Osteoarthritis and Cartilage (2002) **10,** 518–527

1063–4584/02/$35.00/0
doi:10.1053/joca.2001.0513, available online at http://www.idealibrary.com on IDEAL®

Osteoarthritis and Cartilage

International Cartilage Repair Society

OARSI OSTEOARTHRITIS RESEARCH SOCIETY INTERNATIONAL

A prospective, randomized, pragmatic, health outcomes trial evaluating the incorporation of hylan G-F 20 into the treatment paradigm for patients with knee osteoarthritis (Part 2 of 2): economic results

G. W. Torrance*†, J. P. Raynauld‡, V. Walker†, C. H. Goldsmith*, N. Bellamy§, P. A. Band‖, M. Schultz¶ and P. Tugwell**, in collaboration with the Canadian Knee OA Study Group††

**Department of Clinical Epidemiology and Biostatistics, McMaster University, Hamilton, Ontario, Canada*

†*Innovus Research Inc., Burlington, Ontario, Canada*

‡*Department of Medicine, University of Montreal, Montreal, Quebec, Canada*

§*Department of Medicine, The University of Queensland, Queensland, Australia*

‖*Biomatrix, Inc., Ridgefield, New Jersey, U.S.A.*

¶*Rhône-Poulenc Rorer Canada Inc., St Laurent, Quebec, Canada*

***Department of Medicine, University of Ottawa, and Ottawa Hospital, Ottawa, Ontario, Canada*

Summary

Objective: Viscosupplementation with hylan G-F 20 has recently become registered for treatment of patients with osteoarthritis (OA) of the knee in most parts of the world. The cost effectiveness and cost utility of this new therapeutic modality were determined as part of a Canadian prospective, randomized, 1-year, open-label, multicentered trial.

Design: A total of 255 patients were randomized to 'Appropriate care *with* hylan G-F 20' (AC+H) or 'Appropriate care *without* hylan G-F 20' (AC). Costs (1999 Canadian dollars) were collected from the societal viewpoint and included all costs related to OA of the knee and OA in all joints. Patients completed a number of outcomes questionnaires including the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) and the Health Utilities Index Mark 3 (HUI3). Data were collected at clinic visits (baseline, 12 months) and by telephone (1, 2, 4, 6, 8, 10, and 12 months).

Results: The AC+H group over the year had higher costs ($2125–$1415=$710, $P<0.05$), more patients improved (69%–40%=29%, $P=0.0001$), greater increases in HUI3 (0.13–0.03=0.10, $P<0.0001$) and increased quality-adjusted life years (QALYs) (0.071, $P<0.05$). The incremental cost-effectiveness ratio was $2505/patient improved. The incremental cost–utility ratio was $10 000/QALY gained. Sensitivity analyses and a second cost perspective gave similar results.

Conclusion: The cost–utility ratio is below the suggested Canadian adoption threshold. The results provide strong evidence for adoption of treatment with hylan G-F 20 in the patients and settings studied in the trial.

Key words: Hylan G-F 20, Osteoarthritis, Knee, Economics, Cost and cost analysis, Health-related quality of life.

Introduction

Hylan G-F 20 (Synvisc® Genzyme Corporation, Cambridge, MA, U.S.A.) is a high-molecular weight viscosupplementation product for injection into the intraarticular space of the knee as a synovial fluid replacement. The product has molecular weight and viscosity similar to the synovial fluid found in healthy knees[1]. Hylan G-F 20 has been recently approved for the treatment of patients with osteoarthritis (OA) of the knee in most countries in the world. Accordingly,

Received 28 June 2001; revision requested 5 November 2001; revision received 22 November 2001; accepted 6 December 2001.

The study was funded by Biomatrix, Inc and Rhône-Poulenc Rorer Canada Inc.

Address correspondence to: Dr George Torrance, 1016-A Sutton Drive, Suite 200, Burlington, ON, Canada L7L 6B8. Tel: (905) 331 9911; Fax: (905) 331 9912; E-mail: torrance@mcmail.mcmaster.ca

††The Canadian Knee OA Study Group included the Steering Committee and clinical investigators. The Steering Committee consisted of J. P. Raynauld and G. W. Torrance, co-principal investigators; N. Bellamy, C. H. Goldsmith and P. Tugwell, co-investigators; P. A. Band, M. Schultz and V. Walker. The clinical investigators were: M. J. Bell, MD, Department of Medicine, University of Toronto, Toronto, ON; R. B. Bourne, MD, Department of Surgery, University of Western Ontario, London, ON; R. Cloutier, MD, Departement D'Orthopedie, Centre Hospitalier Affillie, Quebec, QC; A. M. Crawford, MB, Department of Medicine, University of Calgary, Calgary, AB; J. G. Cinats, Department of Surgery, University of Alberta Hospitals, Capital Health Regional Health Authority, Edmonton, AB; M.-A. Fitzcharles, MD, Department of Medicine, McGill University, Montreal, QC; R. D. Inman, MD, Division of Rheumatology, Toronto Western Hospital, University of Toronto, Toronto, ON; K. W. Marshall, MD, Division of Orthopaedics, Toronto Western Hospital, University of Toronto, Toronto, ON; D. P. O'Hanlon, MB, Department of Rheumatology, University of British Columbia, North Vancouver, BC; W. P. Olszynski, MD, Department of Medicine, University of Saskatchewan, Saskatoon, SK; J. Pope, MD, Department of Medicine, University of Western Ontario, London, ON; J.-P. Raynauld, MD, Department of Medicine, University of Montreal, QC; E. D. Sutton, MD, Department of Medicine, Dalhousie University, Halifax, NS; J. C. Thorne, MD, Department of Internal Medicine and Rheumatology, York County Hospital, Newmarket, ON.

the question we sought to answer in this research project was, given that this is an approved and used treatment, how effective and cost effective is it in the real world compared to appropriate care without its availability? That is, we sought to compare a world *with* hylan G-F 20 to a world *without* hylan G-F 20.

Health-related quality of life (HRQOL), effectiveness, cost-effectiveness and cost–utility are studied and reported here. The clinical and safety results of this study are reported in the accompanying manuscript[2]. The study was conducted following the Canadian guidelines for health economic studies[3], which in turn are consistent in most respects with similar guidelines in other countries[4–6]. This is a pragmatic trial. To enhance the real world generalizability of the results the study was conducted in multiple sites, with both rheumatologists and orthopedic surgeons, the study was 1 year in length, the inclusion/exclusion criteria were liberal, and the study was not blinded. The comparator was deliberately selected as appropriate care, not usual care. It was felt that usual care might contain some inappropriate care, and demonstrating that a new treatment is effective and cost-effective compared to inappropriate care is not particularly useful. Appropriate care is the preferred management strategy of specialists, rheumatologists or orthopedic surgeons, encouraged to follow the treatment guidelines published by the American College of Rheumatology[7], and instructed to treat conservatively.

The study was funded jointly by Biomatrix, Inc and Rhône-Poulenc Rorer Canada Inc. Innovus Research Inc., an independent contract research organization (CRO), was contracted to manage the study. An independent Steering Committee was assembled with the responsibility to design the study, develop the analysis plan, and disseminate study results. The Committee consisted of five academics, one representative from each of the two sponsoring companies and one representative from the CRO. The Steering Committee was deliberately structured to be dominated by the five independent academics on the Committee. The Steering Committee was very active and, in fact, dealt with all scientific questions that arose throughout the course of the study, and did so blinded to implications. The contractual arrangement gave the investigators unrestricted rights to publish the study results.

There are several audiences for the study. Clinicians will be interested in the findings of clinical effectiveness and of HRQOL. Many clinicians will also be interested in the findings of the cost-effectiveness and cost–utility analyses, particularly clinicians interested in the efficient use of limited resources and those involved in establishing treatment guidelines. Third-party payers, formulary managers, and fiscal administrators will be interested in all of the findings but particularly the results of the cost-effectiveness and cost–utility analyses.

Methods

STUDY DESIGN

This was a multicenter, 1-year, prospective, randomized, open-label, parallel design trial of appropriate care *with* hylan G-F 20 (AC+H) compared to appropriate care *without* hylan G-F 20 (AC) in the treatment of patients with symptomatic OA of the knee. Patients were recruited from 14 sites across Canada, 10 rheumatologists and four orthopedic surgeons. Patients had to be older than 40 years of age, to have a primary diagnosis of radiologically verified OA in the study knee (knee most symptomatic or with the most predominant musculoskeletal problem), excluding grade IV; to be symptomatic (total pain score greater than 175 mm on the five 100 mm visual analogue pain questions in the Western Ontario McMaster University Osteoarthritis Index (WOMAC)[8] despite prior treatment with acetaminophen or non-steroidal antiinflammatory drugs (NSAIDS) at any point prior to the study, and to be ambulatory.

Protocol-driven costs and outcomes were minimized by limiting study-induced clinic visits. Patients were assessed at the site during the baseline visit and the 12-month termination visit. Patients randomized to AC+H returned to the site for 2 consecutive weeks after baseline for the remaining hylan G-F 20 injections. Other visits could occur on an 'as needed' basis for clinical deterioration, treatment of adverse events, change in medication, or additional treatment with hylan G-F 20 if required; however, no other visits were required by the protocol.

Structured telephone interviews of the patients in both treatment groups were conducted by the CRO at 1, 2, 4, 6, 8, 10, and 12 months. The 12-month termination visit was included for patient assessment by the investigator and for measuring change since baseline. At the baseline visit the following data were collected: patient demographics, appropriate care treatment for knee OA, treatment for overall OA, concomitant medications, and patient self-administered questionnaires (WOMAC Likert 3.0)[8] 4-week recall, the Short-Form 36 (SF-36)[9] 4-week recall, and the Health Utilities Index 3 (HUI3)[10] 4-week recall. Except for patient demographics, the same information was collected at each telephone interview, with the addition of pill counts, adverse events, health care resources (e.g., physician visits, physiotherapy, hospitalizations), any patient expenses (e.g., travel), and lost time from work or usual activities due to OA treatment or OA symptoms. At each telephone interview the information was collected for the time period since the last interview, except for the patient self-administered questionnaires at months 4, 6, 8 and 12 where the recall period was 4 weeks. During the telephone interviews, the patient referred to the self-administered questionnaire and provided his/her answers to the telephone interviewer. To blind the patient to his/her previous answers to the same questions, s/he was instructed not to record the answers, and the questionnaire was laminated with plastic to make it difficult if someone tried to do so. Information collected during the telephone interviews (with the exception of the questionnaires) was compared with the patient's medical chart during monitoring visits and differences were resolved. The investigator reviewed the adverse events for possible attribution to study interventions.

OUTCOME MEASURES

The WOMAC Likert 3.0 is a disease-specific HRQOL instrument that asks the patient questions concerning the study knee. It produces an aggregate total score and scores for three subscales: pain, stiffness and physical functioning.

The outcome measure for the cost-effectiveness analysis (CEA) was patients improved. In the design of the study the Steering Committee provided two definitions of an improved patient. The primary definition was a patient whose WOMAC pain score at month 12 was reduced by

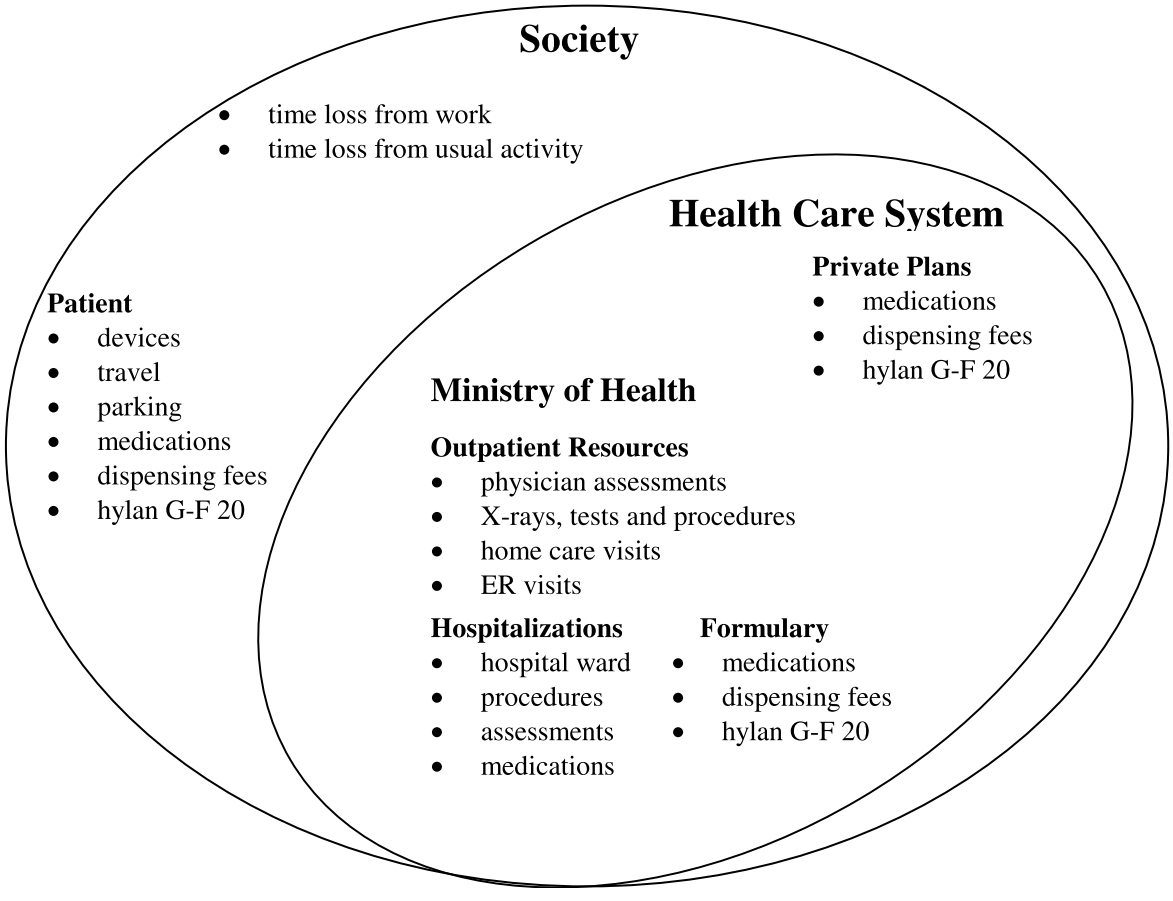

Fig. 1. The types of costs that were included in the societal and health care system perspectives.

20% or more compared with baseline. The secondary definition was a patient who not only reduced their pain score by 20% or greater but also reduced either their stiffness or their physical functioning score by 20% or more as well. The design also specified that the percentage of patients improved in the AC+H group would have to exceed the percentage in the AC group by at least 20% for the results to be clinically important.

The HUI3 is a generic, preference-weighted health status instrument that asks the patient questions about their overall health status and HRQOL. Specifically, the HUI3 measures health status using the following eight attributes: vision, hearing, speech, ambulation, dexterity, emotion, cognition and pain/discomfort. The patient is classified on each attribute into a level varying from normal to severely impaired. The scoring formula for the instrument is based on community preferences as measured by the standard gamble method and thus represents a von Neumann–Morgenstern utility[11]. The instrument provides an overall utility score (min: −0.36; max: 1) on the conventional health utility scale where dead=0.00 and perfect health=1.00. States worse than death can take on negative scores.

The outcome measure for the cost-utility analysis (CUA) is the number of quality-adjusted life years (QALY) gained. The overall utility score from the HUI3 is used as the quality adjustment factor for calculating QALYs gained. Note that the cost-effectiveness analysis focuses on the *study knee* effectiveness, whereas the cost-utility analysis focuses on *patient* effectiveness.

PERSPECTIVES

Figure 1 shows the categories of costs that are included in the different perspectives. Some costs, such as medications and hylan G-F 20, fall in more than one perspective, depending upon the patient's drug plan. A comprehensive societal perspective was adopted as the primary perspective for the economic analyses. In this perspective all costs are counted. Lost time was captured for both the patient and for the unpaid family caregiver, and was categorized into lost work time (for those in paid employment) and lost usual activity time (for those not in paid employment). In the base case analysis only lost work time was included. In a sensitivity analysis, all lost time was included. The health care system (HCS) consists of the two major payers in Ontario, Ministry of Health and private medical plans. This perspective was adopted as the secondary perspective.

RESOURCE UTILIZATION AND COSTING

At each telephone interview patients reported health care received, and indicated which they thought were related to OA (i.e., due to OA in any joint, the treatment of OA in any joint, or the treatment of adverse events related to the treatment of OA). The patient's data were compared with the patient's chart at the investigator's office, and discrepancies were resolved. The physician or the research coordinator at the site reviewed the items and could override the patient's attribution to OA. To improve

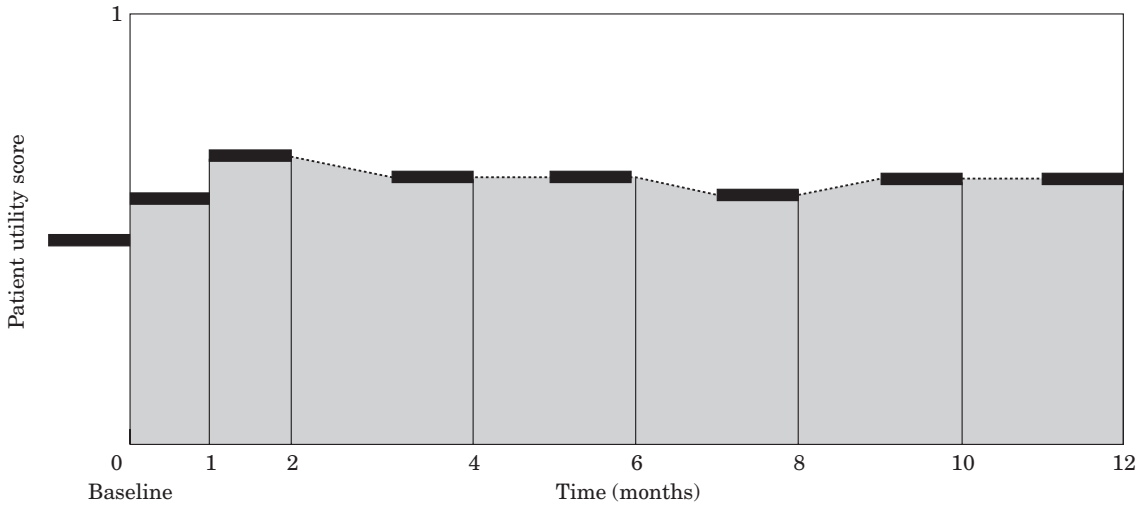

Fig. 2. A typical patient profile for the HUI3 score showing the area-under-the-curve calculation for quality-adjusted life years (QALY). The baseline HUI3 score is shown on the y-axis; however, it is not used to calculate the QALY.

consistency across sites, the three clinicians (JPR, PT, NB) from the Steering Committee reviewed the attribution of all resources, while blinded to treatment allocation. They could override the site's attribution to OA. Only costs related to OA were included in the analysis. The following protocol driven items were not included in the costs: screening visit, X-ray at screening, lab test at baseline, and termination visit.

Costs are reported in 1999 Canadian dollars ($Can). Costs not available in 1999 dollars were adjusted to 1999 using the health and personal care component of the consumer price index[12]. Costs are from the province of Ontario, Canada's largest province.

The market price of hylan G-F 20 in Canada during the study was $339 including tax per course of three injections. Medications were priced according to the Best Available Price for drugs listed on the Ontario Drug Benefit Formulary, or the brand name price from a pharmacy wholesaler's catalogue[13,14]. Prices for outpatient resources were obtained from a variety of appropriate sources; e.g., fees for physician services and laboratory and procedures[15], and cost of other health care professionals[16]. A standard cost ($165.55) for a generic emergency room (ER) visit was used for all ER visits in the study[16]. The reason for hospitalization (e.g. total knee replacement) was coded into an international classification of disease ninth revision clinical modification (ICD9-CM) code. The mean cost for patients hospitalized for that ICD9-CM code for the same length of stay was employed[17]. Patient lost productivity was valued at the Canadian average industrial wage rate ($121.59 per day) for time lost from employment and non-work time losses[18].

STATISTICS

The sample size for the study was calculated based on the primary effectiveness measure for the clinical results, mean change in WOMAC pain score in study knee, as described in the accompanying paper[2]. The sample size was not calculated on the basis of the cost-effectiveness or cost–utility ratio because well-established methods to do so did not exist at the time the study was designed.

All patients randomized were included in the analysis. Missing data were imputed, so that a full data set was available for the statistical analyses. The hot deck method was used to impute data[19]. A patient with missing data was matched to a small group of 'similar' patients with complete data, from which one was selected randomly. Data points missing in the index patient were filled in from the matched patient. Consistent with the comparison of a world with hylan G-F 20 to a world without hylan G-F 20, the few patients in the AC group who violated the protocol by receiving hylan G-F 20 treatment were treated as drop-outs at that point[2]. That is, their data from that point forward were imputed, just like any other drop-out.

The WOMAC and HUI3 questionnaires specified a recall period of 4 weeks, except for the questionnaires at months 1 and 2 in which the recall period was the time since the previous visit. The HUI3 overall utility score represents the mean score for that patient over the recall time period. A typical patient profile is shown in Fig. 2. Note, the horizontal segments in Fig. 2 represent measured scores while the sloping segments represent linear interpolation. The QALY for each patient is calculated by taking the area under the curve for the patient's utility, using years as the unit for time.

Because all patients were not in the study for exactly 365 days, their costs and QALYs were converted to an equivalent annual figure [annualized cost or QALY = (total cost or QALY for time in study/number of days on study) × 365.25 days]. Because the time horizon for the analysis was 1 year, discounting of future costs and consequences was not necessary.

The base case analysis is the primary analysis. The following one-way sensitivity analyses were performed to test the robustness of the results:

- Effectiveness: for the CEA, the incremental effectiveness (difference in proportion of patients improved) was varied to its upper and lower 90% confidence bounds. Similarly, for the CUA, the incremental effectiveness (QALYs gained) was varied to its upper and lower 90% confidence bounds.
- Cost: for the CEA and CUA, the incremental cost was varied to its upper and lower 90% confidence bounds.

Table I
Demographic information and osteoarthritis status, f (percent of n*)**

	AC+H (*n*=127)	AC (*n*=128)
Age, mean (S.D.) years	62.6 (9.4)	63.5 (10.5)
Sex, female	86 (68%)	93 (73%)
Work status		
Full-time	30 (24%)	19 (15%)
Part-time	11 (9%)	16 (13%)
Sick leave	1 (1%)	2 (2%)
Not in paid employment	84 (66%)	90 (70%)
Not specified	1 (1%)	1 (1%)
Prescription drug plan coverage		
No plan	15 (12%)	15 (12%)
Employer or private	53 (41%)	39 (31%)
Government	47 (37%)	64 (50%)
Government+(private or employer)	11 (9%)	8 (6%)
Not specified	1 (1%)	2 (2%)
Duration (years) of OA symptoms		
Study knee, mean (S.D.)	9.0 (9.5)	9.9 (9.7)
Other knee, mean (S.D.)	7.4 (8.8)	8.3 (9.3)
OA at baseline		
Other knee affected	109 (86%)	108 (84%)
Other joints affected	86 (68%)	78 (61%)

*f is frequency, *n* is sample size. Not all percentages sum to 100 due to rounding.
OA=osteoarthritis; AC+H=Appropriate Care + hylan G-F 20; AC=Appropriate Care.

- Time loss: the CEA and CUA were re-done using a more liberal costing of time loss that costed all time loss whether work or usual major activity (including leisure). In the base case only time loss from work was costed.

Results

PATIENTS

One hundred and twenty-seven patients were randomized to receive AC+H and 128 to receive AC. The demographic and OA status of the patients are displayed in Table I. The patients had a mean age of 63 years, with the preponderance of them being unemployed women with OA in both knees, and covered by a drug plan. The two groups were well balanced.

COSTS

The mean annual OA-related cost per patient from the societal perspective by type of cost is shown in Table II. There were too many different kinds of costs to show unit costs within type (e.g. 20 types of injections, 80 types of outpatient resources, 30 types of assistive devices). The total annual cost per patient in a world without hylan G-F 20 (AC group) was $1415. The total in a world with hylan G-F 20 was $2125, an excess of $710. The 95% confidence

Table II
Mean annual OA-related cost per patient from the societal perspective

	AC+H (*n*=127)		AC (*n*=128)		Mean difference ([AC+H]−AC)
hylan G-F 20	676.01	(370.89)	0.00	(0.00)	676.01
Knee OA appropriate care treatment					
Injections (e.g. corticosteriods)	4.05	(10.42)	18.45	(17.31)	−14.40
Medications (e.g. NSAIDs)	200.63	(242.95)	370.10	(529.13)	−169.48
Other therapy (e.g. physiotherapy)	237.32	(831.22)	305.10	(669.22)	−67.78
Assistive devices (e.g. cane)	5.38	(11.61)	16.38	(54.58)	−11.00
Procedures (arthroscopy)	1.70	(19.19)	18.12	(118.65)	−16.42
Subtotal (knee treatment)	449.08		728.15		−279.08
Concomitant medications					
OA in other joints (e.g. NSAIDs)	16.91	(67.62)	17.81	(72.06)	−0.90
Adverse events due to OA treatment (e.g. antacid, analgesics)	53.88	(179.05)	50.08	(123.68)	3.80
Subtotal (concomitant meds)	70.79		67.89		2.90
Outpatient resources (e.g. physician visits)	245.72	(399.96)	134.02	(135.11)	111.70
Hospitalization	194.53	(1012.28)	101.57	(752.54)	92.96
Time loss from work					
by patient					
Due to OA	229.13	(942.26)	190.37	(1085.09)	38.76
Due to OA treatment	53.49	(150.86)	37.95	(180.66)	15.54
by caregiver					
Due to OA	0.37	(4.15)	0.06	(0.69)	0.31
Due to OA treatment	35.30	(350.30)	6.56	(26.32)	28.74
Subtotal (time loss)	318.29		234.94		83.35
Out-of-pocket expenses (e.g. transportation)	170.30	(250.09)	148.00	(215.23)	22.30
Total cost	2124.71	(2528.35)	1414.58	(2032.74)	710.13

All costs are in 1999 Canadian dollars. Mean (S.D.).
OA=osteoarthritis; AC+H=Appropriate Care+hylan G-F 20; AC=Appropriate Care; NSAIDs=non-steroidal antiinflammatory drugs.

interval for the difference in mean total costs was a lower bound of $147 and an upper bound of $1273. Thus, the cost difference between groups was statistically significant at the 5% level (95% confidence interval did not include 0). From a HCS perspective, the total annual OA-related cost was also greater in the AC+H group, and by almost the same amount. The difference was $705 which was also statistically significant at the 5% level (data not shown).

The major contributor to the societal incremental cost of $710 was the cost of the hylan G-F 20 itself, $676. This was the average cost of hylan G-F 20 per patient over the year in the AC+H group. The actual cost of the product for a treatment of three injections was $339, but because many patients had the other knee done as well, and some had additional treatments throughout the year, the average cost was $676. The second major contributor to the incremental cost of $710 was a savings in other treatment costs for the knee OA of $279 (Table II, knee OA appropriate care treatment). The third major contributor was the $112 extra for outpatient visits, primarily the visits to receive injections of hylan G-F 20. At $93 hospitalizations were the next largest contributor. In the base case analysis there were a total of five hospitalizations attributable to OA in the AC+H group and three in the AC group. The five in the AC+H group were: total knee replacement in study knee, total knee replacement in other knee, total hip replacement, triple ankle fusion, and tibia osteotomy. The three in the AC group were: total knee replacement in study knee, total knee replacement in other knee, and bunionectomy. Interestingly, there were two additional total knee replacements in the study knee that were not counted in the base case analysis because they occurred after the two patients in question had violated protocol by receiving hylan G-F 20. The fifth largest contributor to the cost difference was the additional cost of lost work time for the AC+H group at $83, which could be due to the visits needed for the hylan G-F 20 injections. Out of pocket expenses were also slightly higher possibly for the same reason, i.e., travel costs for visits.

CONSEQUENCES

The percent of patients improved at 12 months using the primary definition of improvement was 69% in the AC+H group and 40% in the AC group for an increment of 29%. Using the secondary definition of improvement the results were 62% and 35% for an increment of 27%. Both increments were statistically significant (P=0.0001) and exceeded the clinically important difference of 20% established a priori as part of the research design.

The improvement in mean utility from baseline to termination as measured by the HUI3 was 0.13 in the AC+H group compared to 0.03 in the AC group, for a difference of 0.10 units of utility (P<0.0001). Figure 3 displays the change in mean utility score from baseline to each interview for both treatment groups. Both groups improved sharply for the first 2 months and then tailed off. However, the AC+H group improved more and tailed off less, thus giving a substantial area between the two curves. The area between the two curves over the 12 months represents the difference in QALYs between the two groups. The patients in the AC+H group gained 0.071 QALYs compared to the patients in the AC group. The 95% confidence interval for the difference in QALYs was a lower bound of 0.017 and an upper bound of 0.126. The difference between groups was statistically significant at the 5% level (95% confidence interval did not include 0).

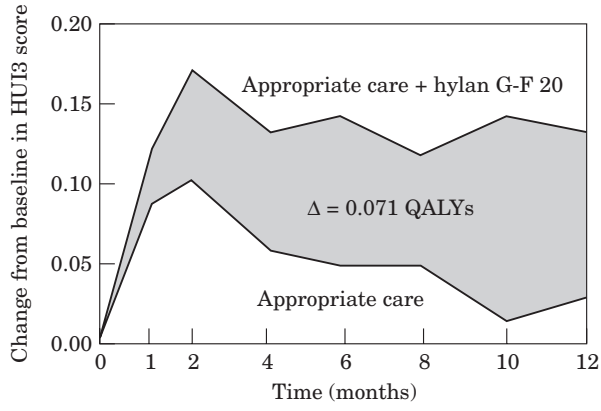

Fig. 3. Difference between treatment groups in mean change from baseline in Health Utilities Index 3 utility score. HUI3=Health Utilities Index 3; QALYs=quality-adjusted life years.

BASE CASE ANALYSIS

The base case CEA and CUA are shown in the first row of Table III. The AC+H group was more costly and more effective. The incremental cost per patient over 1 year was $710 and $705 from the societal and HCS perspective, respectively. The incremental effectiveness was an increase of 0.2834 proportion of patients improved. The C/E ratio was $2505 or $2488 per patient improved, from the societal and HCS perspective, respectively. For the CUA the incremental effectiveness was 0.071 QALYs per patient. The C/U ratio was $10 000 or $9930 per QALY gained, from the societal and HCS perspective, respectively.

SENSITIVITY ANALYSES

Table III displays the results of the sensitivity analyses for the CEA and CUA. There are five sensitivity analyses: effectiveness high, effectiveness low, costs high, costs low, and alternative definition of lost time. To help interpret these results the CUA sensitivity analyses are plotted on a cost-effectiveness graph in Fig. 4. Note that the slope of the line through the point is the cost per QALY of that point. Thus, lower slopes are more cost-effective, and vice versa. To enhance the interpretation we have also plotted on Fig. 4 the decision thresholds suggested by Laupacis *et al.*[20]: cost per QALY between $0 and $20 000=strong evidence for adoption; between $20 000 and $100 000=moderate evidence for adoption; and above $100 000=weak evidence for adoption. Figure 4 demonstrates that the results are robust; four of the five sensitivity analyses fall in the decision sector ‘strong evidence for adoption’ while the fifth falls in the adjacent sector ‘moderate evidence for adoption’.

Discussion

Although the trial was powered only for the primary clinical outcome (change in mean WOMAC pain score), the outcomes for the economic evaluation (gain in percent of patients improved, gain in QALYs, and cost difference) also achieved statistical significance at the 5% level. Thus the findings are particularly robust, especially for a prospective economic evaluation study.

Table III
Cost-effectiveness and cost–utility analyses: base case and sensitivity analyses from the societal and health care system perspectives

	Annual cost difference		Difference in proportion of patients improved	Cost per patient improved*		QALYs gained†	Cost per QALY gained‡	
	Societal	HCS		Societal	HCS		Societal	HCS
Number of patients (AC+H/AC)§	127/128	127/128	127/127	127/128	127/128	127/128	127/128	127/128
Base-case analysis	$710	$705	0.2834	$2505	$2488	0.071	$10 000	$9930
Sensitivity analyses on outcomes‖								
High	$710	$705	0.3820	$1859	$1846	0.117	$6068	$6026
Low	$710	$705	0.1848	$3842	$3815	0.025	$28,400	$28,200
Sensitivity analyses on costs‖								
High	$1183	$1008	0.2834	$4174	$3557	0.071	$16,662	$14,197
Low	$238	$402	0.2834	$840	$1418	0.071	$3352	$5662
Sensitivity analysis using alternative costing for time loss**	$938	n/a††	0.2834	$3310	n/a††	0.071	$13,211	n/a††

All costs are in 1999 Canadian dollars.
*The cost per patient improved=incremental cost ([AC+H]−AC)/incremental effectiveness ([AC+H]−AC).
†QALY gained is adjusted for baseline differences.
‡The cost per QALY gained=incremental cost ([AC+H]−AC)/incremental QALY ([AC+H]−AC).
§The mean cost per patient and QALYs gained were calculated from 128 patients; the proportion of patients improved was calculated from 127 patients.
‖High represents the upper 90% CI for the difference between groups, and Low represents the lower 90% CI for the difference between groups.
**The base-case analysis included time loss from work. The sensitivity analysis included time loss from usual major activities also.
††A ratio will not be calculated as the cost of time loss was not included in the HCS perspective costs.
QALY=quality-adjusted life year; HCS=health care system; AC+H=Appropriate Care+hylan G-F 20; AC=Appropriate Care; CI=confidence interval.

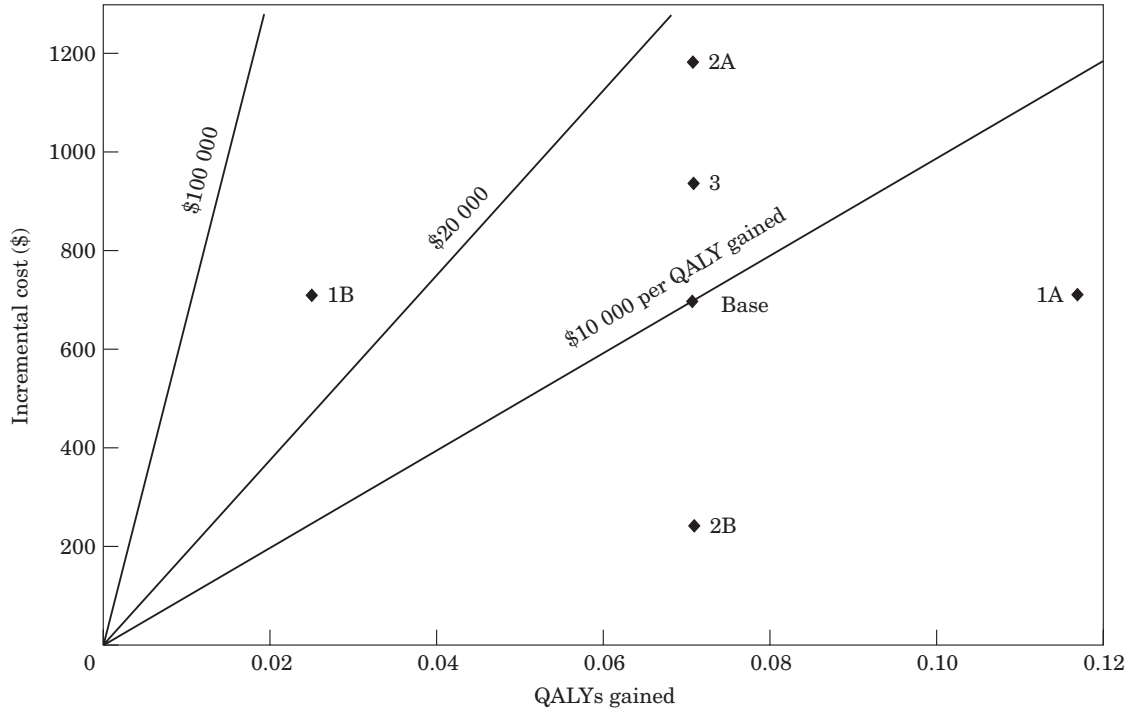

Fig. 4. Base-case (Base) and sensitivity analysis (1A-3) results for the cost–utility analysis from the societal perspective. Sensitivity analyses assume: 1A, upper 90% CI for difference in QALYs gained between groups; 1B, lower 90% CI for difference in QALYs gained between groups; 2A, upper 90% CI for difference in total costs between groups; 2B, lower 90% CI for difference in total cost between groups; 3, annual cost of time loss from work or usual major activity for all patients and caregivers. CI=confidence interval; QALY=quality-adjusted life year; $Can=Canadian dollars.

The cost findings are relatively easy to interpret. The use of hylan G-F 20 reduced the need for and the cost of other treatments for OA, but not enough to offset the increased costs due to the price of the product and due to the costs associated with the extra physician visits required to administer the treatment.

The patient outcome findings are also straightforward. The patients in the AC+H group were better off, and

statistically significantly so, by both the disease specific measure (WOMAC), and by the health utility measure (HUI3). The important outcomes for the economic analysis were the incremental proportion of patients improved in the AC+H group compared to the AC group (29%) and the incremental QALYs gained in the AC+H group compared to the AC group (0.071). The former outcome, 29%, exceeded the a priori threshold for clinical importance which had been set at 20%. However, no threshold had been established a priori for an important increment in QALYs.

Is a mean gain of 0.071 QALYs per patient important? One way to address this question, is to return to the theory on which the HUI3 instrument is based, von Neumann–Morgenstern utility theory and the standard gamble measurement. On the basis of this theory a direct interpretation is that a gain of 0.071 QALYs over a year is equivalent to a reduction in mortality rate of 0.071. That is, providing an *ongoing* improvement in quality of life of this magnitude (0.071 QALY per year) is equivalent to finding a group of healthy individuals (no HUI3 disabilities) who are at high risk (50%) of immediate sudden death and providing them with an absolute risk reduction in mortality of 7.1% (i.e., reducing their risk to 42.9%). If the group of individuals has compromised quality of life like patients with knee OA, the interpretation is even more dramatic. According to von Neumann–Morgenstern utility theory a patient like those at baseline in the AC+H group with a utility score of 0.50 and no risk of immediate death would be willing to take a risk of immediate death of 12.4%, $0.124=1.000-(0.500/(0.500+0.071))$, to achieve an ongoing improvement in quality of life of 0.071. Thus, there is little question that a QALY gain of this magnitude is important. Moreover, any QALY gain can be important depending on the cost required to produce the gain and on the overall context of the gain[21].

The cost-effectiveness finding is that the incremental cost per patient improved over 1 year is $2505 (societal) and $2488 (HCS). That is, an expenditure of approximately $2500 will purchase an improved patient for a year. Is this good value for money? There is no absolute answer. Decision-makers responsible for allocating resources will have to weigh this opportunity against other choices. If the other choices are not expressed in the same metric, improved patients, the comparison becomes difficult. This highlights the advantage of cost–utility analysis.

The finding of the cost–utility analysis is that the incremental cost per QALY gained is $10 000 (societal) and $9930 (HCS). That is, an expenditure of approximately $10 000 will purchase a gain of 1 QALY. Is this good value for money? There are several ways to approach the question. One approach is to compare the results to other studies using a league table in which studies are ranked from best to worst according to their cost per QALY gained. Current methodological advice is that indiscriminate comparisons of this type can be misleading, and that league tables should be restricted to high-quality studies that use comparable scientific methods, and possibly further restricted to interventions targeted at one condition (e.g., musculo-skeletal problems)[22].

Chapman *et al*. from Harvard University undertook a comprehensive literature review of cost–utility studies 1976–1997 and categorized them into 'Panel-worthy' or not, and further subdivided the list by disease categories one of which is musculo-skeletal[23]. 'Panel-worthy' studies are those that met a minimum standard of methodological quality established by Chapman *et al*. based on the recommendations of the Panel on Cost-Effectiveness in Health and Medicine[24]. There has been only one 'Panel-worthy' study in the field of musculo-skeletal diseases, a cost-effectiveness analysis of total hip arthroplasty for OA of the hip, published in 1996 by Chang *et al*. In addition, there is a relevant 'Panel-worthy' study in the digestive system category, a cost-utility analysis of the use of misoprostol prophylaxis for rheumatoid arthritis patients receiving NSAIDs drugs, published by Gabriel *et al*. in 1994. These two studies contain four cost–utility ratios. The four ratios are included in our league table (Table IV).

Table IV
Cost/QALY League Table (1998 US dollars)

Cost/QALY gained	Treatment and comparator
Cost-saving	Total hip arthroplasty vs no total hip arthroplasty in white 60-year-old women with hip osteoarthritis in American College of Rheumatology function class III (significant functional limitation, but not dependent)[23]
$5500	Total hip arthroplasty vs no total hip arthroplasty in white men ≥85 years old with hip osteoarthritis in American College of Rheumatology function class III (significant functional limitation, but not dependent)[23]
$6500	Appropriate Care+hylan G-F 20 vs Appropriate Care for knee osteoarthritis, health care system perspective (this study)
$6600	Appropriate Care+hylan G-F 20 vs Appropriate Care for knee osteoarthritis, societal perspective (this study)
$7500	Total hip arthroplasty vs no hip arthroplasty for all patients, 3 year follow-up[25]
$11 000	Prophylaxis for NSAID-associated gastric ulcers with low-dose misoprostol (100 mcg four times daily) for elderly (>60 years old) vs no prophylaxis for all NSAID users in rheumatoid arthritis patients on NSAIDs[23]
$12 000	Prophylaxis for NSAID-associated gastric ulcers with low-dose misoprostol (100 mcg four times daily) for all vs prophylaxis for elderly (>60 years old) in rheumatoid arthritis patients on NSAIDs[23]

In addition we have included, for comparison, one relevant Canadian study[25]. Although it did not meet the criteria for 'Panel-worthy', we believe it can be usefully interpreted. One shortcoming of the study, lack of discounting, we have corrected in the data shown here using a discount rate of 5% per year. Another shortcoming, lack of incremental costing (they did not measure the costs that would have occurred without hip replacement) was conservative. On the positive side, the study was Canadian and, thus, is more directly comparable to our hylan G-F 20 study. The study prospectively measured costs (from the perspective of the health care system) and time trade-off utilities for total hip arthroplasty over 1 year, and modeled the analysis for 2 additional years for a total analytic horizon of 3 years.

For consistency with the Harvard table of 'Panel-worthy' studies, all entries in the league table (Table IV) have been adjusted to 1998 US dollars. The two Canadian ratios were first adjusted to 1998 Canadian dollars, using the Health Care component of the Canadian Consumer Price Index[26], and then converted to US dollars using the mean exchange rate for 1998, 1.4831[27]. As shown in the league table, hylan G-F 20 provides 'value for money', from either perspective, that is not as good as total hip arthroplasty for 60-year-old

US women as studied by Chang *et al*., but is similar to total hip arthroplasty for ≥85-year-old US men studied by Chang *et al*. or for Canadians studied by Laupacis *et al*.[25], and is better than misoprostol prophylaxis for rheumatoid arthritis patients taking NSAIDs.

A second approach to answering the question of value for money is to compare the results to some external standard. For example, Laupacis *et al*.[20] suggest that if a new therapy is more effective and more costly than the existing one and costs less than $20 000/QALY gained, there exists strong evidence for adoption of the new therapy. Similarly, $20 000 to $100 000/QALY gained provides moderate evidence for adoption, and over $100 000/QALY gained provides weak evidence for adoption. These costs are in 1990 Canadian dollars, and the thresholds in 1999 dollars may be larger. Thus, the cost–utility results for the use of hylan G-F 20 in the knee fall in the category of strong evidence in favour of adoption.

STUDY STRENGTHS

The study was designed according to rigorous standards put forth in guidelines for economic evaluations. All of the participating investigators had a high degree of experience treating patients with hylan G-F 20, therefore it was possible to measure effectiveness, or 'real world' clinical effects, the outcome required for an economic evaluation. Hylan G-F 20 was compared to an appropriate comparator in that current practice guidelines were employed rather than placebo. The study was open-label and therefore physicians could practice according to their normal routine. Both treatment groups had equal access to the full repertoire of appropriate care. It was possible to limit the amount of protocol-driven costs by employing telephone interviews to collect data. Costs included indirect and direct costs, and overhead costs were included. The study time horizon was 1 year, which enabled measurement of downstream costs and consequences associated with subsequent courses of hylan G-F 20, adverse events, and treatment failure.

STUDY LIMITATIONS

One of the limitations was that the study was open-label and patients or physicians may have been biased in favour of hylan G-F 20 treatment which in turn could have affected outcomes and costs. On the other hand, many in the AC group also received a knee injection (corticosteroid), and all patients in both groups received appropriate care. The ongoing telephone interviews may have influenced the patient assessments. The patients might have improved because of the attention they received, or they might have felt worse because they focused more on their symptoms when answering symptom questionnaires. However, the potential telephone interview biases would have been similar in both groups, therefore it is unlikely there was a differential from this source.

GENERALIZABILITY

The study applies to patients treated by rheumatologists and orthopedic surgeons in Canada. The results are not directly applicable in other countries. Readers in other countries have to decide which aspects of the study apply, and which aspects need to be modified. It is generally felt that clinical findings travel fairly well. One would expect similar findings in the patient outcomes—WOMAC scores, SF-36 scores and HUI3 scores. Moreover, although the HUI3 is scored based on preferences from a Canadian population, there is considerable evidence that preference scores from the general public are independent of country (for example, see Johnson *et al*.[28] and Gales *et al*.[29]). On the other hand, because the health care systems differ among countries, the utilization of health care resources may differ. Moreover, the prices of health care resources including hylan G-F 20 differ in different countries. Thus, the costs can not be assumed to apply in other countries. Those interested in other countries will have to modify the study results appropriately[30] or use this study as a prototype from which to conduct a study in their own country.

Conclusions

This study demonstrates that hylan G-F 20, when used in conjunction with appropriate care, provides an improvement in outcomes that is both clinically important and statistically significant. Total costs are higher when hylan G-F 20 is selected as a treatment option for patients with OA of the knee, but the cost per QALY gained is well below the suggested Canadian threshold for adoption.

Acknowledgments

The authors would like to thank individuals at Biomatrix, Inc. and Innovus Research Inc. who were involved in the study at various stages: Biomatrix, Inc.: Jean Bonomo, Katie Kubler, and Sarita Wilson. Innovus Research Inc.: Bill Bell, Lisa Bernard, Harminder Bilen, Linda Bursic, Helen Crabbe, Paule Desjardins, Julie Gordon, Susan Gow, Lorraine Hotchkies, Marg Hux, Natalie Milkovich, Nancy Ryan, Tammy Sarre, Tammy Slote, Sandra Therrien, John Walker, Irene Zivko, Barb Zrinscak. A special thanks to Shelley Lee for study coordination and Dan Pericak for statistical analysis.

References

1. Synvisc Hylan G-F 20 US label. CI 5014-1. 8005US-01. Issued August 28, 1997.
2. Raynauld JP, Torrance GW, Band PA, Goldsmith CH, Tugwell P, Walker V, *et al*, in collaboration with the Canadian Knee OA Study Group. A prospective, randomized, pragmatic, health outcomes trial evaluating the incorporation of hylan G-F 20 into the treatment paradigm for patients with knee osteoarthritis (Part 1 of 2): clinical results. Osteoarthritis Cart 2002;10:506–17.
3. Canadian Coordinating Office for Health Technology Assessment. Guidelines for Economic Evaluation of Pharmaceuticals: Canada. 2nd ed. Ottawa: CCOHTA, November 1997.
4. Australian Commonwealth Department of Human Services and Health. Guidelines for the Pharmaceutical Industry on Preparation of Submissions to the Pharmaceutical Benefits Advisory Committee: including major submissions involving economic analyses. Canberra: Australian Government Publishing Service 1995.

5. Weinstein MC, Siegel JE, Russell LB, Gold MR. Recommendations for reporting cost-effectiveness analyses. Panel on cost-effectiveness in health and medicine. JAMA 1996;276:1339–41.
6. Drummond MF, Jefferson TO. Guidelines for authors and peer reviewers of economic evaluations to the BMJ. The BMJ Economic Evaluation Working Party. BMJ 1996;313:275–83.
7. Hochberg MC, Altman RD, Brandt KD, Clark BM, Dieppe PA, Griffin MR, *et al*. Guidelines for the medical management of osteoarthritis. Part II. Osteoarthritis of the knee. Arthritis Rheum 1995;38: 1541–6.
8. Bellamy N, Buchanan WW, Goldsmith CH, Campbell J, Stitt LW. Validation study of WOMAC: a health status instrument for measuring clinically important patient relevant outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip or knee. J Rheumatol 1988;15:1833–40.
9. Ware JE Jr, Sherbourne CD. The MOS 36-item short-form health survey. (SF-36). I. Conceptual framework and item selection. Med Care 1992;30:473–83.
10. Torrance GW, Furlong W, Feeny D, Boyle M. Multi-attribute preference functions. Health utilities index. Pharmacoeconomics 1995;7:503–20.
11. Von Neumann J, Morgenstern O. Theory of Games and Economic Behaviour. Princeton, NJ: Princeton University Press 1944.
12. Statistics Canada. (1995) Consumer Price Index, January 1996 to 1998 (http://www.statcan.ca/Daily). Ottawa, Ontario: Ministry of Industry.
13. Ontario Drug Benefit Formulary/Comparative Drug Index Edition No. 35.
14. Medis June 1998 Pharmaceuticals catalogue.
15. Ontario Schedule of Benefits. Physician Services under the Health Insurance Act. April 1, 1998.
16. Browne G, Gafni A, Roberts J, Goldsmith A, Jamieson E. Approach to the Measurement of Costs (Expenditures) when Evaluating Health and Social Programmes, System-Linked Research Unit, McMaster University. November, 1995.
17. Ontario Case Costing Project. 1994/1995 & 1995/96. 20 Adelaide St. East, Toronto, ON, M5G 2T6.
18. Statistics Canada. Average industrial aggregate. Ottawa (ON): Statistics Canada. February 1999.
19. Little RJA, Rubin DB. Statistical Analysis with Missing Data. Toronto, ON: Wiley 1987.
20. Laupacis A, Feeny D, Detsky AS, Tugwell PX. How attractive does a new technology have to be to warrant adoption and utilization? Tentative guidelines for using clinical and economic evaluations. CMAJ 1992;146:473–81.
21. Hays RD, Wooley JM. The concept of clinically meaningful difference in health-related quality of life research: how meaningful is it? Pharmacoeconomics 2000;18:419–23.
22. Drummond M, Torrance G, Mason J. Cost-effectiveness league tables: more harm than good? Soc Sci Med 1993;37:33–40.
23. Chapman RH, Stone PW, Sandberg EA, Bell C, Neumann PJ. A comprehensive league table of cost-utility ratios and a sub-table of 'panel worthy' studies. Med Dec Mkg 2000;20:451–67.
24. Gold MR, Siegel JE, Russell LB, Weinstein MC, Eds. Cost-effectiveness in Health and Medicine. New York: Oxford University Press 1996.
25. Laupacis A, Bourne R, Rorabeck C, Feeny D, Wong C, Tugwell P, *et al*. Costs of elective total hip arthroplasty during the first year. Cemented versus non-cemented. J Arthroplasty 1994;9(5): 481–7.
26. Statistics Canada, CANSIM, Matrix 9940, Consumer price index, 1996 classification, annual health care, historical summary.
27. The Canada Customs and Revenue Agency. Average Exchange Rates for 1998.
28. Johnson JA, Ohinmaa A, Murti B, Sintonen H, Coons SJ. Comparison of Finnish and US-based visual analog scale valuations of the EQ-5D measure. Med Dec Mkg 2000;20:281–9.
29. Le Gales C, Buron C, Costet N, Rosman S, Slama G. The French Health Utilities Index Mark 3. Abstract. Value in Health 2000;3:103.
30. O'Brien B. A tale of two (or more) cities: geographic transferability of pharmacoeconomic data. Am J Managed Care 1997;3:S33–9.

Appendix

AC+H=Appropriate care *with* hylan G-F 20
AC=Appropriate care *without* hylan G-F 20
WOMAC=Western Ontario and McMaster Universities Osteoarthritis Index
HUI3=Health Utilities Index 3
QALYs=quality-adjusted life years
OA=osteoarthritis
HRQOL=Health-related quality of life
CRO=contract research organization
NSAIDs=non-steroidal antiinflammatory drugs
SF-36=Short-Form 36
HCS=health care system
$Can=Canadian dollars
ER=emergency room
ICD9-CM=international classification of disease ninth revision clinical modification
CEA=cost-effectiveness analysis
CUA=cost-utility analysis