Clinical Trial

Comparing Strategies Targeting Osteoporosis to Prevent Fractures after an Upper Extremity Fracture (C-STOP Trial): A Randomized Controlled Trial†

Sumit R Majumdar (deceased), MD, MPH, Professor, Department of Medicine, University of Alberta, Edmonton, Alberta Canada, T6G 2G3

Finlay A McAlister, MD, MSc, Professor, Department of Medicine, University of Alberta, Edmonton, Alberta Canada, T6G 2G3

Jeffrey A Johnson, PhD, Professor, School of Public Health, University of Alberta, Edmonton, Alberta Canada, T6G 2G3

Brian H Rowe, MD, MSc, Professor, Department of Emergency Medicine, University of Alberta, Edmonton, Alberta Canada, T6G 2G3

Debbie Bellerose, RN, BScN, Department of Medicine, University of Alberta, Edmonton, Alberta Canada, T6G 2G3

Imran Hassan, MSc, Biostatistician, EPICORE Centre, Department of Medicine, University of Alberta, Edmonton, Alberta Canada, T6G 2G3

Douglas A Lier, Health Economist, Department of Medicine, University of Alberta, Edmonton, Alberta Canada, T6G 2G3

Stephanie Li, MD Assistant Clinical Professor, Department of Medicine, University of Alberta, Edmonton, Alberta Canada, T6G 2G3

Walter P Maksymowych, MB ChB, Professor, Department of Medicine, University of Alberta, Edmonton, Alberta Canada, T6G 2G3

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Matthew Menon, MD, MHSc, Associate Professor, Department of Surgery, University of Alberta, Edmonton, Alberta Canada, T6G 2G3

Anthony S Russell, MD, Professor, Department of Medicine, University of Alberta, Edmonton, Alberta, Canada, T6G 2G3

Brian Wirzba, MD, Clinical Professor, Department of Medicine, University of Alberta, Edmonton, Alberta Canada, T6G 2G3,

***Lauren A Beaupre,** PT, PhD, Professor, Department of Physical Therapy, University of Alberta, Edmonton, Alberta Canada, T6G 2G4; PH: 780-492-8626; EMAIL: lauren.beaupre@ualberta.ca

*** CORRESPONDING AUTHOR**

Abstract

We compared osteoporosis care after upper extremity fragility fracture using a low-intensity Fracture Liaison Service (FLS) versus a high-intensity FLS in a pragmatic patient-level parallel-arm comparative effectiveness trial undertaken at a Canadian academic hospital. A low-intensity FLS (active-control) that '*identified'* patients and notified primary care providers was compared to a high-intensity FLS (case manager) where a specially-trained nurse '*identified'* patients, '*investigated'* bone health and '*initiated'* appropriate treatment. 361 community-dwelling participants 50 years or older with upper extremity fractures who were not on bisphosphonate treatment were included; 350 (97%) participants completed 6-month follow-up undertaken by assessors blinded to group allocation. The primary outcome was difference in bisphosphonate treatment between groups 6-months post-fracture; secondary outcomes included differences in bone mineral density (BMD) testing and a pre-defined composite measure termed "appropriate care" (taking or making an informed decision to decline medication for those with low BMD; not taking bisphosphonate treatment for those with normal BMD). Absolute differences (%), relative risks (RR with 95% confidence intervals [CI]), number-needed-to-treat (NNT) and direct costs were compared. 181 participants were randomized to active-control and 180 to case-manager using computer-generated randomization; the groups were similar on study entry. At 6 months, 51 (28%) active-control vs 86 (48%) case-manager participants started bisphosphonate treatment (20% absolute difference; RR 1.70 [95%CI 1.28-2.24]; p<0.0001; NNT=5). Of active-controls, 108 (62%) underwent BMD testing compared to 128 (73%) case-managed patients (11% absolute difference; RR 1.17 [95%CI 1.01-1.36]; p=0.03). Appropriate care was received by 76 (44%) active-controls and 133 (76%) case-managed participants (32% absolute difference; RR 1.73, [95%CI 1.43-2.09]; p<0.0001). The direct cost per participant was $18 Canadian (CDN) for the active-control intervention compared to $66 CDN for the case-manager intervention. In summary, case-management led to substantially greater improvements in bisphosphonate treatment and appropriate care within 6-months of fracture than the active control. This article is protected by copyright. All rights reserved

Trial Registration: ClinicalTrials.gov: NCT01401556

Key Words: Osteoporosis, Clinical Trials, Injury/Fracture Healing, Fracture Prevention, Aging

INTRODUCTION

Osteoporosis is common in people older than 50 years of age with at least 25% of women and 12% of men affected;(1-4) its silent onset is generally not recognized until a "fragility" fracture occurs, often of the upper extremity (i.e., fractures of the distal radius and ulna or proximal humerus). Once an initial fracture has occurred, the risk for additional fracture increases markedly,(5;6) and these recurrent fractures are associated with substantial morbidity and increased mortality.(7-9) The health care costs associated with osteoporosis-related fractures are considerable;(3) the USA had more than two million osteoporosis-related fractures in 2005 with estimated costs of $17 billion dollars. By 2025, it is estimated that the number of fractures will surpass three million at an estimated cost of $25.3 billion dollars.

Secondary prevention programs such as Fracture Liaison Services (FLS) have been shown to be both clinically effective and cost-effective in preventing future fractures;(10-14) however they have not gained widespread acceptance, perhaps because they are perceived as high resource interventions. FLS can vary from low intensity interventions that '*identify'* patients and notify primary care providers (denoted as "1i FLS"), through to high intensity interventions using a case-management approach where a specially-trained allied health professional '*identifies'* patients, '*investigates'* bone health and then '*initiates'* appropriate treatment (denoted as "3i FLS"). Even 1i FLS can have useful impact compared to usual care within 6-months of fracture, although a substantial majority of patients remain untreated.(10;15;16) The 3i FLS have been more commonly used in hip fractures,(10;11) although limited data suggests that this higher intensity approach may improve care for less harmful and less expensive but still serious non-hip fractures.(13;17)

Therefore, our goal was to test how to increase the proportion of appropriate bisphosphonate treatment in patients with osteoporosis-related upper extremity fragility fractures of the distal radius and/or ulna or proximal humerus. We undertook an active comparator randomized controlled trial (RCT) comparing a proven low intensity multifaceted intervention (1i+ FLS) (16) to a higher intensity nurse case manager approach (3i FLS). We compared osteoporosis care between these groups with the primary outcome the difference in the proportion of those receiving bisphosphonate treatment 6-months post fracture in each group. Pre-specified secondary outcomes were examining differences between groups in BMD testing and a predefined composite measure termed "appropriate care."

MATERIALS and METHODS

Setting and Subjects: The Edmonton Health Zone (Edmonton, AB, Canada) serves 1.5 million residents who have universal healthcare coverage with free and uniform access to bi-annual BMD testing. Participants for this trial were recruited from the Emergency Department or Fracture Clinic of a large tertiary academic hospital (n=885 beds). Inclusion criteria were community-dwelling patients 50 years or older with an upper extremity (distal radius and/or ulna, or proximal humerus) fracture. Patients were excluded if they were already receiving bisphosphonate therapy, sustained a pathological (e.g., Paget's disease or tumor/metastatic) or multiple (e.g., major trauma) fractures, lived outside of the metropolitan health zone at time of fracture, were unable to understand or converse in English, or were unable to provide written informed consent.

Study Design: This was a pragmatic patient-level parallel-arm comparative effectiveness trial comparing a low intensity multi-faceted (hereafter "active control") intervention (16) to a nurse-

led case manager (hereafter "case manager"). We chose to use an active control group on clinical and ethical grounds as we had previously demonstrated that this low intensity multifaceted intervention improved treatment relative to usual care, but still left approximately 70% of patients untreated for osteoporosis at one year after fracture.(16) The current trial received ethics approval from the University of Alberta (PRO00018520) and was registered at ClinicalTrials.gov (NCT01401556). After agreeing to participate and providing written informed consent, participants were randomized via computer-generated randomization at a 1:1 group allocation with variable block size. Research nurses collected outcomes without knowledge of allocation status and investigators were blinded to both allocation status and outcomes.

Sample Size: Based on our pilot study,(13) we assumed post-fracture bisphosphonate treatment proportions of 22% for the active control and 43% for the case manager group for our sample size calculation. Using standard calculations with the patient as the unit of analysis, 2-tailed alpha=0.05, beta=0.8 and effect size=20% (43% vs 22% in the original pilot study), with attrition rates of 20%, we calculated that a minimum of 100 participants were required in each study arm (n=200). To ensure pilot study-related effect sizes were not under-estimated, allow for secondary analyses, and examine exploratory outcomes, we inflated the total sample size to 180 participants per study arm (n=360), which was also adequate to detect clinically important differences in patient-reported health related quality of life (HRQL) outcomes.

Protocol for Active Control: A detailed explanation of the active control intervention has been previously published.(16) In brief, at 2-4 weeks post-fracture, participants received a short (~10-15 minutes) phone call from the research nurse regarding osteoporosis and its potential relationship with their recent fracture. The nurse encouraged the participants to follow-up with

their family physician. In addition, family physicians received a patient-specific fax that notified them that their patient had recently sustained an upper extremity fracture that may indicate risk for osteoporosis. The family physicians were also sent evidence-based treatment guidelines that were endorsed and signed by five peer-nominated local opinion leaders and contained an actionable summary of osteoporosis treatment guidelines.

Protocol for Nurse Case Manager: Similar to our previous trial of osteoporosis case management for hip fracture(11) and our pilot work in wrist (distal radius or ulna) fracture,(13) a specially trained and experienced registered nurse undertook the case manager role. She contacted participants to see them in clinic where she educated and counselled them about the association between fractures and osteoporosis, and the need for BMD testing and recurrent fracture prevention. She then arranged and interpreted BMD tests and undertook standardized laboratory tests. If participants had undergone BMD testing within two years before sustaining their fracture, the previous result was used to direct current treatment as the health care system only covers BMD testing on a bi-annual basis. For those with normal bone mass, no further investigations or treatments were offered. For those who had low bone mass, she considered suitability for bisphosphonate treatment (i.e., no severe esophagitis, not lacking capacity to follow medication instructions, no renal failure or allergies to bisphosphonates precluding treatment). She counseled those who were eligible for bisphosphonate treatment about potential benefits, common side effects and potential harms. For those who were eligible and accepted treatment, she initiated prescription treatment guided by a physician-approved protocol, typically 70mg of generic alendronate or 35mg of generic residronate weekly for 1 year. Referrals to an osteoporosis specialist were provided for those not suitable for bisphosphonate therapy or who requested a consult; participants who received medications other than bisphosphonates were

considered untreated in the primary outcome, but considered treated under the appropriate care outcome. While the case manager only undertook one pre-specified in-person visit as per study protocol, she did undertake telephone follow-up if indicated for osteoporosis management. All test results and treatment plans were communicated to the family physician via fax.

Main (Primary) Outcome: The pre-specified primary outcome was initiating bisphosphonate treatment within 6-months of fragility fracture; because this was an active control comparator trial, and based on previous work, the study team considered at least a 20% absolute difference in treatment rates to be clinically meaningful.(13) This outcome was determined by patient self-report and confirmed through pharmacy dispensing records that were available for all participants in both groups via a provincial database.

Secondary Outcomes: We also assessed whether a BMD test and a composite measure that we named "appropriate care" were completed within 6-months of fracture. BMD test results were available through the electronic medical record for most participants who underwent BMD testing, but occasionally the test was confirmed to have happened, but test results were not available electronically. Only BMD tests ordered after the fracture were considered in this secondary outcome. Appropriate care was defined as undergoing a BMD test (either within 24-months prior to fracture or within 6-months after fracture) and (1) receiving bisphosphonates or other bone health medication if bone mass was low (i.e. a T-score -1.0 or lower at any skeletal site) or (2) refusing bisphosphonate treatment when it was offered in the presence of low bone mass after counseling, or (3) not receiving bisphosphonate treatment if bone mass was normal (i.e. a T-score of greater than -1.0 at all skeletal sites). This composite measure was classified as "appropriate" as we anticipated that up to 30% of participants would have normal bone mass and it would be inappropriate to treat with bisphosphonates(1;2;4;18) and we considered patients

who refused treatment after counseling to have made an educated choice about bone health management.

Additional Outcomes: We used validated HRQL measures at study entry and 6 months post fracture to assess health status (SF-12(19)) and upper extremity specific functional outcomes (Disabilities of the Arm, Shoulder and Hand(20) [DASH]) as well as disease-specific HRQL using the Osteoporosis Quality of Life(21) (OptQoL) tool. In these follow-up evaluations, participants were also asked if they were offered treatment and if so, whether they accepted or refused treatment.

We also undertook a micro-costing analysis of trial participants to estimate intervention costs based on activity time reported by the study nurse and local collective agreement salary rates. This also included costs of employee benefits, administrative clerk, office supplies, postage and overhead.

Data Analysis: The pre-specified analysis was performed according to the Intention-to-Treat principle whereby participants were analyzed in the group to which they were allocated and those with missing data (n=11; 3%) were imputed as a patient who did not start bisphosphonate treatment (i.e., missing=failure) for the primary outcome. Baseline evaluations were undertaken to assess for any systematic group differences. For the primary and secondary outcomes, we used chi-square tests to compare between groups. We determined the absolute difference and statistical significance as well as assessed the strength of the association using relative risks (RR) with accompanying 95% confidence intervals (CI). We also calculated the number needed to treat (NNT) to start one more patient on bisphosphonate treatment. T-tests were used to compare

HRQL measures between groups. P-values <0.05 were considered statistically significant. The data were analyzed using SAS software version 9.4 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Between July 2011 and February 2016, we screened 1837 potential candidates, excluding 1476 because they did not meet the screening criteria (n=1273) or refused participation (n=203). The most common reasons for exclusion were patients already being treated with bisphosphonates (n=386 [26%]) or who were unable to commit to the study intervention and follow-up (n=230 [16%]). We randomly assigned 181 participants to the active control intervention and 180 participants to case manager. At 6 months, only 11 (3%; 7 in the active control group and 4 in the case manager) were lost to follow-up or had died (**Figure 1**).

Baseline Characteristics: The groups were similar in socio-demographic and injury characteristics, health status and previous bone health management at study entry (**Table 1**). Most participants were female with good self-reported health literacy. Almost all patients sustained the fracture as a result of a fall, with distal radius/ulna fractures far more common than proximal humerus fractures. More than 30% of participants reported a fall in the past year with over 40% reporting a previous fracture; the majority of participants had undergone previous BMD testing (**Table 1**).

Bisphosphonate Treatment (Primary Outcome): At 6 months after fracture, 51 (28%) participants receiving the active control intervention and 86 (48%) participants receiving the case manager started bisphosphonate treatment (p<0.0001); the absolute difference was 20% (RR 1.70 [(95% CI 1.28-2.24]); and the NNT was 5 (**Figure 2**).

Bone Mineral Density Testing: By 6-months after their fracture, 108 (62%) participants from the active control group had undergone BMD testing compared to 128 (73%) participants in the case manager group (11% absolute difference; RR 1.17 [95% CI 1.01-1.36]; p=0.03) (**Figure 2**). There were no differences in bone mass between groups for those who underwent BMD testing (p=0.63); 46 (20%) had normal bone mass, 104 (44%) had osteopenia (T score -1.0 to -2.49), 36 (15%) had osteoporosis (T score -2.5 or worse) and 50 (21%) participants had unknown results of their BMD test (i.e., there was confirmation of test completion, but results were not available electronically).

Appropriate Care: Overall, 76 (44%) active controls and 133 (76%) case manager intervention patients received the pre-defined appropriate care (32% absolute difference, RR 1.73, [95% CI 1.43-2.09]; p<0.0001) (**Figure 2**). Of participants eligible and offered bisphosphonate treatment, 11 (6%) active controls and 21 (12%) case managed patients refused treatment (p=0.07). Defining appropriate care as only participants who accepted treatment when indicated or did not require treatment, we saw similar results between groups (26% absolute difference, RR 1.70, [95% CI 1.40-2.2]; p<0.0001).

Other Outcomes: There were no differences in patient reported outcomes between groups at the 6-month evaluation (**Table 2**). The active control intervention participants had a mean exposure time of 11 minutes (standard deviation [SD] 3.3) each and this cost $18 Canadian (CDN), whereas the nurse case manager had a mean exposure time of 51 minutes (SD 11.4) per participant at a cost of $66 CDN per participants (p<0.0001).

DISCUSSION

Although both interventions led to better osteoporosis care than previously published rates of usual care within 6 months of a fragility fracture,(15;16;22) the case manager intervention was significantly better than active control on all measures of effectiveness of osteoporosis care. Within 6-months of fracture, almost half of the case manager participants were on bisphosphonate treatment compared to less than 30% of the active control. Although BMD testing was similar between groups (73% vs. 62%), BMD testing led to higher treatment rates in the case manager group despite similar bone mass measurements between groups.

Perhaps more importantly, within 6-months of fracture, 76% of case manager participants were considered to have received appropriate osteoporosis care compared to only 44% of the active control. Most previous studies of osteoporosis interventions do not consider the more complete decision making process reflecting not only those who should receive bisphosphonate treatment,(10) but also those who have normal bone mass not requiring therapy and those who refuse treatment after counselling. Treating these two sub-groups as 'un-managed' underestimates the impact of osteoporosis management programs and clinical decision-making. This composite measure should be included in studies of osteoporosis management, particularly in non-hip fractures, where up to 30% of participants could have normal bone mass and not require bisphosphonate treatment; indeed, 20% of our trial participants had normal BMD test results.

There has been increasing recognition of the need for patient education regarding secondary prevention following a fracture.(23-27) Langer et al. (2017) recently surveyed more than 1000 patients and even among patients rated high risk for secondary fracture using the FRAX tool,

most perceived their future fracture risk as low.(25) In our own trial, patients did not recognize the need for further evaluation of their bone health after fracture.(27) More work is needed to understand and address these ongoing issues related to under-treatment of community-based patients who remain at high risk of future fractures.

Our high quality trial had excellent participant retention and multiple outcomes assessed and is the largest comparative effectiveness trial to date, demonstrating that both low and high intensity FLS approaches can positively affect treatment rates. That said, there are important limitations. First, though one of the largest studies conducted in the field, we did not examine fracture rates as this would have required a substantially larger sample with longer follow-up. In this report of the primary outcome of the trial, we also only followed patients for the short-term and would benefit from longer follow-up to assess adherence and persistence to bisphosphonate therapy;(17;28;29) further follow-up of trial participants is underway to assess these outcomes at 24-months post-fracture.

Second, we examined differences between nurse case-managers delivering new and more costly care compared with busy family physicians who have many other episodes of care to deliver. Formal cost-effectiveness analysis is underway to determine the overall impact to the healthcare system of introducing new service providers (i.e., case managers) in terms of both clinical outcomes and costs. Third, we considered participants refusing offered care after counselling as "appropriate" and others may consider this inappropriate or worthy of more attention. In addition, we may have under-estimated the number of active control participants who refused treatment after discussion with their family physician as we had only self-report regarding refusal of treatment at the scheduled follow-ups in this group. Fourth, we had a substantial number of potential participants (n=203) refuse participation in the trial; at least some of these

refusals could be due to lack of interest in osteoporosis care rather than refusal to be a study participant. This may limit the generalizability of our findings to the overall upper extremity fracture patient population. Lastly, we undertook the trial in a single metropolitan region in Canada, where there is universal access to healthcare, including BMD testing. However, we believe our results are likely generalizable to other health care centres, systems and countries where socialized medical systems exist.

In summary, although both osteoporosis treatment approaches substantially improved care compared to reported usual care rates,(10;15;16;22) the case manager intervention led to 76% of participants receiving appropriate osteoporosis care with 48% starting bisphosphonate treatment within 6-months of an upper extremity fracture. We believe our findings support the use of case-management interventions where possible while at the same time supporting simpler methods to improve secondary fracture prevention when resources are constrained. Our models may also contribute to the current debate about optimal care models for chronic diseases (such as diabetes mellitus, asthma, hypertension, osteoporosis, or dyslipidemia) where nurse- or pharmacist-led care appear promising, but require further evaluation.(30;31)

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Contributor Information

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Figure 1. CONSORT Flow Diagram of Study Participants with Upper Extremity Fracture

Figure 2. Quality of Osteoporosis Care after an Upper Extremity Fracture by Randomized Arm

Table 1 Baseline Characteristics of Participants with Upper Extremity Fracture

Characteristics	**Active control (n=181)**	**Case manager (n=180)**
Age, mean (SD)	63 (9)	63 (9)
Female (%)	163 (90)	159 (88)
Married (%)	108 (60)	101 (56)
Retired (%)	63 (35)	70 (39)
Good health literacy (%)	122 (67)	131 (73)
Distal radius &/or ulna (Colles+Smith+other)	132 (73)	144 (80)
Fall-related Fracture (%)	179 (99)	178 (99)
Fall in past 12-months (%)	53 (30)	61 (34)
Any broken bone in past (%)	87 (48)	69 (38)
Family history of osteoporosis (%)	76 (42)	59 (33)
Parental history of hip fracture if parent had osteoporosis (%)	17/59 (29)	15/43 (35%)
Body Mass Index, mean (SD)	27 (5)	27 (6)
Menopause (%)	156/163 (96)	152/159 (96)
Two or more health problems (%)	131 (72)	138 (77)
Diabetes (%)	18 (10)	18 (10)
Rheumatoid Arthritis (%)	7 (4)	4 (2)
Thyroid Disease (%)	44 (24)	52 (29)
Current smoking (%)	17 (9)	13 (7)
More than 2 alcoholic drinks per day (%)	7 (4)	5 (3)
Prescription medications (%)	119 (66)	122 (68)
Steroid Use (%)	14 (8)	22 (12)
SF-12		
Physical Component Score, mean (SD)	45 (10)	45 (10)
Mental Component Score, mean (SD)	51 (10)	51 (10)
DASH score, mean (SD)	50 (17)	48 (17)
Bone density measured (%)	130 (72)	133 (74)
BMD result		
Normal (%)	25 (19)	32 (24)
Low (%)	100 (77)	91. (68)
Unknown (%)	5 (4)	10 (8)
Hormone Replacement (%)	42 (23)	44 (24)
Calcium supplements (%)	89 (49)	91 (51)
Vitamin D supplements (%)	125 (69)	125 (69)

Legend: SD = standard deviation; DASH = Disabilities of the Arm, Shoulder or Hand Index

Table 2. HRQL Outcomes at 6 months after Upper Extremity Fracture by Randomized Arm

	Active Control	**Case manager**	**P-value**
SF-12	n=144	n=146	
PCS, mean (SD)	47 (10)	47 (9)	0.85
MCS, mean (SD)	51 (10)	53 (8)	0.07
OptQOL*	n=158	n=161	
Physical function score, mean (SD)	77 (22)	80 (21)	0.16
Adaptation score, mean (SD)	72 (21)	72 (22)	0.75
Fear score, mean (SD)	74 (25)	75 (25)	0.60
DASH	n=155	n=158	
DASH score, mean (SD)	21 (18)	19 (18)	0.52

Legend: HRQL = Health Related Quality of Life; SF-12 = Short Form -12; PCS = Physical Component Score; MCS = Mental Component Score; SD = Standard Deviation; OptQoL = Osteoporosis Quality of Life Index; DASH = Disabilities of the Arm Shoulder and Hand Index

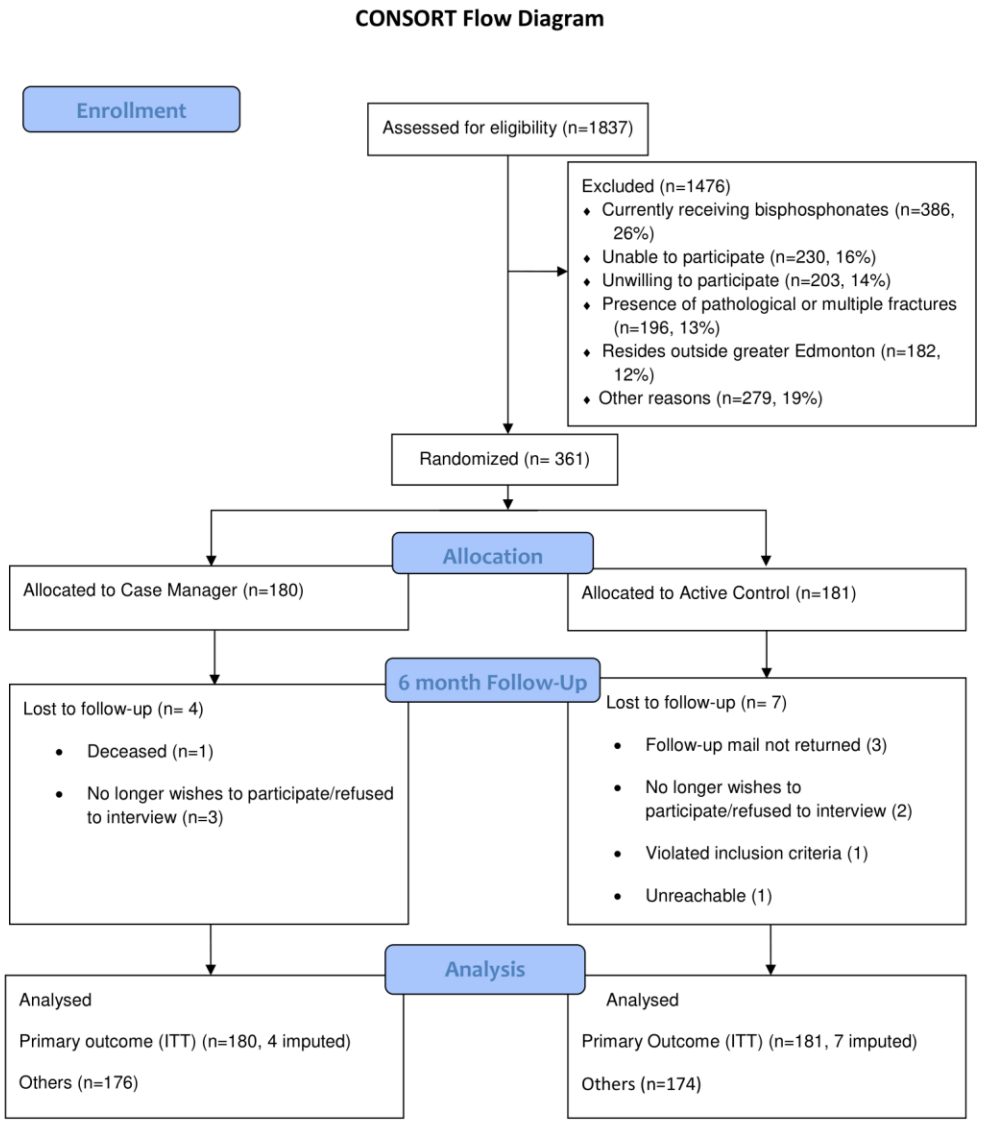

Figure 1

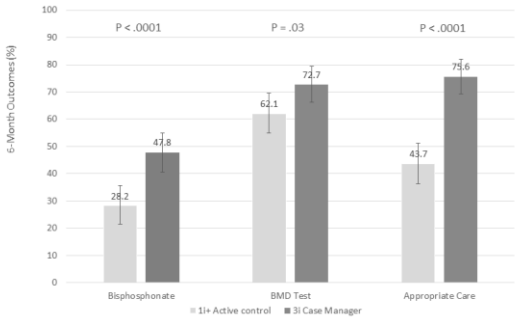

Figure 2