

Chapter 25. Osteoarthritis/arthrosis Short Term Studies: Pain and Function Improvement

Jean-Pierre Raynauld, M.D. ¹

Johanne Martel-Pelletier, Ph.D. ¹

Boulos Haraoui, M.D. ¹

Jean-Pierre Pelletier, M.D. ¹

¹ Osteoarthritis Research Unit
Centre hospitalier de l'Université de Montréal (CHUM)
Hôpital Notre-Dame
Département de Médecine
Université de Montréal
Montréal, Québec
CANADA

I. INTRODUCTORY REMARKS

Osteoarthritis (OA) is the most common form of arthritis and is a leading cause of disability. More than 75% of those over age seventy exhibit radiographically detectable changes consistent with osteoarthritis. About 40-60% of subjects with radiological OA changes suffer from clinical symptoms such as pain, joint stiffness, and joint deformities.

Patients with OA have pain that typically worsens with weight bearing and activity and improves with rest, as well as morning stiffness, gelling of the involved joint after periods of inactivity, and limited joint motion. As OA progresses, pain at rest can also be present. With a few exceptions, the causes of OA are not known so that the main goals of therapy are pain relief and improved physical and social function.

Pharmacologic therapy of OA typically begins with analgesics such as acetaminophen in doses up to 4 g/day, progresses to low dose nonsteroidal anti-inflammatory drugs (NSAIDs), and then to full dose NSAIDs (including COX-2 selective inhibitors). NSAIDs, while useful, have a ceiling effect and can be limited in their use because of their side effects, particularly those affecting the gastrointestinal tract, liver, and kidney; the risks of which increase with advanced age.

The primary parameter of this study is the proportion of subjects who achieve adequate pain control (% with moderate, good, or excellent pain control) during 56 days of a new DRUG X. This parameter will be assessed with a pain control assessment performed at study entry, at each telephone contact, and at each visit. Among secondary parameters are the effect on pain intensity, quality of life, functionality, and global assessment of change.

II. RATIONALE FOR STUDY DESIGN

This trial is an observational, therapeutic use study investigating the effect of DRUG X treatment on pain control in subjects with moderate to severe pain due to OA of the hip or knee that is inadequately controlled with acetaminophen or a traditional NSAID.

DRUG X has been demonstrated to be safe and efficacious in chronic non-cancer pain in several randomised clinical trials. Moreover, DRUG X has been demonstrated to be preferred over several NSAIDs with the main reason being that better pain control was achieved. DRUG X was also associated with a better safety profile. The effect of 8 weeks treatment with DRUG X on pain control, quality of life, and functionality has not been previously investigated in a clinical study of subjects with moderate to severe OA pain of the hip or knee that is inadequately controlled with NSAIDs.

II.1. Outline of a Typical Development Plan

Multi-center, randomized, double-blind, placebo-controlled, parallel group study with mild to moderate primary knee (or hip) OA fulfilling the American College of Rheumatology (ACR) criteria (see Appendix A), who have been completely withdrawn from their previous analgesics or anti-inflammatory medications or have been newly diagnosed with mild to moderate primary knee (or hip) OA and who are not currently taking any analgesics or anti-inflammatory medications.

II.2. Short-Term Studies: Pain and Function Improvement

II.2.A. Objectives

The objective of this study is to investigate the short-term effect of a new DRUG X at a dose of Y mg compared to placebo, on pain control in subjects with moderate to severe pain due to OA according to the ACR (see Appendix A) of hip or knee that is inadequately controlled with simple analgesics or NSAIDs.

II.2.B. Primary endpoints

To determine the proportion of subjects with symptomatic osteoarthritis of the hip or knee who achieve adequate pain control (% of subjects with moderate, good, or excellent pain control) during 56 days of treatment with DRUG X.

II.2.C. Secondary endpoints

To compare the scores from the Numerical Pain Intensity Rating scale, WOMAC Osteoarthritis Index questionnaire and Acute SF-36 Health Survey after 56 days of treatment with DRUG X to baseline. Physician and Subject Global Impression of Change scales and Subject Treatment Assessment questionnaire will be done at the Final Visit.

II.2.D. Study design

This is a placebo-controlled, multicentre study.

Eligible subjects will undergo screening procedures. Subjects must show evidence of symptomatic hip or knee OA (ACR Functional Class \geq grade 2) and meet the ACR hip or knee OA criteria, have “poor” or “very poor” pain control (on a five-point scale of excellent, good, moderate, poor, or very poor), and have at least moderate to severe pain demonstrated as a pain score \geq 5 on a numerical pain intensity rating scale of 0 to 10 (with “0” representing no pain and “10” representing worst possible pain).

The duration of study treatment is 56 days. At Visit 1 (Study Entry) subjects will start on DRUG X at a dosage Y and will remain on this dose for the trial period.

During each study visit subjects will be required to complete a Pain Control Assessment indicating the amount of pain control experienced that day, a Western Ontario and McMaster Universities (WOMAC) Osteoarthritis Index and an SF-36 Acute Health Survey (Appendix B). Physician and Subject Global Impression of Change scales (7-point scale, see Efficacy Evaluations section) will be conducted at Visit 4. In the event that a subject withdraws early, all Visit 4 procedures will be performed.

At Visit 1 (Study Entry) subjects will start on DRUG X. Supplementary analgesic medication consisting of acetaminophen, 500 mg tablets, will be allowed during the study on an as needed basis, provided the total daily dose of acetaminophen does not exceed 4 g (8 tablets).

Eligible subjects who are enrolled into the study will be randomly allocated to be treated with DRUG X or a placebo for 56 days. Insufficient analgesia will be determined by the investigator, using his or her clinical judgement and taking into account the subject’s level of pain severity, level of pain control, use of supplementary acetaminophen, 500 mg tablets, and individual response and tolerance to the dose.

Subjects will be provided with acetaminophen, 500 mg tablets, as supplementary analgesic medication for any additional pain in the target OA hip or knee joint and will be taken as needed throughout the study (provided the total daily dose of acetaminophen does not exceed 4 g or 8 tablets). Subject use of acetaminophen, 500 mg tablets will be recorded in the Patient diary on a daily basis (Appendix C).

Concomitant analgesic opioid medication is NOT allowed during the course of the study. Weak opioid medication must be discontinued at the time of study entry.

Inhaled steroids for asthma or topical corticosteroid preparations for minor dermatological use will be allowed during the study.

Alcoholic beverages and sedating antihistamines may also produce additive depressant effects and should be used with caution.

ASA (acetylsalicylic acid) for cardiac prophylaxis, up to 325 mg/day, will be allowed during the study and should be used with caution with concomitant use of acetaminophen.

All medications (prescriptions or over-the-counter (OTC) medications, including supplements or nutraceuticals) and medical procedures ongoing in the week preceding study entry that are continued at the start of the study or are started during the trial and are different from the trial medication, must be documented on the Concomitant Therapy Form of the CRF. If any medication or medical procedure is started, stopped, or if the dose or frequency is modified, this must also be documented on the CRF. The sponsor must be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies are administered.

For any concomitant therapy given as a treatment for a new condition or a worsening of an existing condition, the condition must be documented on the Adverse Event Form of the CRF.

III.2.F. Planned sample

Approximately 80 subjects will be required to be able to estimate the proportion of subjects achieving "excellent", "good" or "moderate" pain control within $\pm 11\%$ with DRUG X compared to placebo with 95% confidence. Because only Visit 2 efficacy response is required for the evaluable population, no contingency is built in the required sample size.

Approximately 80 subjects who have a history of symptomatic OA of the hip or knee with chronic pain for at least 3 months, who have been on a stable daily dose of acetaminophen for at least two weeks prior to Study Entry, and who have uncontrolled pain, will be enrolled into the study.

Approximately 80 subjects from 10 sites will be screened and enrolled in the study. Each site will enrol approximately X subjects. Subjects are OA subjects, suffering with chronic hip or knee pain for at least 3 months (for at least 20 days of each month), and who are not hospitalised. The target joint selected will be an OA hip or knee joint that causes the most pain to the subject. In case of pain of equal severity in hip *and* knee, one target joint must be selected.

III.2.G. Study population

Potential study subjects must have a history of symptomatic osteoarthritis of the hip or knee with chronic pain for at least 3 months and must have been on a stable daily dose of acetaminophen at least 2 weeks prior to the study. The study will be explained to subjects and informed consent will be obtained.

III.2.H. Specific Inclusion Criteria

Subjects must satisfy the ALL of the following inclusion criteria before entering the study:

- a. Male or female of ages ≥ 40 .
- b. Must be in generally good health as confirmed by medical and previous medication history, and baseline physical examination including vital signs.
- c. Female subjects must be postmenopausal for at least 2 years, surgically sterile, or practising an effective method of birth control prior to entry and throughout the study, and have a negative urine pregnancy test at the baseline visit. The subject may continue in the study using abstinence as a form of birth control provided that she is completely abstinent, has a negative urine pregnancy test prior to study entry and at the final visit or upon termination (if the subject discontinues the trial early). It must be documented in the medical notes that the subject has been counselled about the birth control and the risks of becoming pregnant.
- d. Symptomatic OA of the target hip or knee joint as evidenced by hip or knee pain for at least 3 months (for at least 20 days of each month) and osteophytes confirmed by an x-ray taken within the last two years and who must meet the OA hip or knee criteria of the American College of Rheumatology (Appendix A).

- e. After a full explanation of the study, subjects must understand the nature of the study and sign the informed consent form to participate.
- f. Subjects with moderate to severe pain of the target OA hip or knee joint whose pain is not adequately controlled with an NSAID. This will be defined as subjects with a pain control assessment of “poor” or “very poor” (on a five-point scale: excellent, good, moderate, poor, or very poor) and a mean pain score ≥ 5 (on a numerical pain intensity rating scale of 0-10) at Baseline.

III.2.I. Specific Exclusion Criteria

Potential subjects who meet any ONE of the following exclusion criteria will NOT be eligible to participate in the study:

- a. Subjects who have previously failed on DRUG X therapy or those who previously have discontinued DRUG X due to adverse events.
- b. Subjects who have received treatment with a strong opioid (e.g. morphine, hydromorphone, methadone, long-acting oxycodone, oxymorphone, levorphanol, heroin, etc.) in the 4 weeks preceding study entry. Subjects cannot take strong opioids during the study.
- c. Subjects for whom a treatment is planned within the study period that could alter the degree or nature of pain (e.g. arthroscopic techniques, osteotomy, joint replacement surgery, etc.).
- d. Subjects who are experiencing another type of continuous pain that is more severe in intensity in comparison with the OA target joint pain (e.g. low back pain, fibromyalgia, ankylosing spondylitis, etc.).
- e. Subjects who have had target joint intra- or periarticular corticosteroid injections within 6 weeks of study entry or hyaluronan injections within 6 months of study entry. Injections are not allowed during the study. Subjects cannot have had arthrolysis within 4 weeks or arthroscopic techniques (e.g. joint débridement, abrasion, arthroplasty, chondral holes, etc.) within 3 months prior to the study or during the study.
- f. Subjects taking glucosamine will not be eligible unless they have been on a stable dose for greater than 2 months preceding study entry. If subjects were taking a stable dose for at least 2 months prior to the study, the dosage should remain constant throughout the study. Glucosamine cannot be started at anytime during the study.
- g. Subjects taking NSAIDs, COX-2 selective inhibitors, or steroidal drugs for at least 4 weeks before study entry may continue these medications during the study; however, they must have been taking a stable dose (consistent daily milligram dose $\pm 25\%$) for at least 2 weeks before study entry and the dosage must be kept constant throughout the study. If these medications were started within the 4 weeks preceding the study, the subject will be excluded, but can be rescreened at a later time. These medications cannot be started at anytime during the study.
- h. Subjects who have had major surgery in the 3 months preceding the study.
- i. Subjects with a significant psychiatric disorder (including major depression) or subjects receiving anti-psychotic medication.
- j. Subjects who have taken sedatives, hypnotics, phenothiazines, anticonvulsants, tranquilizers or muscle relaxants two weeks preceding study entry. These medications cannot be started during the study.
- k. Subjects who are taking tricyclic antidepressants if not expected to remain on a stable dose of these medications for the duration of the study. These medications cannot be started during the study.
- l. Subjects who have applied topical analgesic preparations to the target joint and/or taken general anaesthetics in the one week preceding study entry. These medications cannot be started during the study.
- m. Subjects with documented or suspected history of alcohol or drug abuse, or who have a documented or suspected history of an addictive personality.
- n. Subjects who have started any form of physiotherapy, acupuncture, TENS, massage or active physical therapy within the 4 weeks preceding study entry. Such therapies can continue if they were started more than 4 weeks before the start of the study and if they continue at the same frequency of administration throughout the study. Any such therapies cannot be started during the study.

- o. Female subjects who are breast-feeding.
- p. Subjects known to have any of the following:
 - significantly abnormal renal or hepatic function;
 - any disease or condition that compromises the function of those body systems that could result in altered absorption, excess accumulation, or impaired metabolism or excretion of the test medications;
 - a life-threatening disease (e.g. AIDS, malignant disease, etc.) that would preclude completion of study or interfere with protocol compliance;
 - any condition that in the investigator's judgement precludes participation in the study.
- q. Subjects who have received an investigational drug or have used an investigational device in the 30 days preceding study entry.

II.2.J. Tools for assessing endpoints

Clinic assessments will be completed at four different time points during the 8 week study: Days 7, 14, 28 and 56 (± 1 day) and at a fifth time point if tapering-off is required. Subjects will be advised to contact the investigator or site staff should their pain not be controlled and therefore may require additional in-clinic visits. Telephone contacts will be made to subjects on Days 3, 6, and 9 to ensure adequate pain control is achieved through dose titration and that possible side-effects are managed appropriately.

For eligible subjects, the following items will be recorded: standard demographic data; full medical, surgical, and pain medication history; status of OA (including x-ray diagnostic of the diseased joint, ACR Functional Class, OA classification per ACR criteria); the nature, dosage and evaluation of the analgesic treatment of the past month. An x-ray diagnostic of OA taken within the last two years will be acceptable.

Physical examinations will be recorded at the beginning and end of the study. Vital signs will be taken at each visit. Height will be recorded at Visit 1. Weight will be recorded at Visit 1, 3, and 4. All adverse events will be recorded from the first study-related procedure to the last study-related procedure. A statement that the subject meets all eligibility criteria will be documented in the source notes by the Investigator.

The primary objective of this study is to determine the proportion of subjects who experience "moderate", "good", or "excellent" pain control during 56 days of treatment with DRUG X. Secondary analyses will include comparisons of the scores from the WOMAC Osteoarthritis Index questionnaire and SF-36 Acute Health Survey (see Appendix B) during 56 days of treatment with DRUG X compared to baseline. Physician and Subject Global Impression of Change scales (7-point scale, see Efficacy Evaluations section) will be done at the Final Visit.

Efficacy Evaluations

Efficacy of DRUG X to treat the signs and symptoms of moderate to severe pain due to OA of the hip or knee will be measured by:

Pain Control Assessment. Subjects will indicate the level of pain control at baseline and during the 14 day treatment period with DRUG X at each visit and at each telephone contact. The question should be asked at approximately the same time of day to ensure consistency. This consists of a five-point evaluation scale from excellent to very poor. For this assessment the subject will be asked: "Think about the pain in your _____ (study joint). Would you rate your pain control today as being: excellent, good, moderate, poor or very poor?"

Functional Status. Subjects will rate their pain, stiffness and physical function at baseline and each visit by means of the WOMAC Questionnaire (Western Ontario and McMaster University Osteoarthritis Index). A one-week recall period will be applied to all questions.

Quality of life. Subjects will complete a 36-item health survey used to evaluate the subject's physical, social, mental, and general well-being at baseline and each visit by means of the SF-36 Acute Health Survey (see Appendix B). A one-week recall period will be applied to all questions.

Subject/Physician Global Impression of Change. At the completion of the study (or at the early withdrawal visit) the subject and the investigator will answer the question: "Since the start of the study, my [the subject's] overall target joint status is?" - Very much improved, much improved, minimally improved, no change, minimally worse, much worse, very much worse.

Efficacy Criteria

The primary efficacy parameter of this study is the pain control of the target osteoarthritis hip or knee joint defined as a score of "excellent", "good", or "moderate" on the five-point scale: excellent, good, moderate, poor, and very poor. The proportion of subjects with pain control will be given per time point and at endpoint together with a 95% confidence interval. Outcomes are results from the WOMAC Osteoarthritis Index questionnaire, the SF-36 Health Survey and the Physician and Subject Global Impression of Change scores.

Safety Evaluations

All subjects will be considered for the safety evaluation. The incidence of all adverse events will be determined. Special attention will be given to those subjects who have discontinued the trial because of an adverse event, who experienced a severe or serious adverse event or who discontinued the trial due to lack of efficacy. Vital signs and the findings from physical examinations will be assessed.

The following will assess safety:

- a. Vital signs including sitting pulse and blood pressure (after a 5-minute rest), and respiratory rate will be measured at each visit.
- b. Weight will be recorded at Visit 1, 3, and 5 and height will be recorded at Visit 1 only.
- c. A complete medical history will be done at screening only and physical examinations will be done at screening and at Visit 4.
- d. Adverse events will be recorded from the time of the first study-related procedure to the time of the last study-related procedure.

II.2.L. Data analysis method

Efficacy Evaluations

Efficacy analyses will be carried out using the evaluable population. The evaluable population will consist of all subjects who have pain control information at Visit 2 (Week 2). In this case, missing values will be imputed using last observation carried forward (LOCF). Secondary analyses will also be carried out using the observed cases without imputation of missing values. Statistical tests will be carried out at the two-tailed 5% significance level unless specified otherwise.

The primary efficacy parameter will be the proportion of subjects on DRUG X achieving "excellent", "good" or "moderate" pain control compared to placebo on the 5 point scale: excellent, good, moderate, poor and very poor at Week 8 (Day 56). The results will be tabulated and plotted over time. Point estimates and 95% confidence intervals will be provided. A secondary analysis will be carried out using the observed cases.

Secondary analysis will be carried out using the evaluable population as well as the observed cases. Secondary responses include the WOMAC questionnaire, Acute SF-36 Health Survey Quality of Life questionnaire and Physician and Subject Global Impression of Change Scale. For the analyses using the evaluable population LOCF will be used to impute missing instrument scores. Tabulations will include

summary statistics such as the number of observed cases, the mean, standard deviation, minimum and maximum values.

WOMAC scores will be tabulated and plotted over time. Separate results will be tabulated for pain, stiffness, physical functioning and total scores. Significant differences between baseline and Week 8 will be assessed using the paired t-test. Acute SF-36 QoL scores will be tabulated and plotted over time. Significant differences between Baseline and Week 8 will be assessed using the paired t-test. Separate results will be tabulated for total score as well as for sub-scores for physical functioning, physical role limitation, emotional role limitation, social functioning, body pain, general mental health, vitality perception, and general health perception. Global Impression of Change scales provided by investigators and subjects will be tabulated.

Exploratory Analysis

The following tabulations and analysis will be presented as part of additional exploratory analyses.

- a. A tabulation of the average and final titration doses.
- b. A tabulation of the number of acetaminophen 500 mg tablets consumed per week.
- c. A tabulation of the Treatment Assessment Questionnaire scores provided by subjects.
- d. A comparison of the primary response between subjects taking NSAIDs and a weak opioid/acetaminophen combination and subjects taking only a weak opioid/acetaminophen combination prior to the study will be carried out using the exact Fisher test.

III. SUGGESTED READINGS

1. Altman R, Asch E, Bloch D, Bole G, Borenstein D, Brandt K, Christy W, Cooke TD, Greenwald R, Hochberg M, et al. Development of criteria for the classification and reporting of osteoarthritis. Classification of osteoarthritis of the knee. Diagnostic and Therapeutic Criteria Committee of the American Rheumatism Association. *Arthritis Rheum* 1986;29:1039-49.
2. Altman R, Alarcon G, Appelrouth D, Bloch D, Borenstein D, Brand T K, Brown C, Cooke TD, Daniel W, Feldman D, et al. The American College of Rheumatology criteria for the classification and reporting of osteoarthritis of the hip. *Arthritis Rheum* 1991;34:505-14.
3. 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* 1996;15:1833-40.
4. Badley EM, Rasooly J, Webster GK. Relative importance of musculoskeletal disorders as a cause of chronic health problems, disability, and health care utilisation: Findings from the 1990 Ontario Health Survey. *J Rheumatol* 1994;21:505-14.
5. Grammas DA, Lane NE. Osteoarthritis In: Treatment of the rheumatic diseases. Weismann MH, Weinblatt ME, editors, Saunders, Philadelphia. 1995;286-311.
6. Hochberg MC, Altman RD, Brandt KD, Clark BM, Dieppe PA, Griffin MR, Moskowitz RW, Schnitzer TJ. Guidelines for the Medical Management of Osteoarthritis: Osteoarthritis of the hip. *Arthritis Rheum* 1995;38:1535-40.
7. Hochberg MC, Altman RD, Brandt KD, Clark BM, Dieppe PA, Griffin MR, Moskowitz RW, Schnitzer TJ. Guidelines for the Medical Management of Osteoarthritis: Osteoarthritis of the knee. *Arthritis Rheum* 1995;38:1541-46.
8. Wolfe MM, Lichtenstein DR, Singh G. Gastrointestinal toxicity of nonsteroidal anti-inflammatory drugs. *N Engl J Med* 1999;340:1888-99.

**APPENDIX A. The American College of Rheumatology criteria
for the classification and reporting of osteoarthritis**

Classification Criteria for Osteoarthritis of the Hip

Traditional format

Hip pain plus at least two of the following:

- ESR of less than 20 mm per hour
- Femoral or acetabular osteophytes on radiographs
- Joint space narrowing on radiographs

Classification-tree format

Hip pain plus femoral or acetabular osteophytes on radiographs

or

hip pain plus joint space narrowing on radiographs and an ESR of less than 20 mm per hour

ESR= erythrocyte sedimentation rate

Adapted with permission from Altman R, Alarcon G, Appelrouth D, Bloch D, Borenstein D, Brandt K, et al. The American College of Rheumatology criteria for the classification and reporting of osteoarthritis of the hip. *Arthritis Rheum* 1991; 34:505-14

Classification Criteria for Idiopathic Osteoarthritis of the Knee

Traditional format

Knee pain plus osteophytes on radiographs and at least one of the following:

- Subject age older than 50 years
- Morning stiffness lasting 30 minutes or less
- Crepitus on motion

Classification-tree format

Knee pain and osteophytes on radiographs

or

knee pain plus subject age of 40 years or older, morning stiffness lasting 30 minutes or less and crepitus on motion.

ESR= erythrocyte sedimentation rate

Adapted with permission from Altman R, Asch E, Bloch D, Bole D, Borenstein K, Brandt K, et al. Development of criteria for the classification and reporting of osteoarthritis. Classification of osteoarthritis of the knee. *Arthritis Rheum* 1986; 29:1039-49.

APPENDIX B. Quality of Life (SF-36) Questionnaire

SF-36 ACUTE VERSION

INSTRUCTIONS: This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities.

Answer every question by marking the answer as indicated. If you are unsure about how to answer a question, please give the best answer you can.

1. In general, would you say your health is:

(circle one)

- Excellent 1
- Very good 2
- Good 3
- Fair 4
- Poor 5

2. Compared with one week ago, how would you rate your health in general now?

(circle one)

- Much better now than one week ago 1
- Somewhat better now than one week ago 2
- About the same as one week ago 3
- Somewhat worse now than one week ago 4
- Much worse now than one week ago 5

3. The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

(circle one number on each line)

ACTIVITIES	Yes, Limited A Lot	Yes, Limited A Little	No, Not Limited At All
a. Vigorous activities , such as running, lifting heavy objects, participating in strenuous sports	1	2	3
b. Moderate activities , such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	1	2	3
c. Lifting or carrying groceries	1	2	3
d. Climbing several flights of stairs	1	2	3

e. Climbing one flight of stairs	1	2	3
f. Bending, kneeling, or stooping	1	2	3
g. Walking more than a mile	1	2	3
h. Walking half a mile	1	2	3
i. Walking one hundred yards	1	2	3
j. Bathing or dressing yourself	1	2	3

4. During the past week, have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

(Circle one number on each line)

	YES	NO
a. Cut down on the amount of time you spent on work or other activities	1	2
b. Accomplished less than you would like	1	2
c. Were limited in the kind of work or other activities	1	2
d. Had difficulty performing the work or other activities (for example, it took extra effort)	1	2

5. During the past week, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

(circle one number on each line)

	YES	NO
a. Cut down on the amount of time you spent on work or other activities	1	2
b. Accomplished less than you would like	1	2
c. Didn't do work or other activities as carefully as usual	1	2

6. During the past week, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbours, or groups?

(circle one)

Not at all	1
Slightly	2
Moderately.....	3
Quite a bit	4
Extremely	5

7. How much bodily pain have you had during the past week?

(circle one)

- None1
- Very mild.....2
- Mild3
- Moderate.....4
- Severe5
- Very severe.....6

8. During the past week, how much did pain interfere with your normal work (including both work outside the home and housework)?

(circle one)

- Not at all1
- A little bit.....2
- Moderately.....3
- Quite a bit4
- Extremely5

9. These questions are about how you feel and how things have been with you during the past week. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past week:

(circle one number on each line)

	All of the Time	Most of the Time	A Good Bit of the Time	Some of the Time	A Little of the Time	None of the Time
a. Did you feel full of life?	1	2	3	4	5	6
b. Have you been a very nervous person?	1	2	3	4	5	6
c. Have you felt so down in the dumps that nothing could cheer you up?	1	2	3	4	5	6
d. Have you felt calm and peaceful?	1	2	3	4	5	6
e. Did you have a lot of energy?	1	2	3	4	5	6
f. Have you felt downhearted and low?	1	2	3	4	5	6
g. Did you feel worn out?	1	2	3	4	5	6
h. Have you been a happy person?	1	2	3	4	5	6
i. Did you feel tired?	1	2	3	4	5	6

10. During the past week, how much of the time have your physical health or emotional problems interfered with your social activities (like visiting friends, relatives, etc.)?

(Circle one)

- All of the time.....1
- Most of the time2
- Some of the time3
- A little of the time4
- None of the time.....5

11. How TRUE or FALSE is each of the following statements for you?

(circle one number on each line)

	Definitely True	Mostly True	Don't Know	Mostly False	Definitely False
a. I seem to get ill a little easier than other people	1	2	3	4	5
b. I am as healthy as anybody I know	1	2	3	4	5
c. I expect my health to get worse	1	2	3	4	5
d. My health is excellent	1	2	3	4	5

APPENDIX C. Patient Diary

1. Please record the number of tablets of EXTRA STRENGTH TYLENOL* you take each day for the pain in your _____ (study joint). It is best if you can complete this information at the end of each day so you don't forget to record any tablets you have taken.

Please complete an entry for each day even if you did not require any EXTRA STRENGTH TYLENOL* and write down "0" for those days where you did not take any.

Date DD-MON-YYYY	Number of tablets of Extra Strength Tylenol taken	Date DD-MMM-YYYY	Number of tablets of Extra Strength Tylenol taken
Extra days, if applicable		Extra days, if applicable	
Extra days, if applicable		Extra days, if applicable	

*Tylenol is a register trademark of McNeil-PPC, Inc.