EFFECTIVENESS OF GROUP COGNITIVE BEHAVIORAL THERAPY ON PAIN, FUNCTIONAL DISABILITY AND PSYCHOLOGICAL OUTCOMES AMONG KNEE OSTEOARTHRITIS PATIENTS SEEN AT MALAYSIAN GOVERNMENTHOSPITAL

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Table of Contents

Figure

Table

CHAPTER 1 INTRODUCTION

1.0 INTRODUCTION

Osteoarthritis (OA) is thought to be the most prevalent chronic joint disease. The incidence of osteoarthritis is rising because of the ageing population and the epidemic of obesity. Pain and loss of function are the main clinical features that lead to treatment, including non-pharmacological, pharmacological, and surgical approaches (Bijlsma, Berenbaum, & Lafeber, 2011).

OA is a "joint degenerative disease characterized by the breakdown of articular cartilage, osteophyte formation, joint swelling, stiffness and pain. The disease progresses from an initial hypertrophy of the articular cartilage to degeneration of the cartilage and underlying bone. Osteophytes also grow throughout the affected joint" (Binder, Hirokawa & Windhorst, 2009). However, there are sometimes local signs of inflammation and it is not primarily an inflammatory disorder. Besides, it is not a pure degenerative disorder but a dynamic phenomenon since it shows features of both destruction and repair.

OA is the most common source form of arthritis globally. OA is the most prevalent chronic joint disease, which is a serious, painful and potentially life- altering joint disease mainly affecting hands, knees and hips (*Figure 1*) (Bijlsma, Berenbaum & Lafeber, 2011; Fernandes, Hagen, Bijlsma, Andreassen, Christensen, … & Vlieland, 2013). Furthermore, OA usually affect persons aged 40 years and above and it happens gradually (National Center for Chronic Disease Prevention and Health Promotion, 2011). There are two types of OA, primary and secondary. Primary OA is related to aging, and secondary OA is usually caused by an injury that related to a person' occupation that requires kneeling or squatting for a long period of time, or diabetes, or obesity (Teitel & Zieve, 2011).

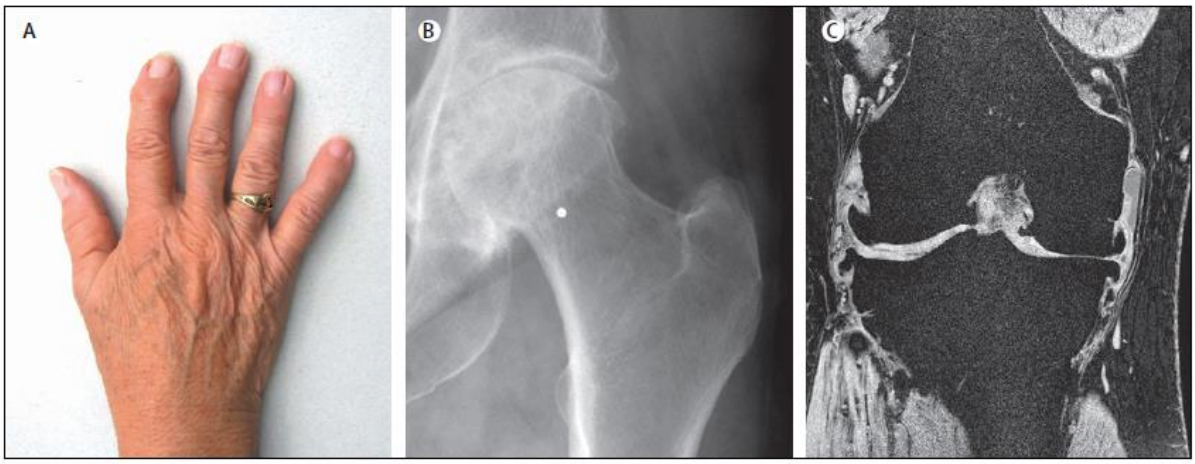


Figure 1: Osteoarthritis joints of the hand, hip and knee

"(A) Osteoarthritis is predominantly identified in the distal interphalangeal and proximal interphalangeal joints – deformations of the distal interphalangeal joints are clearly visible. (B) Plain radiograph of an osteoarthritic hip joint showing the narrowing of the joint space and clearly visible osteophytes. (C) MRI of an osteoarthritic knee with clear medial cartilage loss and osteophyte formation, with minor synovial swelling".

1.1 PROBLEM STATEMENTS

The impact of osteoarthritis (OA) relates to pain and loss of joint mobility and functions. It affects individual independency and psychosocial functioning. This may lead to changes in a person's life and the outcome of negative effects on quality of life and wellbeing (Ridder, Geenen, Kuijer & Middendorp, 2008). There are numerous studies have studied mortality among persons with OA. Nuesch, Dieppe, Reichenbach, Williams, Iff and Juni (2011) have done a study on the cause and disease specific mortality among 1163 patients aged 35 years and above with symptomatic and radiologic evidence based knee or hip OA patients. They examined that patients with OA have higher risk of death compared with general population (standardized mortality ratio 1.55, 95% confidence interval 1.41 to 1.70). Furthermore, the results revealed that OA patients with severe walking disability showed significant higher risk of death ($p<0.001$).

Australian Bereau of Statistics (2007) has reported that diseases of the musculoskeletal system are one of the underlying causes of death in less than one percent of all registered deaths in Australia. Arthritis and musculoskeletal diseases contribute standardized death rate of 4.3 per 100, 00 population in year 1998 and increases to 4.6 per 100, 000 population in year 2007, and 3.6 per 100, 000 for males and 5.3 per 100, 000 for females in year 2007, predominantly among persons aged 75 to 94 years.

According to a study on deaths from arthritis and other rheumatic conditions which done by Sacks, Helmick and Langmaid (2004) in United States, there are about 0.2 to 0.3 deaths per 100, 000 pupation due to OA within year 1979 to 1988. Besides, OA contributes approximately six percent of all arthritis- related deaths. There is an estimation of 500 deaths per year due to OA and it increases for the past ten years.

A person is defined with clinically OA if the person has the basis of symptoms and physical examination findings. A case definition of symptomatic knee or hip OA is defined where pain is present in a joint with radiographic evident based OA. In addition, radiographic defined OA is based on Kellgren or Lawrence scale or American College of Rheumatology criteria.

Lawrence, Felson, Helmick, Arnold, Choy, … and Wolfe (2008) estimated that 13.9% of adults aged 25 and above and 33.6% (12.4 million) of those aged 65 years and above are affected by OA corresponds to 2005 United States population. Besides, the estimation of 21 million of United States adults have defined with clinical OA in year 1995 increases to 27 million for 2005.

For radiographic OA, the prevalence per 100 for hand is 7.3 (9.5 for female and 4.8 for male) (Dillon, Hirsch, Rasch & Gu, 2007); feet, 2.3 (2.7 for female and 1.5 for male) (Lawrence, Felson, Helmick, Arnold, Choy, … & Wolfe, 2008); knee, 0.9 (1.2

for female and 0.4 for male) (Dillon, Rasch, Gu and Hirsch, 2006); and hip, 1.5 (1.4 for female and 1.4 for male) (Lawrence, Felson, Helmick, Arnold, Choy, … & Wolfe, 2008).

Furthermore, the reported prevalence per 100 for symptomatic OA is hand contributes 8% (8.9% female; 6.7% male) corresponds to 2.9 million adults aged 60 years and above (Dillon, Hirsch, Rasch & Gu, 2007); feet contributes 2% (3.6 female; 1.6 male) corresponds to persons aged 15 to 74 years (Lawrence, Felson, Helmick, Arnold, Choy, … & Wolfe, 2008); knee contributes 12.1% (13.6% female; 10% male) corresponds to adults aged 45 years and above (Jordan, Helmick, Renner, Luta, Dragomir, … & Hochberg, 2007); hip contributes 4.4% (3.6% female; 5.5% male) corresponds to adults aged 55 years and above (Lawrence, Felson, Helmick, Arnold, Choy, … & Wolfe, 2008).

OA is one of the ten most disabling diseases in developed countries. There are estimation of 9.6% of men and 18% of women aged over 60 years have symptomatic OA. 80% of those with OA will have limitations in movement , and 25% of them are unable to perform their major daily activities of life (Wittauer, Smith & Aden, 2013).

The most common region attribute by osteoarthritis in Malaysia is osteoarthritis of the knee. There are no exact figures of Malaysian population with knee osteoarthritis. However, Chia, Ng, Rabia et al. (2006) found that 21.2% of the studied population reported knee pain in the previous six months prior to the survey. This knee pain problem in Malaysia is more common in adults aged 40 years and above, and it affects Indian ethnicity the most. The Community Oriented Program for the Control of Rheumatic Diseases (COPCORD) study that done in Malaysia reported that knee was responsible for 64.8% of all complaints pertaining to the joints, and more than half those examined with knee pain had clinical evidence of osteoarthritis. Besides, there were 23% of patients over 55 years who complained in pain rate, and it increased to 39% in those over sixty five years (Veerapen, Wigley & Valkenburg, 2007).

In a systemic review done by Barlow, Wright, Sheasby, Turner and Hainsworth (2002), they emphasized on self- management which the patient is able to manage the symptoms, treatment, physical and psychosocial consequences and life style changes inherent with a chronic condition. Furthermore, self- management needs to incorporate with the “ability to monitor one’s condition and to effect the cognitive, behavioral and emotional responses necessary to maintain a satisfactory quality of life”. Behavioral change and new coping strategies are very important of self-management for osteoarthritis because symptoms have a great impact on many years of life (Newman, Steed & Mulligan, 2004).

Unfortunately, most of the patients with osteoarthritis of the knee are often difficult to achieve optimum self- management and thus resulting in reduced quality of life and poor psychological wellbeing. In fact, there are no self- management interventions for patients with osteoarthritis of the knee with the main focus of reducing pain and improving physical and psychological functioning which has not been previously studied in Malaysia.

The key features of cognitive behavioral intervention are the aim of increasing patients’ involvement and control in their life and its effect on their lives. Cognitive behavioral intervention in this study will be delivered in a basis of group due to

groups have the advantage of participants being able to communicate or interact with each other with similar problems (Critchley, Ratcliff, Noonan, Jones & Hurley, 2007). Consequently, the group cognitive behavioral treatment in this study aims to meet the objectives of reducing pain and improving physical and psychological functioning in patients with osteoarthritis of the knee.

1.2 SIGNIFICANCE OF RESEARCH

There are no risks for subjects on placebo. However, there is little risk in getting cognitive behavioral therapy. Patients may explore painful feelings, emotions and experiences. Besides, they may feel emotionally uncomfortable at times. They may cry, get upset or feel angry during a challenging session, or may also feel physically drained. However, the therapists will minimize any risks. The coping skills patients learn can help to manage and conquer negative feelings and fears.

The results of this study may provide some insights that may lead to better care for patients with recent onset chronic knee pain to enhance in managing pain. It may heightened the potential importance of cognitive behavioral intervention aiming to reduce levels of pain, functional disability, depressive and anxiety severity symptoms, pain catastrophising, fear- avoidance beliefs and increase levels of pain self- efficacy in the management of chronic knee pain patients. The study described in this study will determine comparative efficacy of these programs and the results will assist healthcare providers who are involved in the delivery of non- pharmacological interventions, researchers in the field of osteoarthritis, officials in healthcare governance and policy makers in planning for future arthritis self- management strategies, in order to effectively reduce health and economic burden of knee osteoarthritis.

1.3 RESEARCH OBJECTIVES

The General objective of this study is:

To develop and implement a cognitive behavioral therapy module, and to evaluate its effectiveness in reducing level of knee pain, functional disability, psychological distress (depression, anxiety and stress), pain catastrophising, fear- avoidance beliefs, and improving in self- efficacy in pain management in patients with pain and dysfunction due to osteoarthritis of the knee.

The Specific objectives include:

1. To determine the socio- demography (*age, gender, ethnicity, income, occupation, education Level, type of cohabitation, marital status*) and patients' clinical characteristics (*duration of symptomatic knee OA, comorbidity,*

treatment, knee affected, knee radiography), level of knee pain and functional disability, depression, anxiety, fear- avoidance beliefs, pain catastrophising and self- efficacy in pain management level amongst patients with knee osteoarthritis.

2. To develop and implement a cognitive behavioral therapy module in patients with osteoarthritis of the knee.
3. To evaluate the effectiveness of a cognitive behavioral therapy module in reducing knee pain intensity, functional disability, psychological distress (depression, anxiety and stress), fear- avoidance beliefs and pain catastrophising level among knee osteoarthritis patients.
4. To evaluate the effectiveness of a cognitive behavioral therapy module in improving in self- efficacy in pain management level among knee osteoarthritis patients.

1.4 RESEARCH HYPOTHESIS

H_1: There is no significant difference between the sociodemographic characteristics of patients enrolled at Orthopaedic Clinic in Hospital Serdang and Hospital Putrajaya

H_2: The cognitive behavioral therapy module is effective in reducing knee pain intensity in patients with osteoarthritis of the knee.

H_3: The cognitive behavioral therapy module is effective in reducing functional disability in patients with osteoarthritis of the knee.

H_4: The cognitive behavioral therapy module is effective in reducing depression in patients with osteoarthritis of the knee.

H_5: The cognitive behavioral therapy module is effective in reducing anxiety in patients with osteoarthritis of the knee.

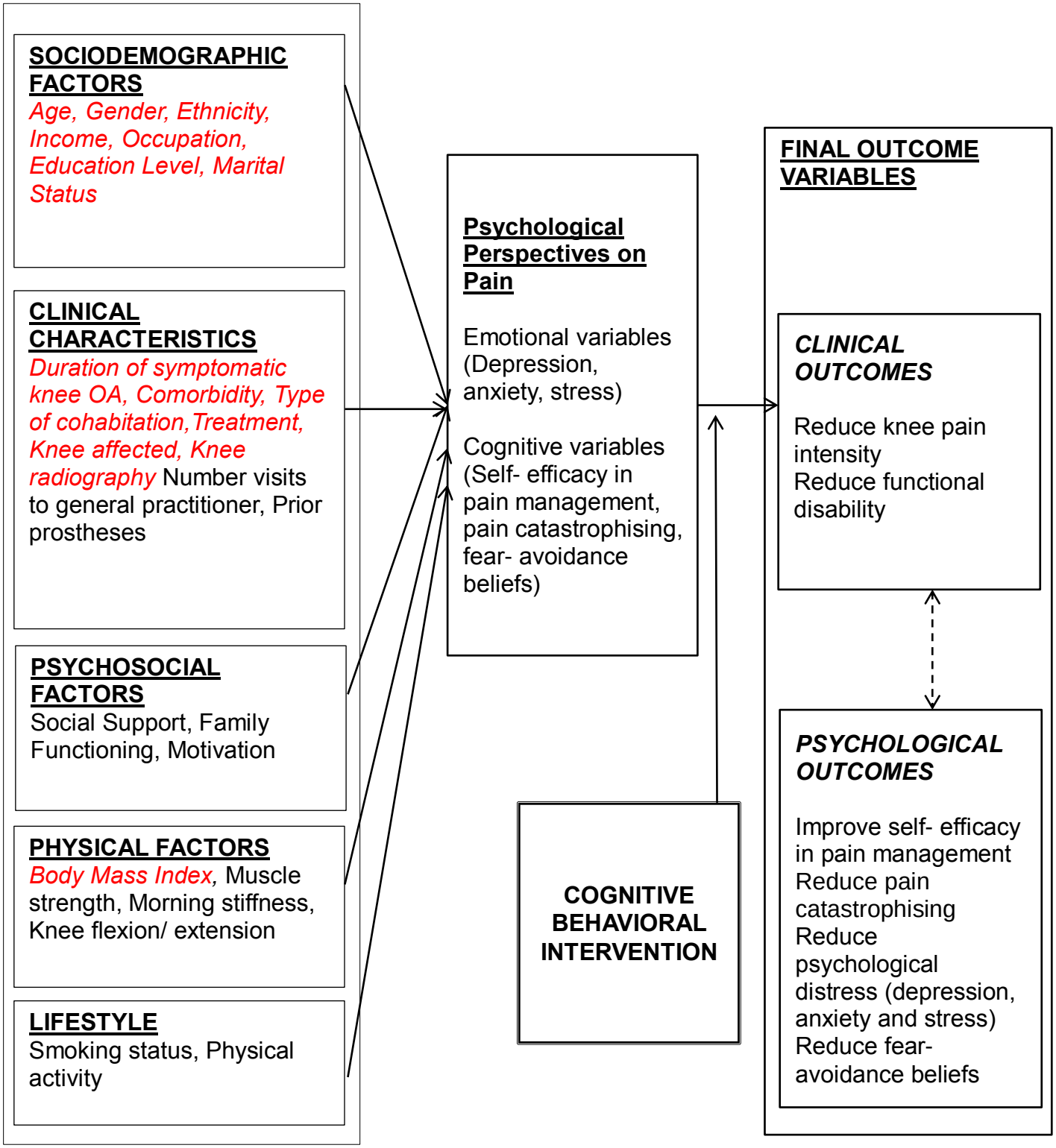
H_6: The cognitive behavioral therapy module is effective in reducing stress in patients with osteoarthritis of the knee.

H_7: The cognitive behavioral therapy module is effective in reducing fear- avoidance beliefs in patients with osteoarthritis of the knee.

H_8: The cognitive behavioral therapy module is effective in reducing pain catastrophising in patients with osteoarthritis of the knee.

H_9: The cognitive behavioral therapy module is effective in improving self- efficacy in pain management in patients with osteoarthritis of the knee.

1.5 CONCEPTUAL FRAMEWORK



Covariates included age, gender and obese status (Keefe et al., 2004).

CHAPTER 2 LITERATURE REVIEW

2.0 EPIDEMIOLOGY

A person is defined with clinically OA if the person has the basis of symptoms and physical examination findings. A case definition of symptomatic knee or hip OA is defined where pain is present in a joint with radiographic evident based OA. In addition, radiographic defined OA is based on Kellgren or Lawrence scale or American College of Rheumatology criteria.

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OA is one of the ten most disabling diseases in developed countries. There are estimation of 9.6% of men and 18% of women aged over 60 years have symptomatic OA. 80% of those with OA will have limitations in movement , and 25% of them are unable to perform their major daily activities of life (Wittauer, Smith & Aden, 2013).

2.1 CLINICAL FEATURES AND DIAGNOSIS

OA patients experience pain where it is the first and predominant symptom of OA. The pain experienced is intermittent, typically worst during and after weight- bearing activities. Besides, patients with OA also experience inflammatory flares, and stiffness, especially in the morning and after an inactivity period. Generally, stiffness caused by OA will resolve in minutes and do not prolong (usually greater than 30 minutes). Patients with OA will have functional disabilities that limit their daily activities. Furthermore, OA patients experience lower quality of life due to symptomatic OA might correlates with depression and disturbed sleep, and these symptoms contribute to disability (Centers for Diseases Control (CDC), 2001).

The diagnosis of the OA is based on clinical and radiological evidence based. Based on the American College of Rheumatology radiological and clinical criteria for classification of clinical and radiographic OA developed by Altman (1991), those patients with clinical evidence based hand OA have following clinical features of (1), (2), (3), (4) or (1), (2), (3), (5), explaining “(1) hand pain, aching, or stiffness for most

days of previous month, (2) hard tissue enlargement of two or more of ten selected joints (include bilateral second and third interphalangeal proximal joints, second and third proximal interphalangeal joints, and first carpometacarpal joint), (3) swelling in two or more metacarpophalangeal joints, (4) hard tissue enlargement of two or more distal interphalangeal joints, and (5) deformity of two or more of ten selected hand joints". For hip OA, the clinical features are "(1) hip pain for most days of previous month, (2) erythrocyte sedimentation rate of less than 20 mm in the first hour, (3) femoral or acetabular osteophytes on radiographs, and (4) hip joint space narrowing on radiographs", and patients with diagnosed hip OA based on clinical and radiographic evidence based if (1), (2), (3), or (1), (2), (4), or (1), (3), (4) are present. Furthermore, the clinical features for clinical knee OA are if following (1), (2), (3), (4) or (1), (2), (5) or (1), (4), (5) are present, explaining "(1) knee pain for most days of previous month, (2) crepitus on active joint motion, (3) morning stiffness lasting 30 minutes or less, (4) age 38 years or older, and (5) bony enlargement of the knee on examination". However, patients with diagnosis of knee OA based on clinical and radiographic evidence based experience following clinical features of (1), (2), or (1), (3), (5), (6), or (1), (4), (5), (6), which consisted of "(1) knee pain for most days of previous month, (2) osteophytes at joint margins on radiographs, (3) synovial fluid typical of osteoarthritis (laboratory), (4) age 40 years or older, (5) crepitus on active joint motion, and (6) morning stiffness lasting 30 minutes or less".

Besides American College of Rheumatology criteria for knee OA, the most common radiological classifications that routinely used to describe severity of knee OA is the Kellgren and Lawrence grading system: Grade 0 (Normal); Grade 1 'Doubtful' (Doubtful narrowing of joint space, possible osteophytes development); Grade 2 'Minimal' (Definite osteophytes, absent or questionable joint space narrowing); Grade 3 'Moderate' (Moderate osteophytes, definite narrowing, some sclerosis, mild joint deformity); Grade 4 'Severe' (Large osteophytes, marked narrowing, severe sclerosis, joint deformity present) (Kellgren, 1963). Furthermore, Schiphof, deKlerk, Koes and Bierma- Zeinstra (2008) have identified 25 classification criteria for knee OA that have good intra- and inter- rater reliability (*Table 1*).

Physical examination is applied to confirm, categorize joint movement, and to exclude pain and functional syndromes that might cause the same pain syndrome as OA, such as "bursitis, tendinitis, muscle spam, tissue response and damaged meniscus". The only first physical sign of symptomatic OA is restricted passive movement. In addition, OA patients feel crepitus on passive or active movement of joint. *Figure 2* shows the joint deformities and joint damage. Neurological and spine examination should be further determined to distinguish between knee pain or hip pain in OA patients, due to patients with hip OA might report knee pain because of "anserine bursitis" (Bijlsma, Berenbaum & Lafeber, 2011).

Imaging investigations such as magnetic resonance imaging (MRI) or scintigraphy are seldom needed to confirm the OA diagnosis but needed to monitor its progression, unless to exclude other diseases from OA, such as "avascular osteonecrosis, Paget's disease, complex regional pain syndrome, inflammatory

Table 1: Classification criteria for knee OA

No	Classification criteria
1.	**Radiological classification criteria: Scoring of features (JSN, OP), cysts, sclerosis, bone deformity)** A. Kellgren and Lawrence (K&L) classification system (≥grade 2) grade 0: normal, grade 1: possible osteophytic lipping, unimpaired JSN, grade 2: definite OP(s) and possible JSN, grade 3: definite multiple OPs, and definite JSN, grade 4: marked JSN, large OPs, sclerosis, and deformity B. Ahlback's classification system (≥grade 1) grade 1: JSN <3 mm, grade 2: joint space obliteration, grade 3: minor bone attrition (0-5 mm), grade 4: moderate bone attrition (5-10 mm), grade 5: severe bone attrition (>10 mm) C. In any of the two tibiofemoral compartments: JSN grade 2 or higher, sum OP compartment score ≥2 or grade 1 JSN in combination with grade 1 OP in the same compartment D. JSN and OP ≥grade 2 E. Any feature ≥grade 2 F. Either an OP ≥grade 2 or JSN ≥grade 2 with either sclerosis, cysts, or an OP grade 1 G. OP grade 1 and any sclerosis or JSN H. Sum of individual radiographic features ≥grade 2 I. JSN ≥grade 1 J. JSN ≥grade 2 K. JSN ≥grade 3 L. OP ≥grade 1 M. OP ≥grade 2 N. OP ≥grade 3 O. OP maximum whole knee (TFJ + PFJ) ≥grade 1, 2, and 3
2.	**Clinical classification criteria** A. ACR clinical list method: knee pain and at least three of six: age >50 yr, stiffness <30 min, crepitus, bony tenderness, bony enlargement, no palpable warmth (for tree method see references) B. ACR clinical + laboratory: knee pain and at least five of nine: age>50 yr, stiffness<30 min, crepitus, bony tenderness, bony enlargement, no palpable warmth, erythrocyte sedimentation rate <40 mm/hr, rheumatoid factor ≤1:80, synovial fluid OA C. Frequent knee symptoms and presence of crepitus on physical exam (frequent knee symptoms are defined as pain in or around the knee on most days of the months during the year of the exam). Frequent knee pain is defined as positive answer on two questions: pain in or around the knee on most days of the month and on most days do you have pain, aching, or stiffness in either of your knees? D. Pain on movement or tenderness in the knee joint line at clinical exam E. Screening question (1): ''During the last month, did you have any knee pain or discomfort when walking 2-3 blocks (one-fourth of a mile)?'' F. Screening question (2): Clin. E + ''Has a doctor ever told you that you have arthritis in your knees?'' G. Screening question (3): Clin. E + ''How long does this stiffness take wear off?'' And ''Have you had knee pain on more than two occasions in the last year?''
3.	**Radiological clinical (combined) classification criteria** A. ACR clinical + radiological: list method: knee pain and OP and at least one of three: age >50 yr, stiffness<30 min, crepitus (for tree method see references) B. JSN≥1 with OP ≥1 in same compartment OR JSN ≥2 OR sum of OP score of both compartments ≥2 with symptomatic knee (subscale Knee Injury and Osteoarthritis Outcome Score, quality of life and two out of four additional subscale with cutoffs: QOL ≤87.5, pain ≤86.1, symptoms ≤85.7, activities of daily living ≤86.8, and sports and recreation ≤85.0) C. Presence of radiological changes (K&L ≥2) in addition to symptoms or clinical signs (reported pain present longer than 1 month in the last 10 years) **D.** K&L grade ≥2 for tibiofemoral compartment OR grade ≥2 OP or grade ≥2 JSN and grade ≥1 OP for patellofemoral compartment AND affirmative answer to the question: ''On most days, do you have pain, aching, or stiffness in either of your knees?''
Abbreviations: JSN, joint space narrowing; OP, osteophyte (s); TFJ, tibiofemoral joint; PFJ, patellofemoral joint; ACR, American College of Rheumatology; OA, osteoarthritis; Clin. E, clinical classification criteria E; QOL, quality of life (knee-related).	

arthropathies and stress fractures". The imaging investigations are sometimes unnecessary due to these techniques do not define the clinical syndrome of OA. The United States Department of Health, Education and Welfare (1966) examined that there are 40% of OA patients do not show OA symptom but shown evidence with radiographic changes. Furthermore, patients with clearly diagnosed OA and without complicated chronic pain may do not need blood tests, due to its erythrocyte sedimentation rate (ESR) and c- reactive protein test (CRP) are within the acceptable range. However, other laboratory tests such as synovial fluid should be assessed to determine the "synovial fluid is sterile, without crystals and a white- cell count of less than 1, 500 cells per microliter" among OA patients (Bijlsma, Berenbaum & Lafeber, 2011).

A recent study done by Inoue, Ishibashi, Tsuda, Yamamoto, Matsuzaka, … and Toh (2011) have examined that serum haluronan (HA) level is significant correlated with severity of radiographic knee OA ($r= 0.289$, $p< 0.001$), and hence it is useful for the diagnosis of the presence and severity of knee OA.

Knee pain without radiographic changes could be interpreted as a possible sign of early OA. People who with negative radiographs should be offered possibilities to study early phases of developing OA by using sensitive techniques such as magnetic resonance imaging (MRI), bone scintigraphy, and biochemical markers of cartilage and bone turnover (Kenanidis et al., 2011); (Spil et al., 2010); (Garnero et al., 2008).

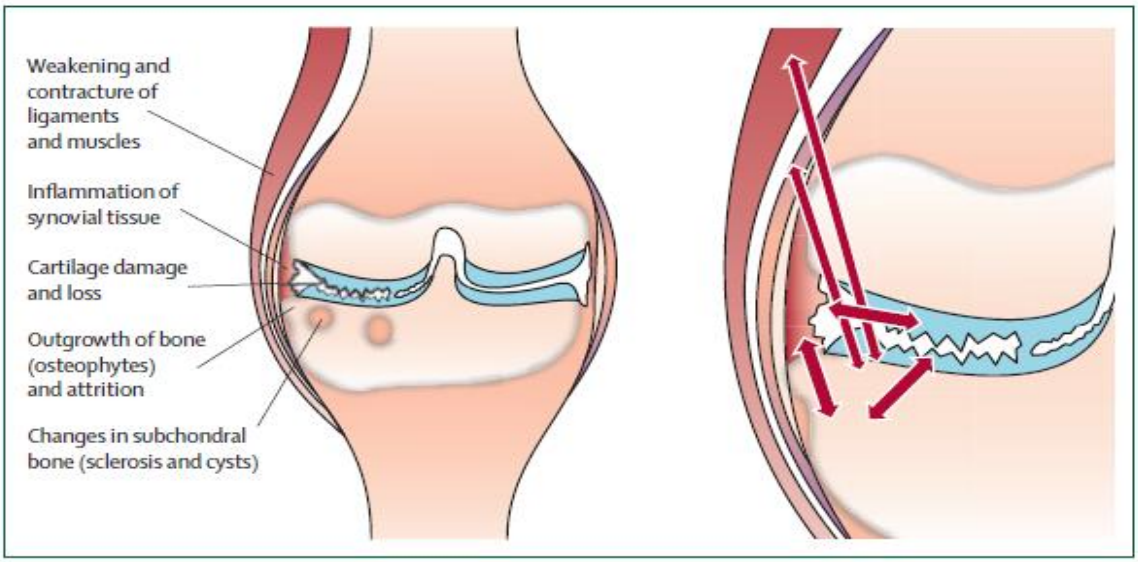


Figure 2: Schematic drawing of an osteoarthritic joint

"The different tissues involved in clinical and structural changes of the disease are shown on the left. Note that cartilage is the only tissue not innervated. On the right the bidirectional interplay between cartilage, bone and synovial tissue involved in osteoarthritis is shown, and the two- way interaction between this interplay and the ligaments and muscles. In the interplay between cartilage, bone, and synovial tissue one of the tissues might dominate the disease, and as such should be targeted for treatment.

2.2 MARKERS OF TISSUE DAMAGE

“Early and minimum tissue damage is difficult to assess in vivo. Biopsies for detailed histochemical and biochemical assessment of cartilage, bone, and synovial tissue in OA are not feasible and are often contraindicated. Besides, tissue changes are often focal and can be missed by random biopsy procedures. Therefore, at present only surrogate markers, as indirect measures of the actual destructive process, can be used for diagnosis and follow-up of tissue damage” (Bijlsma, Berenbaum & Lafeber, 2011). New biomarkers are important in the early diagnosis and treatment of the disease.

There are several semi- quantitative scoring systems (*Table 2*) have been developed that focus on the size and location of the lesions, and on subchondral, cartilaginous, bone, and other abnormalities (Bijlsma, Berenbaum & Lafeber, 2011).

Table 3 lists the most reported biomarkers and their performance. Markers of cartilage degradation, such as CTXII in urine and COMP in serum, have been assessed extensively and show a moderate to good relation with clinical and radiographic variables of OA. However, markers of bone metabolism are less effective, due to the size of the bone compartment (mostly outside the joints) and the high turnover of bone (Bijlsma, Berenbaum & Lafeber, 2011).

Table 2: Imaging techniques for assessment of tissue-structure changes in osteoarthritis

	Primary use	Analyses	Advantages	Disadvantages
Plain radiograph*	**Cartilage thickness**	**(Semi)quantitative**	**Low cost, easy applicable**	**Indirect, two-dimensional image of a three-dimensional problem**
CT				
Standard*	Bone characteristics	Semiquantitative	Three dimensional	Radiation exposure, only bone
CECT	As standard plus cartilage volume	Semiquantitative	Three dimensional, information on cartilage	As standard plus contrast agent needed
Ultrasound				
Standard*	Inflammation	Impression	Cheap	User dependent
Power doppler	Vascularisation	Semiquantitative	Direct measure	Relative importance for osteoarthritis
MRI				
Standard SPGR*	Cartilage morphology	Quantitative	Three dimensional, quantitative	Time-consuming analyses
T2 MRI relaxation	Collagen distribution	Semiquantitative	Information on cartilage quality	Complex interpretation

T1ρ	Proteoglycan distribution	Semiquantitative	Information on cartilage quality	Complex interpretation
^{23}Na MRI	FCD/proteoglycan content	Semiquantitative	Information on cartilage quality	Field strength ≥3T
dGEMRIC	FCD/proteoglycan content	Semiquantitative	Information on cartilage quality, early changes	Contrast agent needed
MRI whole-organ scoring				
KOSS	..	Semiquantitative	Whole-organ score	Time consuming, observer variance
WORMS	..	Semiquantitative	Whole-organ score	Time consuming, observer variance
BLOKS	..	Semiquantitative	Whole-organ score	Time consuming, observer variance

CECT=contrast-enhanced CT. SPGR=spoiled gradient echo. FCD=fi xed charge density. dGEMRIC=delayed gadolinium-enhanced MRI of cartilage. KOSS=knee osteoarthritis scoring system. WORMS=whole-organ magnetic resonance imaging score. BLOKS=Boston Leeds osteoarthritis knee score. *Techniques that have a more common clinical and research applications for the assessment of cartilage (and bone), bone, and synovial infl ammation, as well as quantitative cartilage morphology (at present the most used MRI modality in clinical trials).

Table 3: Overview of published work on biomarkers over the past 5 years for knee and hip osteoarthritis

	Diagnostic value	Relation to burden of disease	Prognostic value	Relation to efficacy of treatment	Overall positive proportion
Cartilage degradation					
CTXII in urine*	12/13	16/25	17/23	4/5	74%
COMP in serum*	9/12	15/26	6/17	1/2	54%
Coll 2-1 (NO2)† in urine and serum	7/8	2/6	2/4	..	61%
KS in serum	1/2	3/8	3/5	1/2	47%
YKL-40 in serum	1/3	5/12	0/4	1/1	35%
C2C in urine and serum	1/1	3/9	0/4	1/3	29%
C1,2C in urine and serum	..	1/6	0/4	0/2	8%
Cartilage synthesis					
PIIANP in serum*	2/2	1/4	2/3	0/1	50%
PIICP in serum	..	3/7	0/4	..	27%
CS846 in serum	0/1	1/7	0/3	..	9%
Bone degradation					
NTX-I in urine and serum*	1/2	1/1	2/5	2/2	60%
(D)PYR† in	2/3	6/15	0/10	2/2	33%

urine					
CTXI in urine and serum	2/4	1/16	1/6	0/1	15%
Bone synthesis					
OC in serum*	1/5	2/12	2/6	1/2	24%
BSP in serum	2/2	1/3	0/2	··	43%
PINP in serum	0/1	1/4	0/4	··	11%
Synovium degradation					
HA in serum*	7/9	7/22	8/11	1/3	51%
Glc-Gal-PYR in urine	2/2	3/4	··	0/1	71%
Synovial synthesis					
PIIINP in serum	1/1	2/4	0/2	··	43%
Data are n/N unless otherwise stated. Biomarkers with less than five reports are not included. The most relevant and best performing commercial biomarkers. †Combined biomarkers: Coll 2-1 with Coll 2-1 NO2 and PYR with D-PYR.					

2.3 RISK FACTORS

Risk factors for occurrence and progression of OA have been identified according to the joints involved (*Table 4*) (Altman, 1991).

2.3.1 SYSTEMIC FACTORS

A consistent finding in epidemiologic studies of knee OA is that the incidence and prevalence of this disease increased directly with age and dominated female population. The prevalence of radiographic and symptomatic knee OA was found to be increased with age in an elderly cohort in the Framingharn Osteoarthritis Study in ages ranging from 63 to 94 years (Felson et al., 1987). Incidence of symptomatic knee OA was shown to be increased directly with age up to 80 years old (Felson et al, 1987). Furthermore, Felson et al. (1987) extended their research on the incidence of knee OA which 2% of women developed radiographic knee OA yearly and 1% of women developed symptomatic and radiographic knee OA yearly, versus 1.4% and 0.7% among men respectively.

In older age groups, there appeared to a widening sex differences in the development of knee OA. Women tended to have higher rates of incident knee OA at after age of 50 as compared with men (Oliveria et al., 1995) and a higher prevalence of radiographic and symptomatic OA (Felson et al., 2000). The Framingham Osteoarthritis Study which done by Felson et al. (1995) determined the mean age of knee OA patients were 71 years old, and women had rates of incidence disease that were 1.7 times higher than in men. Recent epidemiologic studies suggested that postmenopausal estrogen deficiency could be playing a role in the development of knee OA in elderly women (Spector et al., 1997). Women who had taken estrogen replacement therapy seemed to have a lower risk of having knee OA (Zhang et al., 1998).

2.3.2 GENETIC FACTORS

There are 39 – 65% of heritability component of genetic factors that contribute to the development of OA (Cicuttini & Spector, 1997; Spector, Cicuttini, Baker, Loughlin & Hart, 1996).

2.3.3 BIOCHEMICAL FACTORS

OA changes are found to appear sooner in older patients sustaining a meniscal injury compared with younger patients (Roos et al., 1995). OA represents joint failure and changes in any of the tissues in the knee joint can contribute to OA. Muscle weakness, reduced proprioception, and varus- valgus laxity may contribute to the development of knee OA, and these factors could certainly be expected to be involved in the effect of knee OA on physical function (Rymer et al., 1997).

Table 4: Selected risk factors for the occurrence and progression of osteoarthritis in knees, hips, and hands

	Knee	Hip	Hand
Occurrence	Age, sex, physical activity, body-mass index (including obesity), intense sport activities, quadriceps strength, bone density, previous injury, hormone replacement therapy (protective), vitamin D, smoking (protective or deleterious), malalignment (including varus and valgus), genetics	Age, physical activity, body-mass index (including obesity), previous injury, intense sport activities, genetics (including congenital deformities)	Age, grip strength, occupation, intense sport activities, genetics
Progression	Age, body-mass index (including obesity), vitamin D, hormone replacement therapy (protective), malalignment (including varus and valgus), chronic joint effusion, synovitis, intense sport activities, subchondral bone oedema on MRI	Age, symptomatic activity, sex, intense sport activities	Unknown

2.3.4 BODY MASS INDEX

High BMI is a modifiable risk factor for OA and may increase the risk of OA through a combination of metabolic factors and increased mechanical loading on the weight-bearing joints (Felson & Zhang, 1998).

2.3.5 ENVIRONMENTAL FACTORS

The role of environmental factors such as alcohol consumption, smoking and nutrition in the development of osteoarthritis has been examined in several studies. Alcohol consumption is consistently shown to be unrelated to the risk of OA or joint pain (Juhakoski, Heliovaara, Impivaara, Kroger, Knekt, … & Lauren, 2009).

2.4 PROGNOSTIC FACTORS

Alschuler, Molton, Jensen and Riddle (2013) have studied on the use of pain coping skills as prognostic factors for changes in pain and functional disability among knee OA patients. Results revealed that there is a significant relationship between praying or hoping, increased behavioral activities and pain catastrophizing as prognostics of pain outcomes.

2.5 PREVENTION

There are currently no effective pharmaceutical treatments for patients suffer from pain and functional disability. Furthermore, the surgical options are expensive. Therefore, prevention strategies are important in the development and progression of OA. There are two main goals in the pharmacotherapy of OA, first is to decrease the severity of the symptoms, mainly represented by pain and limitation of motion, and second is to control the progression of disease. At the same time, improving the patient's quality of life and minimizing the complications of treatment should focuses on the psychosocial factors that contributed to arthritis burden. The non-operative management of OA is the first line treatment for all patients with knee osteoarthritis.

Harris, Loxton, Sibbritt and Byles (2012) studied on the influences of psychosocial factors which contributed to arthritis burden. The findings from 10, 509 ageing cohort of Australian women revealed that women with arthritis had chronic stress perception, anxiety disorder and poor mental health. Therefore, interventions aimed at importance of psychological needs of women to improve general health are important.

A few studies have examined the relationships among self- efficacy, pain coping strategies, depression, pain intensity and outcomes in patients with chronic pain. Harrison (2004) has done a study on the influence of pathology, pain, balance and self- efficacy on the functional performance among women with osteoarthritis of the knee. Results revealed that pathology was not correlated with functional performance ($p=0.27$). However, level of pain and self- efficacy in pain management was correlated with functional self- efficacy and functional difficulty. Furthermore, functional self- efficacy was correlated with level of pain, functional difficulty and functional performance among women with osteoarthritis of the knee. Turner, Ersek and Kemp (2005) reported that self- efficacy in pain management was highly correlated with disability function, pain coping strategies and depression ($p < 0.001$). However, self- efficacy in pain management was not statistically significant with pain intensity.

Depressive symptoms are significant affect knee pain in persons (mean age of 61 years) with knee pain in a community based study (Riddle, Kong & Fitzgerald ,2011). Harris, Loxton, Sibbritt and Byles (2012) have examined that chronic stress, anxiety and poor mental health are significant increase in having arthritis amongst 10, 509 Australian women (mean age of 59 years). Health- related quality of life is an important psychometric measurement in 154 patients (mean age of 65.6 years) with symptomatic knee OA based on the American College of Rheumatology criteria (Zakaria, Bakar, Hasmoni, Rani & Kadir, 2009).

2.5.1 PRIMARY PREVENTION

Primary prevention strategies are important in identifying factors that increase the risk of OA and to prevent OA from occurring. Risk factors such as gender, age, overweight, nutritional factors, occupational factors, sports participation and quadriceps weakness have been shown to play an important role in the development and progression of OA. Some of these risk factors provide a viable approach for reducing the progression and symptoms of OA. The Centers for Disease Control and Prevention and the Arthritis Foundation (2010) highlighted the importance of injury prevention, weight management and healthy nutrition which are able to prevent disease, injury or disability, or to promote health in a group of persons that without OA.

Being overweight was the single most important potentially modifiable risk factor for development of lower limb osteoarthritis. It was also proven to reduce the risk of symptomatic knee osteoarthritis (Felson, 1992). Higher body mass index (BMI) is not only a major risk factor for diabetes, cardiovascular disease, cancer and premature death but is also implicated as a cause of OA, particularly of the knee (Felson, 1990). Murphy, Schwartz, Helmick, Renner, Tudor, … and Jordan (2008) identified that person who maintain an ideal weight will not easily to develop symptomatic knee OA as they grow older.

Weight loss among people with knee OA has been shown to improve in physical function, self-reported disability, pain symptoms and quality of life. Overweight and obese adults with knee OA who lose one pound gain a four-fold reduction in knee joint load (Messier, Gutekunst, Davis & DeVita, 2005).

In a case control study, they found that patients with OA were 3.5 times more likely than controls who are obese at the age of 20 (Kohatsu et al., 1990). Women who lost 11 pounds decreased their risk for knee OA by 50% (Felson et al., 1992). The other study done by Willims et al. (1981) showed that weight loss resulted in significant reduction of symptomatic OA. Thus, weight loss in overweight patients with OA can have a beneficial effect on the symptoms and progression of the disease. Weight management as primary prevention strategy for the prevention and treatment of OA is underscore the potential public health importance.

Traumatic injury is one of the risk factor for the later development of OA. It contributes 12% of total OA prevalence (Brown, Johnston, Saltzman, Marsh & Buckwalter, 2006). The injuries such as anterior cruciate ligament (ACL) ruptures and ankle fractures are related to the incident of OA (Valderrabano, Hintermann, Horisberger & Fung, 2006). Balance training and other forms of dynamic exercise have been shown to reduce the frequency and rate of falling among older adults. Therefore, it is important to include in the components of a comprehensive physical activity program for older adults (Gillespie, Robertson, Gillerpie, Lamb & Gates, 2009).

2.5.2 SECONDARY PREVENTION

Secondary prevention aims to assure early diagnosis and treatment of OA, even before a person has been diagnosed with symptomatic OA. Therefore, effective interventions are undertaken to minimize the health consequences of the disease.

2.5.3 TERTIARY PREVENTION

Once a person has been diagnosed with OA, tertiary prevention strategies aim to reduce the complications of the disease, such as reducing pain and functional disability, and improving quality of life. Self- management program such as weight control, physical activity and education, cognitive behavioural therapy interventions, rehabilitation services, medical management, and surgical treatments are recommended according to the anatomical distribution, the phase and the progression rate of the disease. Hunter and Felson (2006) have recommended the hierarchy of OA treatment based on the severity of OA symptoms, (1) Non-pharmacological management including education, exercise, weight loss, appropriate footwear; (2) Non- pharmacological management including physiotherapy, braces, and begin pharmacological with simple analgesics such as paracetamol; (3) pharmacological management including NSAIDS, opiods, and aspirate are inject if effusion is present; and (4) Surgery including osteotomy, total joint replacement.

2.5.3.1 NON- PHARMOCOLOGICAL MANAGEMENT

2.5.3.1a SELF- MANAGEMENT PROGRAM

Education is important for patients with knee OA. The arthritis self- management program, a community educational program in United States reported improvement in level of physical activity, better cognitive pain management and decreased in pain (Lorig, 1981). However, meta-analysis evidences suggests only weak effect of health education on pain and functional limitation.(Warsi, 2003).

Coleman, Briffa, Conroy, Prince, Carroll and McQuade (2008) examined that education program showed significant improvement in knee pain, knee stiffnes, physical function of the knee and health- related quality of life over 12-months follow up amongst 79 patients (mean age of 66 years) with knee OA based on the diagnosis by the patients' medical practitioner.

There were few studies on the effectiveness of psychological interventions on knee osteoarthritis pain, pain- related disability and psychological factors, including emotions (e.g. depression, anxiety, psychological distress), cognitions (e.g. self-efficacy for pain control, helplessness, pain catastrophising, pain acceptance, resilient coping) and social context (e.g. pain-related social interactions, pain communication, social support) variables. Emery et al. (2006) have shown that coping skills training (CST) which is one of the psychological intervention had significantly increased nociceptive flexion reflex (NFR) among knee osteoarthritis patients ($F(1, 60) = 16.19$, $p < 0.001$). A randomized controlled study on the effectiveness of spouse- assisted coping skills training and exercise training in patients with osteoarthritis of the knee showed significant improvements in self-efficacy as compared to exercise training alone or standard care alone ($F(3, 57) = 4.37$, $p = 0.008$) (Keefe et al., 2004).

A recent study on the effectiveness of group cognitive behavioural therapy intervention among knee osteoarthritis patients was studied to reduce maladaptive pain coping and to increase self- management of knee osteoarthritis pain and arthritis- related disability (Helminen, Sinikallio, Valjakka, Väisänen-Rouvali, & Arokoski, 2013).

2.5.3.1b PHYSICAL AND OCCUPATIONAL THERAPY/ AEROBIC AND MUSCLE-STRENGTHENING EXERCISES

A randomized controlled trial on the effectiveness of manual physical therapy and exercise in patients with osteoarthritis of the knee showed significant improvement in reducing knee pain, stiffness, and physical disability function, and enhancing walking distance (Deyle, Henderson, Matekel, Ryder, Garber & Allison, 2000).

Perlman, Ali, Njike, Hom, Davidi, … and Katz (2012) done a study on 125 patients with knee OA based on radiographic evidence of American College of Rheumatology criteria. The intervention group received an eight weeks of Swedish massage (30 or

60 minute weekly or biweekly). Results showed improvement knee pain and functionality in the 60- minute (once weekly) massage groups over six- months follow- up.

A Malaysian study on the effectiveness of passive joint mobilization has shown significant reduction in knee pain among 22 patients (mean age of 61.4 years) with sub- acute or chronic OA (based on clinically and radiographically evidence) (Azlin & Lyn, 2011).

Therapeutic exercise program can improve the functional ability and pain knee OA (Ytterberg, 1994) Although the exact exercise intensity best for OA patients still remained unclear, aerobic and muscle- strengthening exercises generally was consider the core aspect in management of OA patients (Roddy, 2005).

Transcutaneous electrical nerve stimulation (TENS) is the most commonly used form of electro analgesia in the treatment of early arthritis pain in the knee. Clinically TENS is applied at varying frequencies, intensities, and pulse durations of stimulation. When high-frequency TENS is applied at low intensity it is referred to as conventional TENS. The analgesic effect is immediate. Pain relief lasts while the stimulus is turned on, but it usually abates when the stimulation stops.

In contrast, when low-frequency TENS is applied at high intensity so that a motor contraction is produced, it is referred to as acupuncture-like TENS (AL-TENS). Although this method may be more effective than conventional TENS, it is uncomfortable, and many patients do not tolerate it. The mechanism of the analgesia produced by TENS is best explained by the gate control theory of pain. A Cochrane review (2000) of seven studies (148 patients received TENS and 146 patients received placebo treatment) concluded that active TENS and AL-TENS treatment for at least 4 weeks effectively reduce pain and knee stiffness (Osiri et al., 2000).

Electromagnetic fields (EMF) have been postulated as a treatment for early OA since their use has stimulated cartilage growth in vitro. EMF causes physical stress on bone leading to the generation of piezoelectc potentials. These then act as transduction signals to promote bone formation and stimulates chondrocytes to increase proteoglycan synthesis. A Cochrane review (2002) by Hulme et al. (2002) investigating the clinical use of EMF showed statistically significant improvements in function and pain in OA, but it remained unclear as to whether this improvement was noticeable clinically. There are no reported side effects of this therapy.

Ultrasound uses mechanical vibrations at frequencies between 1.0 and 3.0MHz. As the energy within the sound wave is passed to a material, it causes oscillation of the particles of that material thus generating heat. In addition to thermal changes, the vibration of the tissues may have a separate mode of action. Pulsed ultrasound has been recommended for acute pain and inflammation, and continuous ultrasound for the treatment of stiffness.

Low level laser therapy (LLLT) is a light source that generates extremely pure light, of a single wavelength. The effect is not thermal, but rather related to photochemical reactions in the cells. A study on meta-analysis revealed that the pooled results show no effect of 1 month of LLLT on pain or overall patient-rated assessment of disease activity. Lower dosage of LLLT was found as effective as higher dosage for reducing pain and improving knee range of motion (Brossea et al., 2004).

2.5.3.1c WEIGHT CONTROL

Being overweight was the single most important potentially modifiable risk factor for development of lower limb osteoarthritis. It was also proven to reduce the risk of symptomatic knee osteoarthritis (Felson, 1992).

2.5.3.1d ORTHOTIC DEVICES

Knee braces improved the proprioception and mechanical support of knee. This helped in pain relief by altered the mal-aligned motion of knee. Walking aids can reduce pain in patients with knee OA. Patients should be given instruction in the optimal use of a cane or crutch in the contra-lateral hand. Frames or wheeled walkers are often preferable for those with bilateral disease (Chan et al., 2005).

2.5.3.2 PHARMOCOLOGICAL THERAPY

2.5.3.2a ORAL DRUG THERAPY

Non- steroidal anti-inflammatory drug(s) (NSAIDs) and Celebrex (celecoxib), COX-2 inhibitors have been shown to be equally effective in the symptomatic treatment of OA, but have no lasting effect after 2 years (Simon, Lanza et al., 1998). Compared to COX-2 inhibitors, the most important drawback of NSAIDs is the increased risk of upper gastrointestinal bleeding. Risk factors for upper gastrointestinal bleeding in patients treated with NSAIDs include age 65 or older, history of peptic ulcer disease or previous upper gastrointestinal bleeding, concomitant use of oral corticosteroids or anticoagulants and possibly smoking and alcohol consumption.

Additionally, the possible side-effects of these drugs and effect on cartilage metabolism should be taken into account as studies suggest that some NSAIDs, such as Naproxen, Ibuprofen and Indomethacin; inhibit matrix synthesis (Chen et al., 2007).

El Hajjaji et al. (2003) have shown that Celecoxib (COX-2-Inhibitor) has a beneficial effect on cartilage matrix metabolism. A consensus exists that the choice between NSAIDs and COX- 2 inhibitors should be made based on the evaluation of risk factors for upper gastrointestinal bleeding, as to date COX-2 inhibitors are more expensive than most NSAIDs.

2.5.3.2b NUTRITIONAL SUPPLEMENTS

Public interest in the use of glucosamine for OA, gained momentum after the 1997 publication of 'The Arthritis Care' which described its ability to provide symptomatic relief with few side effects. Glucosamine is the hexosamine constituent of keratan sulphate, the glycosaminoglycan found in hyaline cartilage along with chondroitin sulphate. Glycosaminoglycans are the major constituents of proteoglycan molecules of hyaline cartilage. The proteoglycan moiety gives hyaline cartilage its visco- elastic property and allows it to act as a cushion.

Glucosamine and chondroitin sulphate are thought to influence cartilage metabolism as suggested by in- vitro models and animal studies. Proponents have promoted glucosamine and chondroitin sulphate as chondro- protective dietary supplements with matrix modifying properties. Both agents have more than one mechanism of action. They may stimulate production of cartilaginous matrix and down regulate the production of proteolytic enzymes. They may also improve synovial fluid characteristics and may have anti-inflammatory properties. It remains unclear as to whether these effects are physiologically significant

A Cochrane review (2005) of eight well-controlled studies failed to show benefit of glucosamine for pain and Western Ontario and McMaster Universities (WOMAC) function (Towheed et al., 2005). Collective analysis of 20 randomized control trials (RCTs) (including those without adequate allocation concealment) with 2570 patients found that glucosamine showed significant improvement in pain and over placebo. WOMAC outcomes did not achieve statistical significance. Reviews done at 6 weeks showed a decrease in pain and improved function, but studies reported at 3 months showed little difference. Two RCTs showed that a glucosamine preparation was able to slow radiological progression of OA of the knee over a 3- year period. However, the reliability of radiographic assessment of the progression of OA remains controversial (Mazzuca et al., 2004).

The reported minor side effects of glucosamine include gastro-intestinal complaints, headache, leg pain, edema, and itching. However, it is generally well tolerated (Hathcock et al., 2007). Evidence based on animal studies suggests that glucosamine may affect the metabolism of glucose and insulin and hence its use in diabetics may be restricted until human studies are available (Anderson et al. 2005); (Dostrovsky et al. 2011). Clegg, Reda, Harris, Klein, O'Dell, … and Williams (2006) reported that combined treatment of glucosamine and chondroitin are significantly more effective in reducing pain than glucosamine and chondroitin sulfate alone in the intervention group over 24 weeks follow- up amongst 1583 patients (≥ 40 years) with symptomatic knee OA (diagnosed with clinical evidence and radiographic evidence).

2.5.3.2c VISCO- SUPPLEMENTATION

Originally described by Balazs and Denlinger in the 1960s, it was first used (intravenously) to treat racehorses with traumatic arthritis. Hyaluronic acid is a component of normal synovial fluid and an important contributor to joint homeostasis. In OA, both the concentration and the molecular weight of hyaluronic acid are

decreased, which reduces the visco-elasticity of synovial fluid. The exact mechanism of action of visco supplementation is unclear.

The actual period that the injected hyaluronic acid stays within the joint space is in the order of hours to days, but the time of clinical efficacy is several months. Other postulated mechanisms to explain the long- lasting effect of visco- supplementation include possible anti-inflammatory and analgesic properties or stimulation of in-vivo hyaluronic acid synthesis by the exogenously injected hyaluronic acid.

Visco- supplemention involves the use of hyaluron and hylan derivatives. Hylans are cross- linked hyaluronic acids, which gives them a higher molecular weight and increased visco- elastic properties. The higher molecular weight of hylan is thought to make it elective and to make it reside longer in the joint space (i e., slower resorption).

The recommended injection schedule is one injection per week for 3 – 5 weeks for various commercial preparations although higher molecular weight preparations can be given as a single injection. Repeat courses of visco- supplementation can be performed after 6 months and are shown to be effective in patients who had a previous favorable clinical response. If effusion is present, aspiration of the joint is recommended before the injection to prevent dilution of the injected hyaluronic acid.

A meta-analysis (2004) on the therapeutic effects of hyaluronic acid on OA knee found significant improvements in pain and functional outcome. Patients older than 65 years of age and those with the most advanced radiographic stage of OA (complete loss of joint space) were found to be less likely to benefit from visco-supplementaion therapy (Wang et al., 2004).

A more recent Cochrane review (2005) also concluded that visco- supplementation is an effective treatment for OA of the knee with beneficial effects on pain, function and patient global assessment. The maximal improvement in symptoms occurred between 5 and 13 weeks following the injection (Bellamy et al., 2005).

2.6 PSYCHOLOGICAL FACTORS IN PERSISTENT PAIN

Harris, Loxton, Sibbritt and Byles (2012) studied on the influences of psychosocial factors which contributed to arthritis burden. The findings from 10, 509 ageing cohort of Australian women revealed that women with arthritis had chronic stress perception, anxiety disorder and poor mental health. Therefore, interventions aimed at importance of psychological needs of women to improve general health are important.

A few studies have examined the relationships among self- efficacy, pain coping strategies, depression, pain intensity and outcomes in patients with chronic pain. Harrison (2004) has done a study on the influence of pathology, pain, balance and self- efficacy on the functional performance among women with osteoarthritis of the knee. Results revealed that pathology was not correlated with functional performance (p=0.27). However, level of pain and self- efficacy in pain management

was correlated with functional self- efficacy and functional difficulty. Furthermore, functional self- efficacy was correlated with level of pain, functional difficulty and functional performance among women with osteoarthritis of the knee. Turner, Ersek and Kemp (2005) reported that self- efficacy in pain management was highly correlated with disability function, pain coping strategies and depression ($p < 0.001$). However, self- efficacy in pain management was not statistically significant with pain intensity. Costa, Maher, McAuley, Hancock and Smeets (2011) determined that self-efficacy in pain management mediated the relationship between pain intensity and disability function among patients (mean age of 43 years) with acute low back pain in primary care.

2.7 COGNITIVE BEHAVIORAL THERAPY

There were few studies have studied the effectiveness of the psychological intervention on knee osteoarthritis pain. However, cognitive- behavioral therapy (CBT) has become a first-line psychosocial treatment for individuals with chronic pain (Ehde, Dillworth, & Turner, 2014). A recent randomized controlled trial study done by Helminen et al. (2013) on the effectiveness of group cognitive behavioural intervention on knee osteoarthritis pain for the duration of 12 months follow- up had addressed the importance of cognitive behavioural therapy intervention to the current conservative treatment care for knee osteoarthritis related pain. However, cognitive behavioural therapy was not widely available for the treatment for knee osteoarthritis pain.

A randomized controlled trial study on the effectiveness of self- management education program based on social cognitive theory and cognitive behavioural therapy was carried out amongst 146 knee osteoarthritis patients. Results revealed that pain and functional disability were reduced significantly in intervention group as compared to control group over a six- months follow- up period (Coleman et al., 2012).

CHAPTER 3 METHODOLOGY

3.0 STUDY LOCATION

This study will be conducted at Orthopaedic Clinic in government hospital, namely Hospital Putrajaya and Hospital Serdang.

3.1 STUDY DESIGN

This study is a 2 arm randomized clinical trial involving diagnosed knee osteoarthritis patients who are eligible to the study from February 2015 to July 2015 at Hospital Putrajaya and Hospital Serdang, Selangor, Malaysia, will be conducted. The sample population will be randomly divided into experimental and control groups by applying block randomization technique in a ratio 1:1. Random allocation will consider and eliminate the possible bias based on the socio- demographic characteristics of the patients. The experimental group will receive Cognitive Behavioral Treatment (CBT) provided with The Knee Book (Ministry of Health, 2013) added to standard routine care, whereas the control group will receive standard routine care only provided with The Knee Book and follow the same schedule of assessment as the experimental group. For standard routine care, patients need to attend their clinic and physiotherapy session as usual based on their fixed appointment date. A baseline measurement on patients' knee pain intensity, functional disability, psychological distress (depression, anxiety and stress), fear- avoidance beliefs, pain catastrophising and self- efficacy in pain management will be collected on respondents in both intervention and control group prior to the introduction of CBT. The efficacy endpoint will then be measured immediately, one month and six months after intervention. Figure 3.1 shows the schematic diagram of the study design.

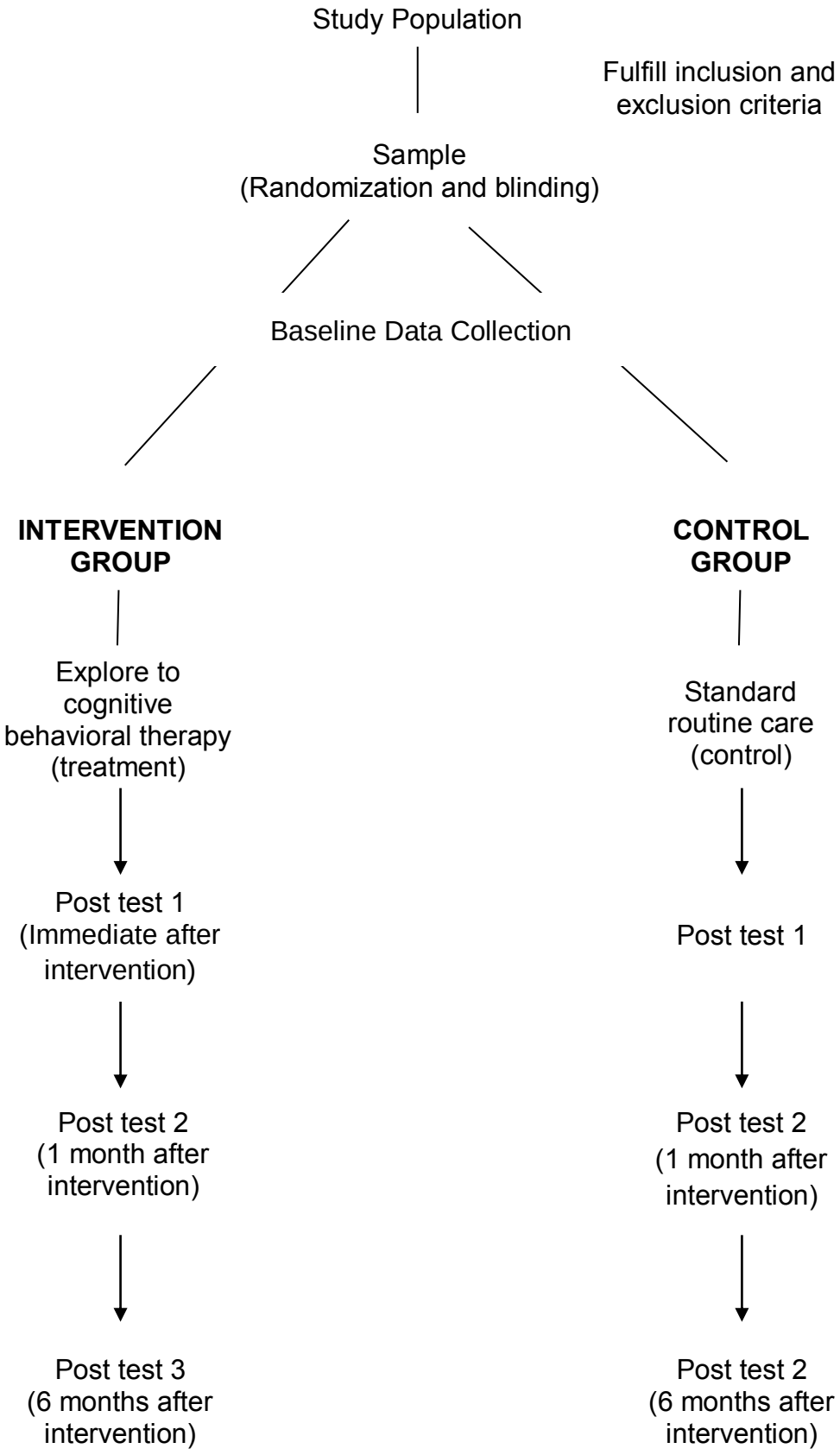

Study Population
Fulfill inclusion and exclusion criteria
Sample
(Randomization and blinding)
Baseline Data Collection
INTERVENTION GROUP
CONTROL GROUP
Explore to cognitive behavioral therapy (treatment)
Standard routine care (control)
Post test 1 (Immediate after intervention)
Post test 1
Post test 2 (1 month after intervention)
Post test 2 (1 month after intervention)
Post test 3 (6 months after intervention)
Post test 2 (6 months after intervention)

Figure 3 Schematic diagram of the study design

3.2 STUDY POPULATION

The sample population is knee osteoarthritis patients assessed and found to be eligible to this study.

3.3 INCLUSION CRITERIA

- Patients with osteoarthritis of the knee who are aged 35 to 75 years.
- Patients who had been diagnosed with primary knee osteoarthritis on the basis of medical evaluation (knee pain for most days of previous month and bony enlargement of the knee) and radiographic examination (Kellgren-Lawrence) of grade 2 or more.
- Patients who had an average pain intensity of 40 or more on a 100mm visual analogue scale in the 7 days before baseline assessment.
- Written informed consent obtained from patient

3.4 Exclusion Criteria

- Patients with knee pain which caused by conditions other than knee osteoarthritis.
- Patients who had knee replacement surgery of the affected knee in the past year.
- Patients who had undergone psychological treatment or any other clinical study during the past 12 months.
- Patients who had been diagnosed with mental disorder, pregnancy or breastfeeding.

3.5 SAMPLE SIZE ESTIMATION

The formula for calculating sample size in hypothesis testing by comparing means will be used (Lameshow et al., 1990):

$$n = \frac{2\delta^2[Z1\text{-}\alpha/2 + Z1\text{-}\beta]^2}{(\mu_1 - \mu_2)^2} \quad \text{(For continuous variable)}$$

Where:
(a) Using an assumed expected outcome of **knee pain intensity decrease** within 6 months of therapy,

δ = estimated standard deviation (assumed to be equal for each group) is 10.85 (Wideman et al., 2014)
μ_1 = estimated mean knee pain score for at least 6months is 16.54
μ_2 = estimated mean baseline knee pain score is 20.68 (Wideman et al., 2014)

Z1-α/2 = standard error when α = 0.05 (95% Confidence Interval) = 1.96
Z1-β = standard error associated with power = 0.842 (β = 0.20)
Power (1-β) = 80%

Effect size (ESμ) = $\mu_1 - \mu_2 / \delta$ where δ = pooled standard deviation = $\sqrt{\delta_1 + \delta_2 / 2}$
ESμ = 0.38 which corresponds to n = 109

Based on the above formula, the required minimum sample size for each group, n is **109**. To factor in 20% attrition, total required per group will be **131;** hence a total of **262** patients will be required for the sample in both groups.

(b) Using an assumed expected outcome of **functional disability decrease** within 6 months of therapy,

δ = estimated standard deviation (assumed to be equal for each group) is 35.61 (Wideman et al., 2014)
μ_1 = estimated mean functional disability score for at least 6 months is 59.50
μ_2 = estimated mean baseline functional disability score is 74.38 (Wideman et al., 2014)

Z1-α/2 = standard error when α = 0.05 (95% Confidence Interval) = 1.96
Z1-β = standard error associated with power = 0.842 (β = 0.20)
Power (1-β) = 80%

Effect size (ESμ) = $\mu_1 - \mu_2 / \delta$ where δ = pooled standard deviation = $\sqrt{\delta_1 + \delta_2 / 2}$
ESμ = 0.42 which corresponds to n = 90

Based on the above formula, the required minimum sample size for each group, n is **90**. To factor in 20% attrition, total required per group will be **108;** hence a total of **216** patients will be required for the sample in both groups.

(c) Using an assumed expected outcome of **depression level decrease** within 6 months of therapy,

δ = estimated standard deviation (assumed to be equal for each group) is 5.83 (Dear et al., 2013)
μ_1 = estimated mean depression score for at least 6 months is 9.65
μ_2 = estimated mean baseline depression score is 12.06 (Dear et al., 2013)

Z1-α/2 = standard error when α = 0.05 (95% Confidence Interval) = 1.96
Z1-β = standard error associated with power = 0.842 (β = 0.20)
Power (1-β) = 80%

Effect size (ESμ) = $\mu_1 - \mu_2 / \delta$ where δ = pooled standard deviation = $\sqrt{\delta_1 + \delta_2 / 2}$
ESμ = 0.41 which corresponds to n = 92

Based on the above formula, the required minimum sample size for each group, n is **92**. To factor in 20% attrition, total required per group will be **111;** hence a total of **222** patients will be required for the sample in both groups.

(d) Using an assumed expected outcome of **anxiety level decrease** within 6 months of therapy,

δ = estimated standard deviation (assumed to be equal for each group) is 5.1 (Wiles et al., 2013)
μ_1 = estimated mean anxiety score for at least 6 months is 9.44
μ_2 = estimated mean baseline anxiety score is 11.80 (Wiles et al., 2013)
Z1-α/2 = standard error when α = 0.05 (95% Confidence Interval) = 1.96
Z1-β = standard error associated with power = 0.842 (β = 0.20)
Power (1-β) = 80%

Effect size (ESμ) = $\mu_1 - \mu_2 / \delta$ where δ = pooled standard deviation = $\sqrt{\delta_1 + \delta_2 / 2}$
ESμ = 0.46 which corresponds to n = 74

Based on the above formula, the required minimum sample size for each group, n is **74**. To factor in 20% attrition, total required per group will be **89;** hence a total of **178** patients will be required for the sample in both groups.

(e) Using an assumed expected outcome of **fear- avoidance beliefs decrease** within 6 months of therapy,

δ = estimated standard deviation (assumed to be equal for each group) is 6.2 (Lamb et al., 2010)
μ_1 = estimated mean fear- avoidance beliefs score for at least 6 months is 11.20
μ_2 = estimated mean baseline fear- avoidance beliefs score is 14 (Lamb et al., 2010)
Z1-α/2 = standard error when α = 0.05 (95% Confidence Interval) = 1.96
Z1-β = standard error associated with power = 0.842 (β = 0.20)
Power (1-β) = 80%

Effect size (ESμ) = $\mu_1 - \mu_2 / \delta$ where δ = pooled standard deviation = $\sqrt{\delta_1 + \delta_2 / 2}$
ESμ = 0.45 which corresponds to n = 77

Based on the above formula, the required minimum sample size for each group, n is **77**. To factor in 20% attrition, total required per group will be **93;** hence a total of **186** patients will be required for the sample in both groups.

(f) Using an assumed expected outcome of **pain catastrophising decrease** within 6 months of therapy,

δ = estimated standard deviation (assumed to be equal for each group) is 1.14 (Cardosa et al., 2012)
μ_1 = estimated mean pain catastrophising score for at least 6 months is 2.20
μ_2 = estimated mean baseline pain catastrophising score is 2.75 (Cardosa et al., 2012)
Z1-α/2 = standard error when α = 0.05 (95% Confidence Interval) = 1.96
Z1-β = standard error associated with power = 0.842 (β = 0.20)
Power (1-β) = 80%

Effect size (ESμ) = $\mu_1 - \mu_2 / \delta$ where δ = pooled standard deviation = $\sqrt{\delta_1 + \delta_2 / 2}$
ESμ = 0.48 which corresponds to n = 68

Based on the above formula, the required minimum sample size for each group, n is **68**. To factor in 20% attrition, total required per group will be **82;** hence a total of **164** patients will be required for the sample in both groups.

(g) Using an assumed expected outcome of **self- efficacy in pain management increase** within 6 months of therapy,

δ = estimated standard deviation (assumed to be equal for each group) is 11.59 (Dear et al., 2013)
μ_1 = estimated mean self- efficacy in pain management score for at least 6 months is 32.28
μ_2 = estimated mean baseline self- efficacy in pain management score is 26.90 (Dear et al., 2013)
Z1-α/2 = standard error when α = 0.05 (95% Confidence Interval) = 1.96
Z1-β = standard error associated with power = 0.842 (β = 0.20)
Power (1-β) = 80%

Effect size (ESμ) = $\mu_1 - \mu_2 / \delta$ where δ = pooled standard deviation = $\sqrt{\delta_1 + \delta_2 / 2}$
ESμ = 0.46 which corresponds to n = 73

Based on the above formula, the required minimum sample size for each group, n is **73**. To factor in 20% attrition, total required per group will be **88;** hence a total of **176** patients will be required for the sample in both groups.

From the sample size estimation of the outcomes, the outcome measure of **knee pain intensity decrease** provides the **largest sample size** (**n = 131 per group**), and this will be used as the sample size for this research study.

3.6 SAMPLING FRAME

A list of all patients with knee osteoarthritis seen at orthopaedic clinic of each recruitment site (obtained from the medical records department of each hospital).

3.7 SAMPLING UNIT

Individual patients who are diagnosed with knee osteoarthritis, assessed and found to be eligible to the study based on medical examination and radiographic evidence criteria.

3.8 SAMPLING METHOD

Randomization and Masking

The participants will be recruited from Hospital Putrajaya and Hospital Serdang. Participants will be identified from physician and from searches of patient records

that had consulted for knee pain problem within the period of February 2015 to July 2015. Patients will be invited to give consent to be contacted by staff nurse for the permission to review patients' medical records for a diagnosis of knee osteoarthritis. Patients of each recruitment site who were eligible will be contacted by researcher to enquire their willingness to participate in this research study. Potentially eligible patients will be invited to attend a face-to-face appointment with a researcher to discuss participating in the trial and to confirm their eligibility. Ineligible patients (and those who declined participation) will be referred back to their general practitioner. Those eligible patients who agreed to participate in this study will be in a list and numbered. The number in the name list of all eligible knee osteoarthritis patients who were agreed for the participation will be randomly chosen by using draw logs until 300 names been obtained from the list, in order to ensure that no bias will be involved in patient recruitment.

The selected 300 names from the sampling frame will be randomly allocated to either of the experimental or control group based on block randomization method by using random allocation software after the written consent obtained and baseline questionnaire administered. Then, the names will be divided into 13 smaller subgroups (eight to ten each subgroup) in each intervention and placebo group. All the names in the subgroups will be contacted personally before every assignment by a hospital staff who will be blinded to group allocation.

Because of the nature of the treatments, the participants or those providing the interventions to treatment assignment will be unable to mask. However, research assistants who obtained and assessed outcomes will be masked to assignment. Besides, the research assistants for treatment and control group are different. The research assistants then will submit the outcome measurements at each time measure to the researcher who is undertaking the analysis task.

The full written informed consent will be obtained from patients at least seven days before the intervention start at waiting area of orthopedic clinic. They will be contacted personally by the hospital staff.

Procedures

Participants will be randomly assigned to Cognitive Behavioral Therapy in addition to standard routine care with the receiving of The Knee Book (Ministry of Health, 2013) or to standard routine care with The Knee Book provided after the written consent obtained and baseline questionnaire administered. Randomization using block randomization method will be implemented by an individual who is not involved in the recruitment process. Therefore, the allocation will be concealed in advance from the participants, researcher involved in recruitment, hospital staffs and therapists.

This research study will be suspended if more than 30 percent of the participants in treatment group show unexpected adverse event. The adverse event can be an increase in the knee pain intensity and emotional breakdown that will present before study enrollment. Serious adverse events were defined as death or admission to hospital, events attributable to the intervention, or events that caused unwarranted distress to a participant. However, the participants will be withdrawn from the study if any criminal illness detected which is non-identified psychiatric disorder. In addition, participants will be removed from the study if the female participant has

become pregnant during the study. The withdrawn participants will not be replaced in this study.

Participants do not have to stop taking medication which is prescribed by Orthopaedic doctor to participate in this study. There will be no rescue medication or procedure prepared but participants may contact with their medical professional in case of emergency. Participants will be asked for any discomfort symptoms along the study period.

3.9 STUDY VARIABLES

The main independent variable of this study is the cognitive- behavioural therapy intervention. There are other independent or predictor variables which include socio-demographic factors (age, gender, ethnicity, income, education, type of cohabitation, marital status, and distance from home to hospital), clinical characteristics (duration of symptomatic knee OA, cormobidity, treatment, and number of visits to general practitioner) and physical factor (body mass index).

Dependent or primary outcome variable of this study will be knee pain intensity, whereas functional disability and psychological outcome measures including depression, anxiety, fear- avoidance beliefs, pain catastrophising and self- efficacy in pain management level will be the secondary outcome.

3.10 OPERATIONAL DEFINITION OF TERMS/ VARIABLES

Cognitive behavioral therapy refers as one of the psychological interventions that promote realistic and optimistic attitude to illness, and it encourages patients to identify advantages after development of illness or to shift from a state of compromised function to improve function. (Sharpe & Curran, 2006)

Pain refers to sensory and emotional experience of discomfort. It is usually associated with actual or threatened tissue damage and is influenced by cognitive processes as well as the social and cultural context in which it is embedded. (Sarafino, 1994)

Functional disability refers to medical condition that captures impairments, activity limitations and participation restrictions in an individual's daily life. (Katz, 1983)

Psychological refers to the important role that cognitive factors (such as beliefs about pain control and feelings of helplessness), emotional factors (such as anxiety and depression), and behavioral factors (such as pain- related social interactions and social support) (Keefe & Somers, 2010).

3.11 INTERVENTION PROTOCOL

Both the intervention and control group will receive standard routine care throughout the study. They have to attend clinic and physiotherapy session as usual on their fixed appointment date. However, the control group will be provided with The Knee Book (Ministry of Health, 2013) and not receive further intervention. Patients in the intervention group will be provided with The Knee Book (Ministry of Health, 2013) and to receive a three sessions of group Cognitive Behavioral Therapy (CBT) (each session will be last for two and a half hour) bi- weekly. The session will be held in a group of eight to ten patients and supervised by an experienced senior clinical psychologist (Dr. Zubaidah) and a physiotherapist. The intervention will be delivered by physiotherapists and nurses who will receive at least one day of training specific to the trial from an experienced senior clinical psychologist with CBT experience. Each session will be audio- recorded with a written consent from the patients. Fidelity of the CBT session will be assessed for a random sample of recordings by the experienced psychologist with the Cognitive Therapy Rating Scale (Blackburn et al., 2000), which is a valid and reliable CBT rating scale. It has high internal reliability which is cronbach alpha 0.95 and good face validity. In addition, patients in the intervention group will assess the Client Satisfaction Questionnaire (CSQ-8) after the last session of group CBT received for measuring satisfaction with the therapy provided (Attkisson, 2012). It has high coefficient alpha (ranged from 0.83 to 0.93).

The outline of the Cognitive Behavioral Therapy module is prepared and modified based on Linton (2005). The CBT intervention will include an introduction, lecture (knowledge and insight), problem solving, skills training, homework assignments and a feedback of the session. An example of a knee OA patient will be applied throughout the intervention as a model for discussion and practice in problem solving, in order to enhance peer support and social bonding. Compliance with CBT is defined as attendance at the initial assessment and at least three subsequent sessions.

3.12 DATA COLLECTION PLAN

A baseline measurement on patients' knee pain intensity, functional disability, psychological distress (depression, anxiety, and stress), fear- avoidance beliefs, pain catastrophising and self- efficacy in pain management will be collected on respondents in both intervention and control group prior to the introduction of CBT. The efficacy endpoint will then be measured immediately, one month and six months after intervention. A structured self- administered questionnaire which is validated and reliable would be used as the data collection tool.

The questionnaire would consist of eight sections, sections A to H (A: Patients' socio- demographic and clinical characteristics; B: knee pain intensity; C: functional disability; D: Psychological distress (depression, anxiety and stress); E: Fear-avoidance beliefs; F: Pain catastrophising: G: Self- efficacy in pain management). The measures will include:

Knee injury and Osteoarthritis Outcome Score (KOOS) (Roos & Lohmander, 2003) will be adapted for the measurement of knee pain intensity and functional disability. The KOOS was developed as an extension of the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) with the purpose of evaluating short-term and long- term symptoms and function in subjects with knee injury and OA. It has 42 items in five separately scored subscales: pain, other symptoms, function in activities of daily living (ADL), function in sport and recreation and knee- related quality of life. However, only the pain, ADL and function in sport and recreation subscale will be adapted.

Depression Anxiety and Stress Scale (DASS) (Lovibond, 1995) will be adapted for the measurement of depression and anxiety outcomes. The DASS is a 21- item questionnaire which designed to measure symptoms of depression, anxiety and stress. Patients are required to rate the extent to which they have experienced in depression, anxiety and stress symptoms over the previous week.

Fear- avoidance Beliefs Questionnaire (FABQ) (Waddell, Newton, Henderson, Somerville, & Main, 1993). The FABQ is a 16- item questionnaire which had been modified to measure fear- avoidance beliefs among knee OA patients. It is designed to predict those patients that have high pain avoidance behaviour.

Pain- related Self Statements (PRSS) (Flor, Behle, & Birbaumer, 1993). The PRSS consists of two scales (coping strategies and catastrophising) which designed based on the concepts of the cognitive system and automatic thoughts where patients with severe pain will present these cognition symptoms. However, only pain catastrophising scale will be adapted in this study. The pain catastrophising scale consists of nine items. Higher scores indicate the presence of catastrophising thoughts.

Pain Self Efficacy Questionnaire (PSEQ) (Nicholas, 2007). The PSEQ is a 10 – item questionnaire which designed to assess the patients' confidence in performing activities while they were in pain.

3.12.1 ANTHROPOMETRIC MEASUREMENT

A standard clinical weighing scale and height scale will be used to measure the weight and height of each patient and recorded in kilograms and centimeters respectively. Body mass index (BMI) will be calculated using the formula weight in kilograms divided by height in meter square. BMI will be categorized into normal weight (BMI of less than 24.99), overweight (BMI of between 25.00 and 29.99) and obese (BMI of more than 30.00) as according to World Health Organization BMI classification.

3.13 DATA ANALYSIS PLAN

Data collected will be analyzed using Statistical Package for Social Sciences software (SPSS) version 21. Parametric tests (T-test, repeated measures ANOVA and correlation analysis) will be performed. P value for test of significance of results will be set at 0.05, alpha level (Type 1 error) at 0.05 (Confidence Interval of 95%). Analysis of outcomes will be by intention-to-treat where all participants who were randomized and entered the trial need to be included in the analysis in the condition to which they were assigned, regardless of whether they completed the trial, or may even have switched over to receive the incorrect treatment, per-protocol (complete case) analysis and chi square test.

3.13.1 INSTRUMENT TESTING

In the initial stage, the construct and items have been identified based on past literature.

3.13.2 PRELIMINARY VALIDATION OF TOOLS

For the preliminary validation of tools, 80 other respondents of similar demographic backgrounds with the study population who have knee osteoarthritis will be randomly selected to answer all items in the questionnaire.

3.13.3 RELIABILITY AND VALIDITY

Confirmatory factor analysis and measurement model in structural equation modelling by Analysis of Moment Structures software will be used to assess the reliability and validity after the data collection.

3.14 CONFIDENTIALITY AND SECURITY OF SOURCE DOCUMENTS AND STUDY DATA

All participants' information obtained in this study will be kept and handled in a confidential manner, in accordance with applicable laws and/or regulations. When publishing or presenting the study results, participants' identity will not be revealed without participants' expressed consent. Individuals involved in this study and in their medical care, qualified monitors and auditors, the sponsor or its affiliates and governmental or regulatory authorities may inspect and copy participants'

medical records, where appropriate and necessary. Participants are given access to the personal information and study data.

Data from the study will be archived for 10 years and may be transmitted outside the country for the purpose of analysis, but participants' identity will not be revealed at any time. The study data will be destroyed after period of storage

3.15 LIMITATIONS

Duration of follow- up of experimental and control groups is for a period of six months. However, a longer follow- up time may be more effective in determining the psychological outcomes of the study. The study is limited to two hospitals and hence may not be generalizable to all knee osteoarthritis patients in Malaysia.

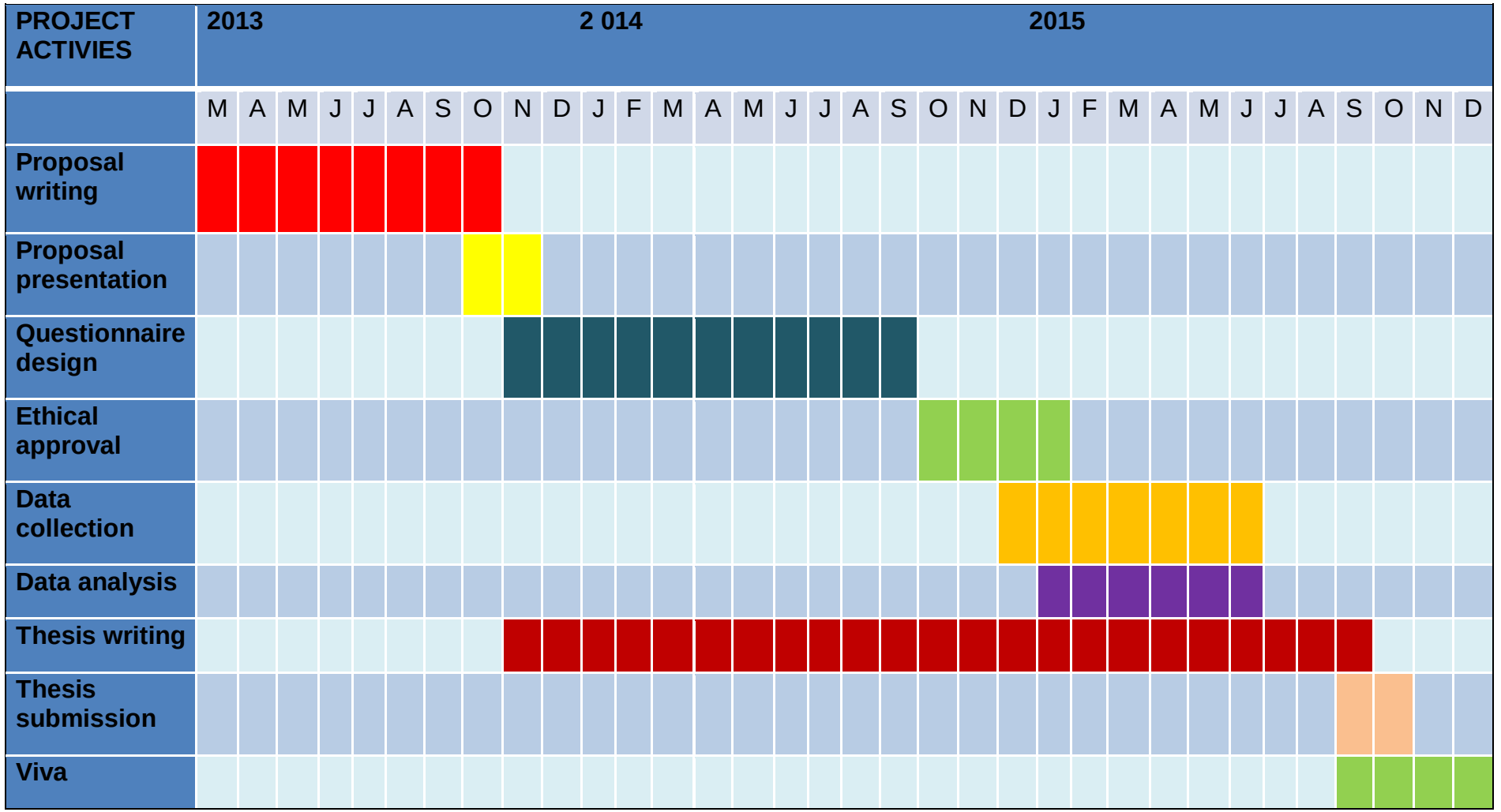
3.16 ETHICAL CONSIDERATIONS

The materials will be presented to the University of Putra Malaysia Ethics committee and the Malaysian Ministry of Health's Institutional Review and Ethics committee for review and approval. An informed consent would be obtained from each participant.

3.17 EXPECTED OUTCOME

This study would give an insight to if cognitive behavioral therapy (CBT) is an effective intervention for tertiary prevention on reducing the symptoms and progression of knee osteoarthritis in patients with knee osteoarthritis.

3.18 GANTT CHART



3.19 BUDGET

Budget details	Amount requested			
	Year 1 (RM)	Year 2 (RM)	Year 3 (RM)	Total (RM)
Salary and wages (1 Hospital-based research assistant and 1 Graduate Research Assistant)	NIL	6,000	NIL	6,000
Travelling and Transportation/ (Transportation costs to-and-from study site)	NIL	1,000	NIL	1,000
Rental	NIL	NIL	NIL	NIL
Research Materials & Supplies (Printing of Questionnaires, forms etc)	500	1,000	500	2,000
Maintenance and Minor Repair	NIL	NIL	NIL	NIL
Professional Services	NIL	2,000	NIL	2,000
Accessories and Equipment	NIL	NIL	NIL	NIL
TOTAL AMOUNT (RM)	500	10,000	500	**11,000**

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