Design of a randomized trial of a multidisciplinary intervention for knee osteoarthritis: Pharmacist Initiated Intervention Trial in Osteoarthritis (PhIT-OA)

Carlo A. Marra, BScPharm, PharmD, PhD, FCSHP; Ross T. Tsuyuki, BScPharm, PharmD, MSc, FCSHP, FACC; Judith A. Soon, BScPharm, PhD, FCHSP; Louise Gastonguay, RN, BSc, MSA; Bridgette Oteng, BSc; Jolanda Cibere, MD, PhD, FRCPC; Catherine McAuley, BSc (PT), MSc (Rehab); John M. Esdaile, MD, MPH, FRCPC; Margaret McGregor, MD, MHSc; Karim Khan, MD, PhD

Arthritis is the leading cause of disability in North America, with osteoarthritis (OA) the most prevalent disease within this classification.[1] In Canada, the economic impact of musculoskeletal disease is second only to cardiovascular disease.[2] It is estimated that, in the next 10 to 20 years, the prevalence of OA will increase by 50%, resulting in a large personal and societal burden.[3] Knee OA, in particular, is common and disabling. Evidence-based management of knee OA involves the use of both nonpharmacological and pharmacological approaches.[4-9] Recent studies, however, have shown gaps in identifying knee OA[10] and in delivering the appropriate interventions.[11]

In the Pharmacist Identification of New, Diagnostically confirmed OA (PhIND-OA) study, we demonstrated that pharmacists could identify people with previously undiagnosed knee OA.[12] A recent randomized controlled trial by Hay and colleagues indicated that enhanced pharmacist medication review was as effective as exercise in the short-term management of knee pain, and both were more effective than usual care.[13] A strategy, therefore, that uses pharmacists to identify those individuals in the community with knee OA in order to perform a medication review and to provide a referral to other health care practitioners (i.e., primary care physicians and physiotherapists) may prove effective in addressing the care gap for knee OA. We hypothesize that

Resources

- The Arthritis Foundation — **www.arthritis.org/disease-center.php?disease_id=32**
- The Arthritis Society — **www.arthritis.ca/types%20of%20arthritis/osteoarthritis/default.asp?s=1**
- EULAR Recommendations 2003: an evidence-based approach to the management of knee osteoarthritis: Report of a Task Force of the Standing Committee for International Clinical Studies Including Therapeutic Trials (ESCISIT). *Ann Rheum Dis* 2003;62:1145-55.
- National Institute of Arthritis and Musculoskeletal & Skin Diseases. Handout on Health: Osteoarthritis — **www.niams.nih.gov/Health_Info/Osteoarthritis/default.asp**

pharmacists could play a role in addressing these gaps in OA patient care.

Methods

Design: This study will use a cluster randomized controlled clinical trial design, with pharmacies randomized to provide the intervention or usual care. Methods are shown in Figure 1. Although participants and their health care providers cannot be blinded, the outcome assessors will be blinded to the intervention status of the subject.

Subjects: We will recruit, using posters and shelf-talkers, those with knee pain who visit participating community pharmacies in metropolitan Vancouver. The study will include participants with the following criteria: age >50 years, experiencing pain, aching, or stiffness in or around knee(s) on most days of the last month; and nonparticipation in a formal exercise program within the past 6 months. Likewise, those who have self-reported difficulty in at least 1 of the following activities attributed to knee pain will be included: lifting and carrying groceries, walking one-quarter mile, getting in and out of a chair, or going up and down stairs, as well as meeting other criteria, as shown in the Inclusion and Exclusion Criteria form in Appendix 1. Participants will be excluded if they have significant comorbid disease, if they are unable to visit the physiotherapist at the Arthritis Center, or if they had a previous knee surgery or a recent knee injury.

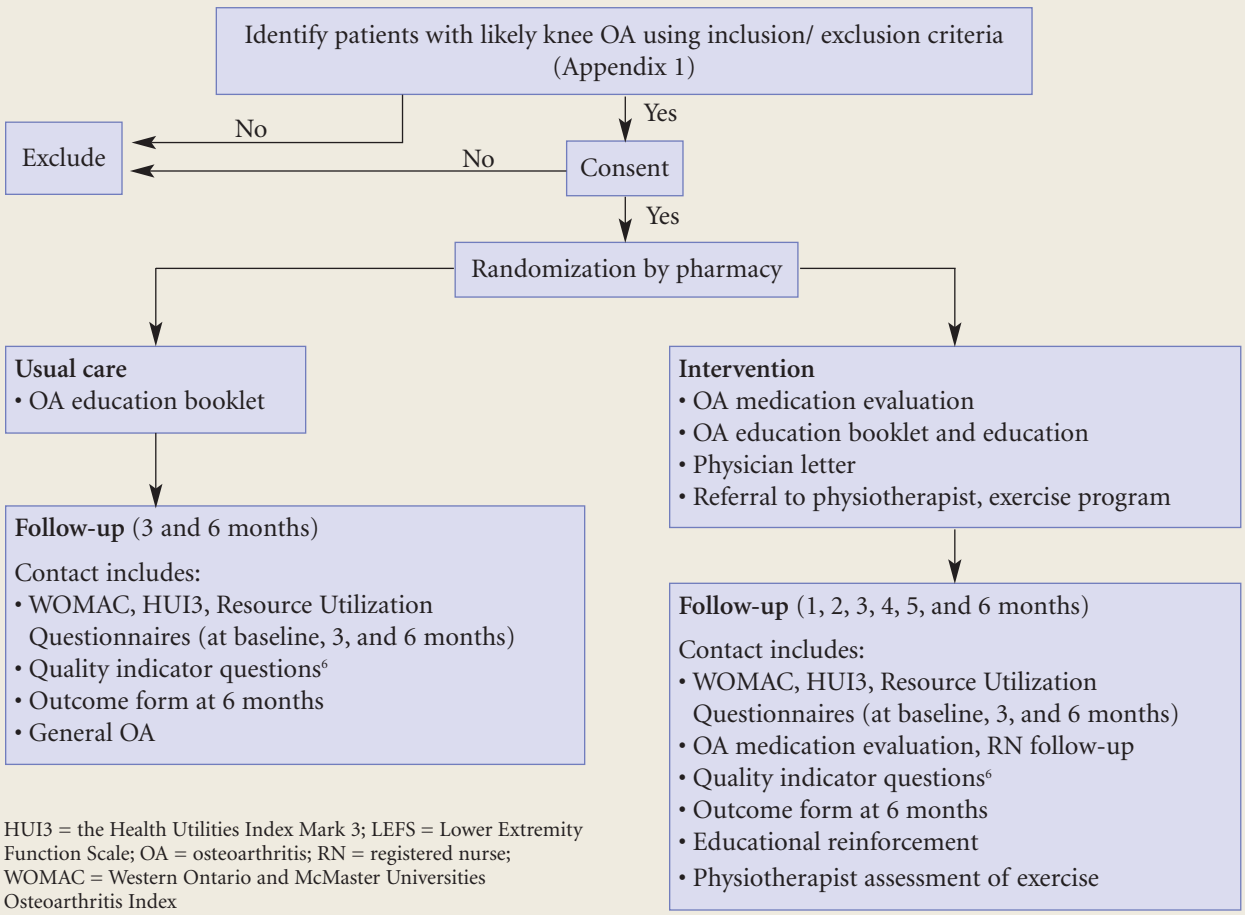
Procedures: Participants who have knee pain and are attending the participating community pharmacies will self-identify to the study pharmacists and will complete the screening questionnaire (Appendix 1). Participants with probable knee OA will be approached to participate. Once written consent is obtained, participants will be notified of their treatment-allocation status.

Knee OA management

Intervention group: Patients assigned to the intervention group will receive the following:

- Education, including counselling on the symp-

FIGURE 1 **Methods**



HUI3 = the Health Utilities Index Mark 3; LEFS = Lower Extremity Function Scale; OA = osteoarthritis; RN = registered nurse; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index

APPENDIX 1 Inclusion and exclusion criteria

Pharmacist-Initiated Intervention Trial in Osteoarthritis (PhIT-OA)

Date screened: _____/_____/_____
dd mm yyyy

Inclusion Criteria
(Exclude the participant if the answer to any of the following questions is "No")

Age >50 years	☐ Yes ☐ No
Pain, aching, or stiffness in or around the knee(s) on most days of the last month	☐ Yes ☐ No
Not actively participating in a formal exercise program within the past 6 months	☐ Yes ☐ No
Self-reported difficulty in at least 1 of the following activities attributed to knee pain: ☐ Lifting and carrying groceries ☐ Getting in and out of a chair ☐ Walking 3 blocks ☐ Going up and down stairs	☐ Yes ☐ No

Exclusion Criteria A
(Exclude the participant if the answer to any of the following questions is "Yes")

Prior total knee arthroplasty	☐ Yes ☐ No
Knee surgery within the previous 4 months	☐ Yes ☐ No
History of acute injury to knee within previous 6 months	☐ Yes ☐ No
Unable to speak and read English	☐ Yes ☐ No
Unwilling or unable to visit the physiotherapist at the regional arthritis treatment centre	☐ Yes ☐ No
Prior knee x-ray within the previous 2 years	☐ Yes ☐ No

Exclusion Criteria B
(Exclude the participant if the answer to any of the following questions is "Yes")

Previous physician-diagnosed arthritis (any form)	☐ Yes ☐ No ☐ Unsure
• Osteoarthritis	☐ Yes ☐ No ☐ Unsure
• Rheumatoid arthritis	☐ Yes ☐ No ☐ Unsure
• Psoriatic arthritis	☐ Yes ☐ No ☐ Unsure
Physician-diagnosed ankylosing spondylitis	☐ Yes ☐ No ☐ Unsure
Physician-diagnosed fibromyalgia (rheumatica)	☐ Yes ☐ No ☐ Unsure
Physician-diagnosed gout	☐ Yes ☐ No ☐ Unsure
A sudden, severely painful, hot, swollen big toe at any time in the past	☐ Yes ☐ No ☐ Unsure
A sudden, severely painful, hot, swollen joint at any time in the past (specify joint:_____)	☐ Yes ☐ No ☐ Unsure

Exclusion Criteria C
(Exclude the participant if the answer to any of the following questions is "Yes")

History of any of the following medications:	
Leflunomide (Arava)	☐ Yes ☐ No ☐ Unsure
Etanercept (Enbrel)	☐ Yes ☐ No ☐ Unsure
Anakinra (Kineret)	☐ Yes ☐ No ☐ Unsure
Sodium aurothiomalate (Myochrysine)	☐ Yes ☐ No ☐ Unsure
Chloroquine (Novo-Chloroquine, Plaquenil)	☐ Yes ☐ No ☐ Unsure
Infliximab (Remicade)	☐ Yes ☐ No ☐ Unsure
Methotrexate (Rheumatrex, Apo-methotrexate)	☐ Yes ☐ No ☐ Unsure
Auranofin (Ridaura)	☐ Yes ☐ No ☐ Unsure
Sulfasalazine (Salazopyrin, SAS-500, PMS-sulfasalazine)	☐ Yes ☐ No ☐ Unsure
Sodium aurothioglucose (Solganol)	☐ Yes ☐ No ☐ Unsure
Allopurinol (Zyloprim, Apo-Allopurinol, Novo-Purol, Alloprin)	☐ Yes ☐ No ☐ Unsure
Colchicine	☐ Yes ☐ No ☐ Unsure

If *Unsure,* pharmacist will check record if participant agrees.

toms and other aspects of knee OA. Patients will be provided with an opportunity to participate in the Arthritis Self-Management Program (ASMP).

- Medication management: The pharmacist will conduct a thorough review of the participants' prescription and over-the-counter analgesic use, in concordance with the current guidelines and indicators pertaining to pharmacologic therapy, and the criteria for acetaminophen, nonsteroidal anti-inflammatory drug (NSAID) and gastroprotective use and their contraindications.[4,6,13-15] To achieve maximum therapeutic benefit and safety, participants will also be counselled on risks, benefits, and appropriate use. (See Appendix 2 for identification of risk factors.)
- Communication with primary care physician: The study coordinator will fax a letter to the family physician, identifying the participant as having a high likelihood of knee OA, according to the pharmacist screening questionnaire and the list of evidence-based quality indicators for knee OA management (Appendix 1). In addition, the pharmacist will provide to the participant's family physician a recommendation on medications, as well as a form for referral to a physiotherapist at the Arthritis Centre.
- Physiotherapy guided exercise program: If the participant is referred, the physiotherapist will schedule a meeting to determine an appropriate, individualized home exercise program.

Usual care group: Participants who are randomized to usual care will receive an educational pamphlet on knee OA, developed by the Arthritis Society. At the end of the study period, participants in the usual care arm will be offered the services provided in the intervention arm.

Follow-up: For the intervention group, the pharmacist or study coordinator will follow up with a telephone call after 2 weeks to determine whether the patient has booked an appointment with the Arthritis Centre physiotherapist and to reinforce education. The intervention group patients will receive subsequent follow-up appointments or telephone calls with the pharmacist or study coordinator at monthly intervals for educational reinforcement and medication issues. Research staff, blinded to the outcomes, will conduct, by telephone, outcome assessments that involve the completion of scripted, predefined questionnaires at 3 and 6 months post-randomization.

For the usual care group, research staff, blinded to the outcomes, will perform outcome assessments at baseline and at 3 and 6 months.

Outcomes

The primary outcome measure will be the Arthritis Foundation Quality Indicators for the Management of OA.[6] Specifically, consistent with other investigators, we will calculate the summary scores of OA quality of care for each subject.[7] This indicates the percentage of indicators passed for a particular patient who may have been eligible for indications, ranging from 0 to 8. We will calculate the summary score as the total number of indicators passed, divided by the total number of indicators for which the patient was eligible. Summary scores will be compared across study groups.

Secondary outcomes will be a reduction in NSAID use, appropriate gastroprotective agent use, compliance with the exercise program and medications, pain control, functional status, and quality of life, as measured by the Western Ontario and McMaster Universities (WOMAC) Osteoarthritis Index,[16] Health Utilities Index Mark 3 (HUI Mark 3),[17] and the Lower Extremity Function Scale.[18] Adverse events will be monitored.

Ethics

This study has been approved by the University of British Columbia Clinical Research Ethics Board. We will obtain informed written consent from each patient. The study protocol was registered with **www.clinicaltrials.gov** to comply with international standards of trial reporting.

Statistical considerations

Sample size: For the primary outcome measure, a difference in the mean quality care score of 20 (with a standard deviation of 30) between the 2 study groups would be considered as clinically significant.[7] Thus, the required sample size for a 2-tailed alpha of 0.05 and 95% power would be 60 patients per arm. To account for loss to follow-up, 65 patients per treatment arm will be recruited. Based upon our experience with the PhIND-OA study, it would be feasible to screen potential candidates and recruit this number of participants within 6 months from 20 community pharmacies in the urban Vancouver area.

Data analysis: The Student's *t*-test will be used to analyze the primary outcome. To adjust for potential confounding factors, the repeated correlated nature of the results (multiple collections per patient), and the potential for missing values at various time points, we will use mixed models for repeated measures to analyze WOMAC scores over time. All analyses will be performed using intention to treat principles.

APPENDIX 2 Identification of risk factors

1. Risk for use of NSAIDs and COX-2 inhibitors ☐ No change since previous assessment

Yes	No	Risk factors for bleeding	Yes	No	Potential drug-related risk for bleeding
		Age >65 years			Anticoagulation therapy
		Prior perforated/bleeding upper GI ulcer			ASA (e.g., cardiovascular disease prevention)
					Corticosteroid therapy
		Serious systemic disease (e.g., coronary artery disease, diabetes mellitus, chronic obstructive pulmonary disease)			COX-2 selective inhibitors (celecoxib, meloxicam)
					NSAIDs (e.g., diclofenac, ibuprofen, indomethacin, naproxen, piroxicam, sulindac, tenoxicam, tiaprofenic acid)
					Nonprescription herbal products

ASA = acetylsalicylic acid; COX-2 inhibitors = cyclooxygenase-2 inhibitors; NSAID = nonsteroidal anti-inflammatory drug

2. Risk for use of NSAIDs due to potential fluid retention ☐ No change since previous assessment

Yes	No	Risk factors for fluid retention
		Congestive heart failure
		Hypertension (uncontrolled)
		Kidney disease

3. Risk for use of acetaminophen ☐ No change since previous assessment

Yes	No	Risk factors for liver dysfunction
		Alcohol intake per week ☐ None ☐ 1–3 ☐ 4–7 ☐ >7
		Liver disorder — please state:
		Nonprescription herbal products
If yes, suggest liver function test		

4. Risk for use of opioid products ☐ No change since previous assessment

Yes	No	Risk factor
		Opioid allergy
		Nonprescription herbal products

5. Gastroprotective drug use ☐ No change since previous assessment

Yes	No	Potential gastroprotective drug use
		Histamine$_2$-receptor antagonist (cimetidine, famotidine, nizatidine, ranitidine)
		Misoprostol
		Proton pump inhibitor (esomeprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole)

Current status of the study

We began recruiting for a pilot to ensure that the procedures are feasible and streamlined. Full recruitment for this study began in May 2007. ■

From the Collaboration for Outcomes Research and Evaluation, Faculty of Pharmaceutical Sciences (Marra, Soon, Gastonguay, Oteng) and the Department of Family Practice (Khan, McGregor), University of British Columbia, the Arthritis Research Centre of Canada (Cibere, Esdaile), the Centre for Clinical Epidemiology and Evaluation (McGregor), and the Mary Pack Arthritis Centre (McAuley), Vancouver, BC; and the EPICORE Centre (Tsuyuki), Faculty of Medicine and Dentistry, University of Alberta, Edmonton, Alberta. Contact Carlo.marra@ubc.ca.

Acknowledgements: *This study was funded by a pilot grant from the Canadian Institutes of Health Research/Canadian Arthritis Network New Emerging Team Grant (Tooling Up for Early Osteoarthritis) and by peer-reviewed operating grants from the Michael Smith Foundation for Health Research and the Canadian Arthritis Network. Dr. Marra is a Health Services Scholar, supported by the Michael Smith Foundation for Medical Research, and is a Government of Canada Research Chair in Pharmaceutical Outcomes. Dr. Cibere is supported by a JW McConnell Family Foundation Scholar Award and a CIHR Clinical Scientist Award. Dr. Tsuyuki is supported by the Merck Frosst/Aventis Chair in Patient Health Management at the University of Alberta. Dr. Khan is a New Investigator at the Canadian Institutes of Health Research.*

References

1. Hughes SL, Dunlop D. The prevalence and impact of arthritis in older persons. *Arthritis Care Res* 1995;8:257-64.

2. Lane R, Desjardins S, Population and Public Health Branch SPDPRD. Economic burden of illness in Canada. 1998 / Policy Research Division, Strategic Policy Directorate, Population and Public Health Branch. Ottawa (ON): Health Canada; 2002.

3. Centers for Disease Control and Prevention. Prevalence of disabilities and associated health conditions among adults — United States, 1999. *Morbidity and Mortality Weekly Reports* 2001;50:120-5.

4. Hochberg MC, Altman RD, Brandt KD, et al. Guidelines for the medical management of osteoarthritis. Part II: osteoarthritis of the knee. *Arthritis Rheum* 1995;38:1541-6.

5. Lane NE, Thompson JM. Management of osteoarthritis in the primary care setting: an evidence-based approach to treatment. *Am J Med* 1997;103:25-30S.

6. Pencharz JN, Maclean CH. Measuring quality in arthritis care: the Arthritis Foundation's quality indicator set for osteoarthritis. *Arthritis Rheum* 2004;51:538-48.

7. Ganz DA, Change JT, Roth CP, et al. Quality of osteoarthritis care for community-dwelling older adults. *Arthritis Rheum* 2006;55:241-7.

8. Maclean CH. Quality indicators for the management of osteoarthritis in vulnerable elders. *Ann Intern Med* 2001:135:711-21.

9. Porcheret M, Jordan K, Croft P. Treatment of knee pain in older adults in primary care: development of an evidence-based model of care. *Rheumatology* 2007;46:638-48.

10. Peat G, McCarney R, Croft P. Knee pain and osteoarthritis in older adults: a review of community burden and current use of primary health care. *Ann Rheum Dis* 2001;60:91-7.

11. Ganz DA, Chang JT, Roth CP, et al. Quality of osteoarthritis care for community-dwelling older adults. *Arthritis Rheum* 2006;55:241-7.

12. Marra CA, Cibere J, Tsuyuki RT, et al. Improving osteoarthritis detection in the community: pharmacist identification of new, diagnostically confirmed osteoarthritis. *Arthritis Rheum* 2007;57(7):1238-44.

13. Hay EM, Foster NE, Thomas E, et al. Effectiveness of community physiotherapy and enhanced pharmacy review for knee pain in people aged over 55 presenting to primary care: pragmatic randomised trial. *BMJ* doi:10.1136/bmj.38977.590752.0B.

14. Rahme E Choquette D, Beaulieu M, et al. Impact of a general practitioner educational intervention on osteoarthritis treatment in an elderly population. *Am J Med* 2005;118:1262-70.

15. Saag KG, Olivier JJ, Patino F, et al. Measuring quality in arthritis: the Arthritis Foundation's quality indicator set for analgesics. *Arthritis Rheum* 2004:51:337-49.

16. Bellamy N, Buchanan WW, Goldsmith CH, et al. 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.

17. Horsman J, Furlong W, Feeny D, Torrance G. The Health Utilities Index (HUI®): concepts, measurement properties and applications. *Health Qual Life Outcomes* 2003;16:54.

18. Binkley JM, Stratford PW, Lott SA, Riddle DL. The Lower Extremity Functional Scale (LEFS): scale development, measurement properties, and clinical application. North American Rehabilitation Research Network. *Phys Ther* 1999;79:371-83.