A COMPARISON BETWEEN A STANDARDIZED (GLA:DTM CANADA) AND AN INDIVIDUALIZED (JOINTEFFORT) EXERCISE PROGRAM ON FUNCTIONAL MOBILITY, QUALITY OF LIFE, PAIN MANAGEMENT, AND INFLAMMATORY BIOMARKERS IN KNEE OSTEOARTHRITIS PATIENTS

STUDY PROTOCOL AND STATISTICAL ANALYSIS PLAN

August 30, 2018

JL Whittaker

ENCORE CATALYST AWARD APPLICATION August 2018

PRINCIPAL INVESTIGATOR: Dr. Jackie L. Whittaker
CO-PRINCIPAL INVESTIGATORS: Kristen I. Barton, Dr. David A. Hart, Dr. Ania Kania-Richmond, Emma Smith, Dr. C. Ryan Martin, Dr. Prism S. Schneider, Dr. Deborah Marshall and Darren Mazzei

TITLE: A comparison between a standardized (GLA:D™ Canada) and an individualized (JointEffort) exercise program on functional mobility, quality of life, pain management, inflammatory biomarkers and willingness to pay in knee osteoarthritis patients.

BACKGROUND: Osteoarthritis (OA) is the leading cause of disability worldwide and affects more than 4.4 million people in Canada (13% of Canadians) [1]. OA symptoms include joint pain, stiffness, range of motion loss, and inflammation, resulting in a significant decrease in quality of life [2, 3]. Current evidence-based guidelines for OA management recommend weight loss, patient education, exercise therapy, bracing, viscosupplementation, and anti-inflammatory/pain medications prior to joint replacement surgery [4]. Unfortunately, current practice trends are not consistent with these guidelines and focus largely on joint replacement. Recently, research from a group in Denmark has shown a reduction in the progression of knee OA symptoms, joint related painkiller use, individuals on sick leave, and higher physical activity levels 12 months after a combined patient education and standardized group exercise therapy program (GLA:D®) [5-7]. Based on the Danish success, the GLA:D® program has been made available in Canada. To date it is unclear if the GLA:D™ Canada program will result in outcomes similar to those seen in Denmark, or how the GLA:D™ program compares to existing individualized OA care programs (i.e. JointEffort).

RESEARCH QUESTIONS:
1. Is the GLA:D™ standardized education and exercise program associated with improvements in functional mobility, quality of life, pain management, and inflammatory biomarkers in knee OA patients in Calgary, Alberta?
2. Is the JointEffort individualized exercise and education program associated with improved functional mobility, quality of life, pain management, and inflammatory biomarkers in knee OA patients in Calgary, Alberta?
3. Do the improvements in functional mobility, quality of life, pain management, and inflammatory biomarkers in knee OA patients differ between those enrolled in the GLA:D™ and the JointEffort education and exercise programs?
4. How does the cost of the programs compare to health outcomes and how much are participants willing to pay to participate in the GLA:D and JointEffort programs?

OBJECTIVES: The objectives of the proposed study are to 1) assess the association between participation in the GLA:D™ standardized program and functional mobility, quality of life, pain management, and inflammatory biomarkers in knee OA patients, 2) assess the association between participation in the JointEffort individualized program and functional mobility, quality of life, pain management, and inflammatory biomarkers in knee OA patients 3) assess if there are any differences in outcomes between the standardized (GLA:D™) and individualized (JointEffort) exercise programs, and 4) Assess how the cost of the programs compare to health outcomes and how much patients are willing to pay to participate in the GLA:D and JointEffort programs.

METHODOLOGY:
Study Participants: A convenience sample of 100 participants ≥50 years of age with a primary care physician or orthopedic surgeon knee OA diagnosis will be included in the study. Specifically, 50 individuals will participate in 1) the GLA:D™ program and 50 sex- and age-matched individuals will participate in 2) the JointEffort program. 100 participants is a conservative estimate based on the ability to detect a moderate effect between study groups ($1-\beta=0.8$, $\alpha=0.05$).
Exercise Programs: The GLA:D™ program consists of 1) pre and post program outcome measurement (self-reported and functional outcomes); 2) 2 1-1.5 hour education sessions including information on OA disease characteristics, treatments and self-help strategies; and 3) a neuromuscular exercise (warm-up,

circuit training, and cool down) training program administered in 1 hour, small (up to 10 persons) group-based, supervised sessions twice weekly for 6 weeks. The goal of the exercises is to restore neutral, functional alignment of the legs by building compensatory functional stability and improving sensorimotor control. The JointEffort program consists of: 1) one appointment aimed at individualized program design; 2) a nutritional seminar taught by a registered dietician explaining dietary recommendations for OA patients and inflammatory conditions, including weight loss and/or management; and 3) an individualized exercise (strength and neuromuscular training, balance training, and range of motion exercises) training program administered in 1 hour, small (up to 10 persons) group-based, supervised sessions twice weekly for 6 weeks.

Study Outcomes:

1) Participant Characteristics, Adherence, and Medication Use: Demographic (age, sex, height, weight, and body mass index), comorbidity, attendance, exercise log, and medication use details will be recorded at each visit. Adherence will be measured by exercise program attendance (number of sessions).

2) Self-Reported of Symptoms, Function, Quality of Life, and Cost Questionnaire: The following self-report questionnaires will be completed at baseline, 2, and 12 months: the Knee Injury and Osteoarthritis Outcome Score (KOOS) [8], the Intermittent and Constant Osteoarthritis Pain (ICOAP) Score [9], and the EuroQOL-5 Dimensions (EQ-5D-5L) Score [10]. A cost questionnaire will be used to capture information about your employment status, gross income, insurance coverage, willingness to pay, and health care visit.

3) Disease Knowledge and Arthritis-Related Self-Efficacy*:* The patient knowledge questionnaire on OA (PKQ-OA) [11] and the arthritis self-efficacy questionnaire [12] will be completed at baseline, 2, and 12 months.

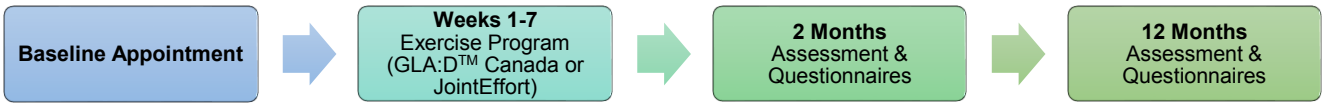
4) Physical Function: All participants will complete the 40m Face-Paced Walk Test and the 30s Chair Stand Test [13] at baseline, 2, and 12 months.

5) Biomarker Analysis: A blood serum sample, collected at baseline, 2, and 12 months will be analyzed to assess for inflammatory biomarkers using a Discovery Assay (42 Custom-Plex human assay) with Luminex®xMAP technology (Eve Technologies).

STATISTICAL ANALYSIS: Descriptive statistics (mean (95% CI), proportion (95% CI) or median (range) will be used report the baseline, 2, and 12 month change in self-report, functional and biomarker outcomes, as appropriate. To account for the matched design, mean within-pair difference (95% CI) will be used to compare treatment groups across outcomes. Finally, conditional logistic regression will be used to assess the relationship between attendance (number of sessions) and 12 month change in each outcome.

SIGNIFICANCE: This project will contribute to the understanding of exercise programming prescription for knee OA patients. If GLA:D™ and/or JointEffort support improvements in functional mobility, quality of life, pain management, and inflammatory biomarkers, it could play a role in the implementation strategy for OA patients within the province. Exercise programming has the potential to be implemented in several sites across Alberta, and thus potentially modifying disease progression and possibly delaying total joint replacement.

PROJECT FLOWCHART:



TIME POINT	GLA:D™ Canada Group (Standardized Exercise Program)	JointEffort Group (Individualized Exercise Program)
Baseline Appointment	1) The GLA:D™ Canada program will be explained. 2) Participants will be asked to complete the questionnaires (KOOS, EQ-5D-5L, ICOAP, PKQ-OA,the arthritis self-efficacy questionnaire and the Arthritis Cost Questionnaire Baseline). 3) Demographics, symptoms, comorbidities, and medication use will be recorded. 4) Blood draw for biomarker analysis. 5) Participants will be asked to complete physical function tests (40m Face-Paced Walk Test and the 30s Chair Stand Test).	1) The JointEffort program will be explained. 2) Participants will be asked to complete the questionnaires (KOOS, EQ-5D-5L, ICOAP, PKQ-OA, the arthritis self-efficacy questionnaire and the Arthritis Cost Questionnaire Baseline). 3) Demographics, symptoms, comorbidities, and medication use will be recorded. 4) Blood draw for biomarker analysis. 5) Participants will be asked to complete physical function tests (40m Face-Paced Walk Test and the 30s Chair Stand Test). 6) Individualized program design.
Weeks 1-7	1) Two education sessions about OA (1-1.5 hours each), including the degeneration process in the joint, how the GLA:D™ Canada exercises improve joint stability, and how to retain joint stability through day to day self-management techniques. 2) Standardized neuromuscular training sessions twice a week for 6 weeks (60 minutes per session).	1) One nutritional seminar taught by a registered dietician explaining dietary recommendations for OA patients and patients with inflammatory conditions, and weight loss and/or weight management. 2) Individualized strength and neuromuscular training sessions twice a week for 6 weeks (60 minutes per session).
2 Months	1) Participants will be asked to complete the questionnaires (KOOS, EQ-5D-5L, ICOAP, PKQ-OA, the arthritis self-efficacy questionnaire and the Arthritis Cost Questionnaire 2-month follow up). 2) Symptoms and medication use will be recorded. 3) Blood draw for biomarker analysis. 4) Participants will be asked to complete physical function tests (40m Face-Paced Walk Test and the 30s Chair Stand Test).	1) Participants will be asked to complete the questionnaires (KOOS, EQ-5D-5L, ICOAP, PKQ-OA, the arthritis self-efficacy questionnaire and the Arthritis Cost Questionnaire 2-month follow up). 2) Symptoms and medication use will be recorded. 3) Blood draw for biomarker analysis. 4) Participants will be asked to complete physical function tests (40m Face-Paced Walk Test and the 30s Chair Stand Test).
12 Months	1) Participants will be asked to complete the questionnaires (KOOS, EQ-5D-5L, ICOAP, PKQ-OA, and the arthritis self-efficacy questionnaire). 2) Symptoms and medication use will be recorded. 3) Blood draw for biomarker analysis. 4) Participants will be asked to complete physical function tests (40m Face-Paced Walk Test and the 30s Chair Stand Test).	1) Participants will be asked to complete the questionnaires (KOOS, EQ-5D-5L, ICOAP, PKQ-OA, and the arthritis self-efficacy questionnaire). 2) Symptoms and medication use will be recorded. 3) Blood draw for biomarker analysis. 4) Participants will be asked to complete physical function tests (40m Face-Paced Walk Test and the 30s Chair Stand Test).

BUDGET:

1. Personnel: Dr. Jackie Whittaker (University of Alberta salaried time); Kristen Barton (AIHS MD/PhD Scientist-Clinician Award); Dr. David Hart (University of Calgary salaried time); Dr. Ania Kania-Richmond (AHS salaried time); Emma Smith (University of Calgary Active Living salaried time); Dr. C. Ryan Martin (AHS salaried time); and Dr. Prism Schneider (AHS salaried time). ***Personnel Total: $0.***

2. Program Instructors: GLA:D™ *Canada Exercise Program (based on one class for 10 participants):* GLA:D™ Canada Certified Instructors (physiotherapists or certified exercise physiologists): 5 x 1 hour baseline appointment @ $75/hour = **$375.00***;* 2 x 1.5 hour group osteoarthritis education sessions @ $75/hour = **$225.00***;* 12 x 1 hour exercise sessions @ $75/hour = **$900.00***;* 2 x 1 hour follow up testing sessions at 2 months @ $75/hour = **$150.00***;* 2 x 1 hour follow up testing sessions at 12 months @ $75/hour = **$150.00**. **Total to run 1 GLA:D™ Canada class = $1,800.00 (i.e. $360.00/person)**. **Run 5 GLA:D™ Canada classes (aim of n=10 participants per class; n=50) = $9,000.00.**
JointEffort Exercise Program (based on one class for 10 participants): JointEffort Instructors (certified exercise physiologists or certified personal trainers): 5 x 1.5 hour baseline appointment and program design @ $45/hour = **$337.50**; 1 x 1 hour group nutritional seminar @ $75/hour = **$75.00**; 11 x 1 hour exercise sessions @ $45/hour = **$495.00**; 2 x 1 hour follow up testing sessions at 2 months @ $45/hour = **$90.00**; 2 x 1 hour follow up testing sessions at 12 months @ $45/hour = **$90.00**. **Total to run 1 JointEffort class = $1,087.50 (i.e. $199.50/person)**. **Run 5 JointEffort classes (aim of n=10 participants per class; n=50) = $5,437.50.**
Program Instructors Total (5 JointEffort and 5 GLA:D™ classes, n=100): $14,437.50.

3. Instructor Training: GLA:D™ Canada Training: 2 instructors x $450 = **$900.00**; JointEffort Training: 5 instructors
x 1 hour (testing protocols) @ $45/hour = **$225.00**. ***Instructor Training Total: $1,125.00.***

4. Equipment and Facilities: *Equipment:* Physio Balls: 10 @ $30/unit (55cm ball) = **$300.00**; 5 @ $35/unit (65cm ball) = **$175.00***;* 15 Mats (2.5' thick): 15 @ $40/unit = **$600.00***;* Glider Discs: 10 @ $30/unit = **$300.00***;* Yoga Foam blocks: 8 @ $20/unit = **$160.00***;* Air Ex Pads: 4 @ $80/unit **= $320.00***;* Slastix Tubing: light x 4 @ $20/unit = **$80.00**, medium x 5 @ $22/unit = **$110.00**, heavy 3 @ $24/unit = **$72.00**, X heavy 1 @ $25/unit = **$25.00**; Aerobic Steps and Risers: 5 @ $80.00/unit = **$400.00**. *Facilities:* University of Calgary Active Living studio rental space to run the GLA:D™ Canada Exercise Program: 12 exercise sessions x 1 hour @ $80/hour = $960 x 5 classes = **$4,800.00***;* University of Calgary Active Living (Fitness Centre) gym space to conduct GLA:D™ Canada baseline, 2 month, and 12 month functional tests: 3 testing dates x 2 hours @ $60/hour = $360 x 5 classes = **$1,800.00***;* University of Calgary Active Living gym space to run the JointEffort Exercise Program: 11 exercise sessions x 1 hour @ $60/hour = $660 x 5 classes = **$3,300.00***;* University of Calgary Active Living (Fitness Centre) gym space to conduct JointEffort baseline, 2 month, and 12 month functional tests: 3 testing dates x 2 hours @ $60/hour = $360 x 5 classes = **$1,800.00**. ***Equipment In-kind contribution from Active Living (University of Calgary): $11,700.00***. ***Equipment and Facilities Total: $2,542.00.***

5. General Materials and Supplies: Administration, registration (with IT assistance), and advertising: **$2,000**. Paper, printing, photocopying, telephones: **$800**. ***General Materials and Supplies Total: $2,800.00.***

6. Biomarker Service (Eve Technologies): Custom-Plex Kit human assay and assay service = **$6,917.00**. ***Biomarker Service Total: $6,917.00.***

7. Other: Parking passes for the first appointment: $7/single entry parking ticket x 100 participants = **$700.00**; Parking passes for follow up testing session at 2 months: $7/single entry parking ticket x 100 participants = **$700.00**; Parking passes for follow up testing session at 12 months: $7/single entry parking ticket x 100 participants = **$700.00**. ***Other Total: $2,100.00.***

TOTAL COST OF PROJECT: $29,921.50
TOTAL IN KIND CONTRIBUTIONS: $11,700.00 (+ personnel in-kind contributions for project from salaries)

TOTAL FUNDS REQUESTED: $30,000.00

DESCRIBE THE TEAM:
Dr. Jackie Whittaker (primary applicant) is an Assistant Professor in Rehabilitation Medicine (Physical Therapy) at the University of Alberta, an Adjunct Professor in the Faculty of Kinesiology at the University of Calgary, and a full member of the McCaig Institute. Her expertise is in secondary prevention of injuries and in the rehabilitation of musculoskeletal conditions. She will lead the project and oversee the coordination of the exercise intervention programs. Kristen Barton (co-applicant) is a MD/PhD student in the Cumming School of Medicine. Kristen is a GLA:D™ Canada Certified Instructor and a Canadian Society for Exercise Physiology Certified Exercise Physiologist. Kristen currently works with the JointEffort program and will coordinate the research evaluation of the exercise programs. She will set up and lead the GLA:D™ Canada exercise program at the University of Calgary Active Living site, facilitate data collection and analysis, and run the group osteoarthritis education sessions. Dr. David Hart (co-applicant) is a Professor at the Cumming School of Medicine (Department of Surgery), full member of the McCaig Institute, and the Alberta Bone and Joint Health Strategic Clinical Network Scientific Director. Dr. Hart's research program is focused on determining inflammatory responses from joint injury and diseases. Further, he has studied novel biomarkers in musculoskeletal conditions, thus will provide expertise regarding biomarker analysis, study implementation, and study interpretation. Dr. Ania Kania-Richmond (co-applicant) is an assistant professor at the Cumming School of Medicine (Community Health Sciences) and the Alberta Bone and Joint Health Strategic Clinical Network Assistant Scientific Director. She will provide expertise in study implementation and program evaluation. Emma Smith (co-applicant) is the University of Calgary Active Living JointEffort Program Coordinator and a Canadian Society for Exercise Physiology Certified Exercise Physiologist. Emma will lead the organization and facilitation of the exercise programs, specifically focusing on program administration and data collection. Dr. C. Ryan Martin and Dr. Prism Schneider (co-applicants; associate and full members of the McCaig Institute, respectively) are orthopedic surgeons at the Foothills Medical Centre. As scientist-clinicians, Dr. Martin and Dr. Schneider will provide clinical expertise, and feedback regarding study design, study implementation, and patient recruitment. Dr. Deborah Marshal is a Professor in the Department of Community Health Sciences at the University of Calgary as well as holds the Canada Research Chair in health system research and the Arthur J.E. Child Chair of Rheumatology Outcomes Research chair. Dr. Marshall is a health economist and will lead the economic evaluation. Darren Mazzei is a physiotherapist and PhD student in the Department of Community Health Sciences. Darren will assist with data collection and analysis of both exercise programs.

RELEVANCE AND POTENTIAL BENEFIT OF YOUR PROJECT TO BONE AND JOINT HEALTH:
Our long-term objective is to optimize non-operative management and improve the quality of life of individuals with knee OA. The majority of patients with knee OA that are referred to orthopedic surgeons (up to 50-75% from Alberta orthopedic surgeons), do not require total joint arthroplasty at that time or are not appropriate surgical candidates due to the degree of OA seen on plain films (i.e. mild-moderate instead of severe), level of severity of functional disability or dysfunction, or co-morbidities, that prevent suitability or readiness for total joint arthroplasty. Therefore, we need to identify those individuals and optimize their non-operative management, with an emphasis on exercise programming to mediate their OA symptoms. Further, we believe that through neuromuscular exercise programming (in both a group or individualized setting), we can prolong the development of OA symptoms and therefore possibly delay and/or prevent the need for total joint arthroplasty surgery. However, current exercise program incur additional costs to the patient. The patients' willingness to pay for neuromuscular exercise programming will differ based on their income level, out-of-pocket cost and expected benefit. Collecting information on these factors will help decision-makers choose whether a public, partial subsidy or private funding model will best help patients manage their osteoarthritis.

We propose to do this by evaluating the effectiveness of the GLA:D™ Canada standardized exercise program in Alberta and evaluating the currently implemented JointEffort individualized exercise program. Further to this, we will assess differences between functional mobility, quality of life, pain management, and inflammatory biomarkers for knee OA. The main differences between the programs include the following: 1) the mode of delivery (standardized vs. individualized program), 2) the two education sessions about OA (GLA:D™), and 3) the nutritional seminar taught by a registered dietician explaining dietary recommendations for OA patients and inflammatory conditions (JointEffort). Evaluating these key components will enable us to determine appropriate exercise prescription management strategies for

individuals with knee OA. If GLA:D™ and/or JointEffort support improvements in functional mobility, quality of life, and pain management, it could play a role in the implementation strategy for OA patients within the province.

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