectiveness outcomes if such revision TKR surgery risks were included in the analysis.

Seventh, one may question why different types of decision-analytic models (Markov and decision-tree) were used for examining different objectives in this study. As described earlier in the methods section, the purpose of studying objective 1 was to compare the long-term (10 years) cost-effectiveness of CAM therapies with conventional medicines in real-world where a patient may experience adverse events or death during its treatment journey. To model these adverse events and deaths, a Markov model was developed to investigate objective 1. The purpose of objectives 2 to 5 was to compare the cost-effectiveness of KOA treatment strategies by exclusively simulating GAIT clinical trial settings, which was achieved by building a decision-tree model.

Conclusion

We compared the cost-effectiveness of CAM therapies (i.e., glucosamine and CS, alone and in combination), conventional medicines (i.e., celecoxib and NSAIDs), and placebo in treating KOA from time-horizons of 24 weeks, 2 years, and 10 years and from perspectives of the US health care payers and patients.

In general, we found that CAM therapies are more cost-effective than conventional medicines in treating KOA in the US. Specifically, mono-therapies of glucosamine or CS were the most cost-effective among overall group of KOA patients. Similarly, among KOA patients with mild knee pain at the baseline, monotherapies of glucosamine or CS were found to be cost-effective from 10-year and 2-year time-horizons; whereas, from 24-week time-horizon, celecoxib was also cost-effective. Further, among KOA patients with moderate to severe knee pain at the baseline, in general, combination therapy of glucosamine and CS was cost-effective in treating KOA from both 24-week and 2-year time-horizons.

Our study is the first to compare cost-effectiveness of CAM therapies and conventional medicines in treating KOA among the US population. Results from our study could help health policy and clinical decision-makers in selecting treatment modalities for KOA patients. However, future research is required to examine the long-term clinical effectiveness and safety of CAM therapies such as glucosamine and CS to treat KOA. Our study has several limitations, including potential for sampling uncertainty in modeling inputs, non-inclusion of risk of CAM therapy associated adverse events in decision-tree models, lack of a life-time of the patients as the study time-horizon, and several assumptions in decision-analytic models design and development.

APPENDICES

Appendix 1: Inclusion and Exclusion Criteria Used in the GAIT Study.

Inclusion Criteria:

1. Male or female, at least 40 years of age, with clinical diagnosis of primary KOA based on the following clinical and radiographic criteria: (Kellgren and Lawrence Grades 2-3).[80, 295]
    a. Pain in the affected knee on motion or weight bearing for the majority of days during the previous month, at least partially relieved by rest, and
    b. Tibiofemoral osteophytes of at least 1 mm assessed by the certified reader at each individual study site.
2. Clinical symptoms of KOA for at least 6 months prior to study entry.
3. Sum of WOMAC pain subscales between 125 and 400 mm inclusive.[125]
4. American Rheumatism Association's (ARA) functional class I, II, or III.[296]

Exclusion Criteria[21, 33]

1. Concurrent medical/arthritic disease that could confound or interfere with evaluation of pain or efficacy including: inflammatory arthritis, gout, episodes of acute monarticular arthritis, psoriatic arthritis clinically consistent with pseudogout, Paget's disease affecting the study joint, history of septic arthritis or avascular necrosis or intra-articular fracture of the study joint, Wilson's disease, hemochromatosis, alkaptonuria, or primary osteochondromatosis.
2. Spine or hip pain of sufficient magnitude to interfere with the evaluation of the index joint.

3. Kellgren and Lawrence Grade 4 in the contralateral knee. Isolated patellofemoral disease manifested by primarily anterior knee pain in the absence of tibiofemoral radiographic finding.
4. History of significant collateral ligament, anterior cruciate ligament or meniscal injury of the index joint requiring at least one week of non-weight bearing.
5. History of arthroscopy of the affected knee within 6 months prior to study entry.
6. If aminotransferase/alanine aminotransferase (AST/ALT) are greater than two times normal.
7. Serum creatinine of >1.8 mg/dl.
8. Uncontrolled hypertension, defined by systolic blood pressure of >150 mm Hg or diastolic blood pressure of >90 mm Hg.
9. Diabetes mellitus, defined by fasting blood glucose of >126 mg/dl.
10. History of any illness that might confound the results of the study or pose additional risk to the patient, in the opinion of the study investigator.
11. Allergy to or history of significant clinical or laboratory adverse experience associated with acetaminophen, celecoxib, other NSAIDs, glucosamine or CS.
12. Allergy to shellfish.
13. Female patients must not be pregnant at entry and all study participants must agree to practice contraception while taking study medications. A urine pregnancy test was performed at 2nd visit (randomization visit).
14. Inability to understand the study procedures and/or give written informed consent.
15. Alcohol use in excess of 3 mixed drinks/day.[297]
16. Corticosteroid treatment as follows:

a. Use of oral corticosteroids within the previous four weeks.
b. Exposure to intramuscular corticosteroids within one month prior to entering the study.
c. Administration of intra-articular steroids to the joint under study, within 3 months of 2nd visit (randomization visit).
d. Administration of intra-articular steroids to any other joint, within 1 month of 2nd visit (randomization visit).

17. Sustained use of NSAIDs including aspirin in anti-inflammatory doses discontinued before study entry in accordance with the washout schedule. However, aspirin may be discontinued for cardiovascular reasons.
18. Intra-articular injection of hyaluronic acid or congeners into the study joint within 12 months.
19. Topical analgesics administration to the study joint, or any oral analgesics within 2 weeks of 2nd visit.
20. Implementation of any other medical therapy for arthritis within one month prior to entry.
21. Other medications, unrelated to the patient's osteoarthritis must have been used at a stable dosage for at least 1 month. In addition, it was anticipated that the dose of the concomitant medication is stable during the entire treatment period.
22. Participation in another clinical study with an investigational agent within the last 4 weeks.
23. Exposure to glucosamine within 3 months or CS within 6 months of 2nd visit.

24. Initiation of physical therapy or muscle conditioning program within 2 months prior to study entry.
25. Concurrent use of the following medications and dietary supplements:
    a. Chronic therapy with tetracycline or tetracycline derivatives.
    b. Other complementary or alternative regimens for the treatment of osteoarthritis.
    c. Vitamin C intake in excess of the amount included in one daily multiple vitamins.
    d. Vitamin D intake in excess of the amount included in one daily multiple vitamins.
26. Allergy to sulfonamides.
27. Use of anticoagulants.
28. Moderately or severely depressed, based on the Beck depression inventory (summed score >19).[298]

Appendix 2: Human Research and Review Committee Study Approval Letter.

THE UNIVERSITY OF NEW MEXICO
HEALTH SCIENCES CENTER

Human Research Review Committee
MSC 08 4560 BMSB Room B71
1 University of New Mexico~Albuquerque, NM 87131-0001
(505) 272-1129 Facsimile (505) 272-0803
http://hsc.unm.edu/som/research/hrrc/

07-Nov-2012

Raisch, Dennis W
College of Pharmacy

SUBJECT: HRRC Determination of Exempt Status
HRRC#: 12-368
Study Title: Cost-Effectiveness of Glucosamine, Chondroitin Sulfate, Glucosamine plus Chondroitin Sulfate, and Clecoxib for the Management of Osteoarthritis: A Study Based on Glucosamine/chondroitin Arthritis Intervention Trial (GAIT)
Approved: 07-Nov-2012

Dear Dr. Raisch:

The Human Research Review Committee (HRRC) has reviewed the above-mentioned research protocol and determined that this research is *exempt* from the requirements of Department of Health and Human Services (DHHS) regulations for the protection of human subjects as defined in 45CFR46.101(b)under category 4, based on the following:

1. HRPO Application received 07.23.12 (*includes Attachment 1)
2. Investigator Protocol received 07.23.12

Acknowledged receipt of the following:
3. COI Committee Decision (Daniel Clegg) received 11.02.12

Because it has been granted exemption, this research project is not subject to continuing review. Also note that the Food and Drug Administration (FDA) regulations as defined in 21CFR50.1 and 21CFR56.101 do not apply to this research.

Changes to the Research: It is the responsibility of the Principal Investigator to inform the HRRC of any changes to this research. A change in the research may disqualify this project from exempt status. Reference the HRRC# and title in all documents related to this protocol.

Sincerely,

Mark Holdsworth, PharmD
Executive Chair
Human Research Review Committee

Appendix 3: Main Effects Model.[172]

	OLS	RE	Mean	Median	Constant forced to unity	
					RE	Mean
c	**0.826**	**0.833**	**0.827**	**0.945**	**1**	**1**
PF2	−0.009	−0.021	−0.014	−0.011	**−0.058**	**−0.060**
PF3	0.008	−0.026	0.008	0.026	**−0.051**	−0.020
PF4	−0.036	**−0.065**	−0.027	0.001	**−0.088**	**−0.060**
PF5	−0.032	**−0.044**	**−0.043**	**−0.064**	**−0.061**	**−0.063**
PF6	**−0.115**	**−0.135**	**−0.096**	**−0.097**	**−0.160**	**−0.131**
RL2	−0.023	**−0.027**	−0.019	−0.026	**−0.056**	**−0.057**
RL3	**−0.035**	**−0.055**	**−0.043**	−0.035	**−0.076**	**−0.068**
RL4	**−0.034**	**−0.055**	**−0.036**	−0.026	**−0.078**	**−0.066**
SF2	−0.015	**−0.034**	−0.027	−0.029	**−0.066**	**−0.071**
SF3	**−0.041**	−0.022	**−0.049**	**−0.079**	**−0.048**	**−0.084**
SF4	**−0.047**	**−0.041**	**−0.057**	**−0.053**	**−0.066**	**−0.093**
SF5	**−0.085**	**−0.089**	**−0.073**	**−0.113**	**−0.109**	**−0.105**
PAIN2	0.011	−0.001	0.008	0.003	**−0.042**	**−0.048**
PAIN3	0.006	−0.018	−0.001	0.002	**−0.046**	−0.034
PAIN4	−0.034	**−0.026**	−0.032	−0.018	**−0.055**	**−0.070**
PAIN5	**−0.065**	**−0.068**	**−0.062**	**−0.102**	**−0.103**	**−0.107**
PAIN6	**−0.159**	**−0.155**	**−0.149**	**−0.191**	**−0.178**	**−0.181**
MH2	−0.033	−0.019	−0.026	**−0.058**	**−0.043**	**−0.057**
MH3	−0.025	**−0.032**	−0.022	**−0.043**	**−0.055**	**−0.051**
MH4	**−0.098**	**−0.093**	**−0.095**	**−0.133**	**−0.115**	**−0.121**
MH5	**−0.131**	**−0.106**	**−0.114**	**−0.165**	**−0.125**	**−0.140**
VIT2	**−0.043**	−0.006	−0.044	**−0.051**	**−0.040**	**−0.094**
VIT3	−0.036	−0.008	−0.037	−0.034	**−0.030**	**−0.069**
VIT4	−0.033	−0.011	−0.029	−0.048	**−0.040**	**−0.069**
VIT5	**−0.077**	**−0.068**	**−0.076**	**−0.090**	**−0.087**	**−0.106**
n	3518	3518	249	249	3518	249
Adjusted R^2	0.204	0.2	0.583	0.577	b	0.508
Inconsistencies	2	2	2	3	4	5
LB	**333.01**	**386.63**	**520.71**	**560.88**	**185.3**	**169.57**

a=All models are estimated with White's heteroscedasticity consistent standard errors. Estimates shown in *bold* are significant at $p<0.05$.

b=No R^2 statistics (GEE estimation).

PF=Physical function; RL=Role Limitation; SF=Social functioning; MH=Mental health; Vit=Vitality; OLS=Ordinary least squares; RE=Random error.

Appendix 4: Models with Interaction Effects.[172]

	RE	Mean	Constant Forced to Unity	
			RE	Mean*
c	**0.799**	**0.788**	**1**	**1**
PF2	−0.023	−0.015	**−0.050**	−0.053
PF3	−0.021	0.011	**−0.038**	−0.011
PF4	**−0.054**	−0.018	**−0.069**	**−0.040**
PF5	**−0.035**	−0.034	**−0.046**	**−0.054**
PF6	**−0.119**	**−0.084**	**−0.145**	**−0.111**
RL2	**−0.030**	−0.021	**−0.051**	**−0.053**
RL3	**−0.042**	−0.030	**−0.058**	**−0.055**
RL4	**−0.041**	−0.024	**−0.063**	**−0.050**
SF2	−0.030	−0.023	**−0.054**	**−0.055**
SF3	−0.012	**−0.040**	**−0.032**	**−0.067**
SF4	**−0.025**	**−0.042**	**−0.044**	**−0.070**
SF5	**−0.071**	**−0.058**	**−0.096**	**−0.087**
PAIN2	−0.005	0.005	**−0.037**	**−0.047**
PAIN3	−0.013	0.004	**−0.034**	−0.025
PAIN4	−0.020	−0.025	**−0.040**	**−0.056**
PAIN5	**−0.055**	**−0.049**	**−0.081**	**−0.091**
PAIN6	**−0.141**	**−0.136**	**−0.167**	**−0.167**
MH2	−0.022	−0.030	**−0.036**	**−0.049**
MH3	**−0.028**	−0.019	**−0.045**	**−0.042**
MH4	**−0.085**	**−0.089**	**−0.099**	**−0.109**
MH5	**−0.098**	**−0.109**	**−0.115**	**−0.128**
VIT2	−0.006	**−0.044**	**−0.032**	**−0.086**
VIT3	−0.002	−0.031	−0.019	**−0.061**
VIT4	−0.001	−0.019	−0.022	**−0.054**
VIT5	**−0.054**	**−0.064**	**−0.073**	**−0.091**
MOST	**−0.052**	**−0.041**	**−0.084**	**−0.070**
LEAST	**0.049**	**0.048**		
n	3518	249	3518	249
Adjusted R^2	0.201	0.591	b	0.526
LB	**388.3**	**524.64**	**164.18**	**189.87**

*=Recommended model to derive preference-based scores for using in health economic evaluations.

a=All models are estimated with White's heteroscedasticity consistent standard errors. Estimates shown in *bold* are significant at $p<0.05$.

b=No R^2 statistics (GEE estimation).

PF=Physical function; RL=Role Limitation; SF=Social functioning; MH=Mental health; Vit=Vitality; RE=Random error.

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