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The effect of OsteoEze Gold™ on pain and functional ability in osteoarthritis of the knee

A research dissertation presented to the
Faculty of Health Sciences, University of Johannesburg, as partial fulfilment for the Masters Degree in Technology: Homoeopathy by

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Johannesburg, 2014
DECLARATION

I, Kim Elizabeth MacQuilkan, declare that this dissertation is my own, unaided work. It is being submitted in partial fulfilment for the Degree of Master Technology at the University of Johannesburg. It has not been submitted before any degree or examination at any Technikon or University.

Kim MacQuilkan

Date
ABSTRACT

Osteoarthritis (OA) is a musculoskeletal condition affecting the synovial joints of the body, most commonly the knee and hip (Colledge et al., 2010). OA is the most prevalent joint disorder worldwide (Ickinger & Tikly, 2010). The prevalence of OA of the knee in developing countries, including South Africa, is expected to increase due to the increase in obesity and life-expectancy (Woolf & Pfleger, 2003). OA not only impacts negatively on many areas of the patient’s personal life, but it also has a considerable impact on health care systems and cost to the patient (Lapsley et al., 2001; Majani et al., 2005). The two main complaints in patients suffering from OA of the knee are knee pain and decreased daily functionality, such as walking (Samson et al., 2007). The main aim of conventional treatment is pain reduction. This treatment does not prevent progression of the OA, and may have negative side-effects (Day & Graham, 2005). Treatments for OA, such as OsteoEze Gold™, may provide an effective and safer alternative.

The aim of this study is to determine the effect of OsteoEze Gold™ on pain and functional ability in osteoarthritis of the knee using the Intermittent and Constant Osteoarthritis Pain (ICOAP) scale: knee version (Appendix D) and the Short Physical Performance Battery (SPPB) test (Appendix E).

This was a 16-week study, conducted at the Homoeopathic Health Centre, Doornfontein campus (DFC), University of Johannesburg (UJ). The study was randomised, double blind placebo controlled, and matched pairs were utilised. Sixty-seven participants, who satisfied the inclusion and exclusion criteria, were recruited, and 48 of the participants completed the study. Participants were recruited by advertisements, placed in and around the UJ Homoeopathy Health Centre (with relevant permission given) and by word of mouth. The participants were split into two groups using matched pairs according to age, gender and severity of symptoms (Appendix H). The participants in group A received the OsteoEze Gold™ capsules, and the participants in group B received the placebo capsules. Each capsule of OsteoEze Gold™ contained 500mg glucosamine sulphate, 267mg of chondroitin sulphate, 50mg of vitamin C and 1mg of manganese. The OsteoEze Gold™ or the placebo capsules were distributed at the initial (week-0) and second (week-8) consultations. The participants were requested to
take one capsule three times a day. Participant compliance was monitored by a participant medication record (Appendix C) which was collected at the second (week-8) and final (week-16) consultations.

The participant’s vital signs were recorded at each consultation (week-0, week-8 and week-16) (Appendix F; Appendix G). Participants were evaluated using the ICOAP scale and SPPB test at the initial, second and final consultation. Subjective data, about the knee pain experienced by the participant and paracetamol usage, was obtained from the ICOAP scale. Objective data, about the participant’s functional ability, was obtained from the SPPB test.

The data from the ICOAP scale and SPPB test was analysed by STATKON. Frequencies, descriptives and cross-tabulations were applied to the data. A test for normality, the Shapiro-Wilk test, was utilized. The Mann-Whitney test was used to compare the placebo and medication groups (inter-group comparisons). Next comparisons within groups, over time (intra-group analysis), was carried out with the Friedman test. The Wilcoxon Signed Rank test was utilized to assess where in time the differences occurred.

The results of the ICOAP scale for the treatment group showed an improvement over the placebo group in reducing the severity of the constant osteoarthritic knee pain experienced by the participants (ICOAP section A). There was a significant reduction, when compared to the placebo group in the quantity of paracetamol used by the participants for their osteoarthritic knee pain (ICOAP section C) as well as a significant reduction overall in the knee pain associated with osteoarthritis of the knee (ICOAP total) in the treatment group. The improvement occurred throughout the 16-week study, with the most significant improvement occurring between the initial and second consultation. There were however no significant results for the treatment group in reducing the intermittent osteoarthritic knee pain experienced by the participants (ICOAP section B).

The results of the SPPB test showed an improvement for the treatment group over the placebo group in improving the functional ability of the participants. The participant’s ability to rise from sitting (the chair test) and walk (the gait test) improved significantly throughout the study. The largest improvement occurred between the second (week-8)
and last (week-16) consultations for the chair test, and between the initial (week-0) and second (week-8) consultations for the gait test.

It can be concluded that OsteoEze Gold™ was more effective than placebo in the treatment of pain and functional ability in osteoarthritis of the knee. The effect of OsteoEze Gold™ was observable from the 8-week mark, and continued to be effective throughout the 16-week trial.
DEDICATION

I dedicate this research dissertation to my parents, Yvonne and Neil MacQuilkan, and my sister, Pamela MacQuilkan. Thank you for your constant support, love and encouragement, not only throughout this degree, but in everything I do.
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# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>DECLARATION</td>
<td>i</td>
</tr>
<tr>
<td>AFFIDAVIT</td>
<td>ii</td>
</tr>
<tr>
<td>ABSTRACT</td>
<td>iii</td>
</tr>
<tr>
<td>DEDICATION</td>
<td>vi</td>
</tr>
<tr>
<td>ACKNOWLEDGEMENTS</td>
<td>vii</td>
</tr>
<tr>
<td>TABLE OF CONTENTS</td>
<td>viii</td>
</tr>
<tr>
<td>LIST OF APPENDICES</td>
<td>xiv</td>
</tr>
<tr>
<td>LIST OF FIGURES</td>
<td>xv</td>
</tr>
<tr>
<td>LIST OF TABLES</td>
<td>xvi</td>
</tr>
</tbody>
</table>

## CHAPTER ONE – INTRODUCTION

1.1 Problem statement 1
1.2 Aim of the study 1
1.3 Benefits of the study 2
1.4 Hypothesis 2
1.5 Null hypothesis 2

## CHAPTER TWO – LITERATURE REVIEW

2.1 Osteoarthritis 3
2.1.1 Definition of osteoarthritis 3
2.1.2 Prevalence of osteoarthritis 3
2.1.3 Impact of osteoarthritis of the knee 4
   2.1.3.1 Impact of osteoarthritis on the patient 4
2.3.4.6 Psoriatic arthritis 26
2.3.5 Complications of osteoarthritis of the knee 26
  2.3.5.1 Calcium pyrophosphate deposition disease (CPDD) 26
  2.3.5.2 Baker’s cyst 27
2.3.6 Special investigations for osteoarthritis of the knee 27
  2.3.6.1 Blood tests 27
  2.3.6.2 Radiology 28
  2.3.6.3 Synovial fluid analysis 28

2.4 Evaluation tools for osteoarthritis 28
  2.4.1 Effect of osteoarthritis on functional ability 28
  2.4.2 The Short Physical Performance Battery (SPPB) test 29
  2.4.3 Pain and lifestyle scales 29
    2.4.3.1 The measure of Intermittent and Constant Osteoarthritis Pain (ICOAP) scale: knee version 29
    2.4.3.2 The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) 30
    2.4.3.3 Other scales and indexes for evaluating osteoarthritis 30

2.5 Treatment of osteoarthritis of the knee 31
  2.5.1 Conventional treatment 31
  2.5.2 Surgery 32
  2.5.3 Alternative treatment 33
    2.5.3.1 Herbal preparations 33
    2.5.3.2 Nutraceuticals 34
    2.5.3.3 Physical therapies 36
    2.5.3.4 Homoeopathy 36

2.6 OsteoEze Gold™ 37
  2.6.1 Chondroitin sulphate 38
  2.6.2 Glucosamine sulphate 39
  2.6.3 Vitamin C and manganese 40
CHAPTER THREE – METHODOLOGY

3.1 Research sample 42
3.2 Recruitment 42
3.3 Inclusion and exclusion criteria 42
   3.3.1 Inclusion criteria 42
   3.3.2 Exclusion criteria 43
3.4 Research design and procedure 43
3.5 Medication administration 47
3.6 Reliability and validity measures 47
3.7 Data collection 48
3.8 Statistical analysis 48
3.9 Ethics 49

CHAPTER FOUR – RESULTS

4.1 Introduction 50
4.2 Statistical tests 50
   4.2.1 Cross tabulations and descriptives of variables 50
   4.2.2 The $p$-value 50
   4.2.3 Shapiro-Wilk and Kolmogorov-Smirnov tests 51
   4.2.4 Mann-Whitney U test and t-test 51
   4.2.5 Friedman test and Wilcoxon Signed Ranks test 51
   4.2.6 Bonfferonni adjustment 52
4.3 Demographics 52
4.3.1 Gender 52
4.3.2 Age 52

4.4 The measure of Intermittent and Constant Osteoarthritis Pain (ICOAP) scale: knee version results 54
4.4.1 Section A – constant pain 54
4.4.2 Section B – intermittent pain 56
4.4.3 Section C – paracetamol usage 57
4.4.4 Total score for the ICOAP scale 59

4.5 The Short Physical Performance Battery (SPPB) test results 61
4.5.1 The chair test 61
4.5.2 The gait test 63

CHAPTER FIVE – DISCUSSION

5.1 Introduction 65

5.2 The measure of Intermittent and Constant Osteoarthritis Pain (ICOAP) scale: knee version 65
5.2.1 Section A – constant pain 65
5.2.2 Section B – intermittent pain 66
5.2.3 Section C – paracetamol usage 67
5.2.4 Total ICOAP score 67

5.3 The Short Physical Performance Battery (SPPB) test 68
5.3.1 The chair test 68
5.3.2 The gait test 68

5.4 Participant variance 69
5.4.1 Matching of participants 69
5.4.2 Demographics of the participants 69
5.4.3 Participant subjectivity and compliance 70
CHAPTER SIX – CONCLUSIONS AND RECOMMENDATIONS

6.1 Conclusion 71

6.2 Recommendations for future research 71

REFERENCES 73
LIST OF APPENDICES

Appendix A: Advertisement                        89
Appendix B: Participant information and consent form  90
Appendix C: Participant medication record          94
Appendix D: A measure of intermittent and constant osteoarthritic pain: ICOAP knee version  95
Appendix E: Short physical performance battery protocol and score sheet         98
Appendix F: Case taking form – initial consultation       99
Appendix G: Case taking form – follow-up consultation       102
Appendix H: Randomisation and procedure                 103
Appendix I: Cross tabulation and descriptive for demographics  104
Appendix J: Inter-group comparisons                     106
Appendix K: Intra-group analysis                       110
LIST OF FIGURES

<table>
<thead>
<tr>
<th>Figure</th>
<th>Description</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Figure 2.1</td>
<td>Frontal view of the right knee with patella reflected</td>
<td>7</td>
</tr>
<tr>
<td>Figure 2.2</td>
<td>Fibrous layer of the knee joint capsule</td>
<td>10</td>
</tr>
<tr>
<td>Figure 2.3</td>
<td>Posterior view of the superficial layer of the knee joint, showing the tibial and fibular collateral ligaments and the two popliteal ligaments</td>
<td>13</td>
</tr>
<tr>
<td>Figure 2.4</td>
<td>Anterior and transverse view of the menisci and ligaments of the knee</td>
<td>14</td>
</tr>
<tr>
<td>Figure 2.5</td>
<td>Arterial blood supply of the knee joint</td>
<td>18</td>
</tr>
<tr>
<td>Figure 2.6</td>
<td>Tibial and common peroneal nerves</td>
<td>19</td>
</tr>
<tr>
<td>Figure 2.7</td>
<td>The bursae of the knee joint</td>
<td>21</td>
</tr>
<tr>
<td>Figure 4.1</td>
<td>Bar graph representing the number and mean ages of participants</td>
<td>53</td>
</tr>
<tr>
<td>Figure 4.2</td>
<td>Bar graph representing the mean value, for section A (constant pain), of the placebo and treatment groups at each consultation</td>
<td>55</td>
</tr>
<tr>
<td>Figure 4.3</td>
<td>Bar graph representing the mean value, for section B (intermittent pain), of the placebo and treatment groups at each consultation</td>
<td>57</td>
</tr>
<tr>
<td>Figure 4.4</td>
<td>Bar graph representing the mean value, for section C (paracetamol Usage) of the placebo and treatment groups at each consultation</td>
<td>58</td>
</tr>
<tr>
<td>Figure 4.5</td>
<td>Bar graph representing the mean value of the total score for the ICOAP scale, for the placebo and treatment groups, at each consultation</td>
<td>60</td>
</tr>
<tr>
<td>Figure 4.6</td>
<td>Bar graph representing the mean value for the chair test, for the placebo and treatment groups, at each consultation</td>
<td>62</td>
</tr>
<tr>
<td>Figure 4.7</td>
<td>Bar graph representing the mean value for the gait test, for the placebo and treatment groups, at each consultation</td>
<td>64</td>
</tr>
</tbody>
</table>
LIST OF TABLES

Table 2.1   The muscles of the knee joint                 15
Table 4.1   Tabulation of participants per age category and relevant percentage per study group  53
Table 4.2   Tabulation of the mean value (descriptives of variables), for section A (constant pain), at each consultation for each group and mean difference from initial to third consultation  54
Table 4.3   Tabulation of the mean value (descriptives of variables), for section B (intermittent pain), at each consultation for each group, and mean difference from initial to third consultation  56
Table 4.4   Tabulation of the mean value (descriptives of variables), for section C (paracetamol usage), at each consultation for each group, and mean difference from initial to third consultation  58
Table 4.5   Tabulation of the mean value (descriptives of variables), for the total score of the ICOAP scale, at each consultation for each group, and mean difference from initial to third consultation  59
Table 4.6   Tabulation of the mean value (descriptives of variables), for the chair test, at each consultation for each group, and mean difference from initial to third consultation  61
Table 4.7   Tabulation of the mean value (descriptives of variables), for the gait test, at each consultation, for each group, and mean difference from initial to third consultation  63
CHAPTER ONE – INTRODUCTION

1.1 Problem statement

Osteoarthritis (OA) is a musculoskeletal condition affecting the synovial joints of the body, including hyaline cartilage, subchondral bone, synovium, joint capsule and supporting muscle. It is the most prevalent joint disorder worldwide (Colledge et al., 2010). The global prevalence of symptomatic OA in adults over 60 years of age is estimated to be about 12% of the population (Ickinger & Tickly, 2010). The prevalence of OA has not been well researched in South Africa. However, the prevalence of OA of the knee in developing countries, including South Africa, is expected to rise due to the increase in obesity and life-expectancy (Woolf & Pfleger, 2003). Conventional treatments for OA of the knee include analgesics, non-steroidal anti-inflammatory drugs (NSAIDS), corticosteroid injections and surgery (Handa & Singh, 2003). Due to the possible side effects and risk factors of conventional treatment, alternative treatments need to be assessed (Day & Graham, 2005).

OsteoEze Gold™ contains a combination of glucosamine sulphate, chondroitin sulphate, manganese and vitamin C. Studies have shown favourable results in the treatment of OA of the knee with a combination of glucosamine sulphate and chondroitin sulphate (Bruyere et al., 2008; Wildi et al., 2010). Leffler et al. (1999) conducted a study on OA of the knee, utilising the same ingredients contained in OsteoEze Gold™, producing favourable results. To date, no research has been done on OsteoEze Gold™ for OA of the knee.

1.2 Aim of the study

The aim of this study is to determine the effect of OsteoEze Gold™ on pain and functional ability in osteoarthritis of the knee, using the measure of Intermittent and Constant Osteoarthritis Pain (ICOAP) scale: knee version and Short Physical Performance Battery (SPPB) test.
1.3 **Benefits of the study**

The benefit of the study is to provide further research to support the use of alternative treatments in reducing the symptoms of OA of the knee as well as preventing further progression of the disease.

1.4 **Hypothesis**

The proposed hypothesis is that OsteoEze Gold™ will significantly improve the symptoms associated with osteoarthritis of the knee, in particular functional ability and knee pain.

1.5 **Null hypothesis**

The null hypothesis is that there will be no significant difference between the OsteoEze Gold™ and the placebo capsules in reducing the symptoms of osteoarthritis of the knee.
CHAPTER TWO – LITERATURE REVIEW

2.1 Osteoarthritis

2.1.1 Definition of osteoarthritis

Osteoarthritis (OA) is a musculoskeletal condition affecting the synovial joints of the body, most commonly the knee and hip (Colledge et al., 2010). It is the most prevalent type of arthritis, and is also referred to as degenerative joint disease or osteoarthrosis (Luqmani et al., 2008). OA is not referred to as a disease, but rather a chronic condition incorporating different processes such as hyaline cartilage breakdown, bone and cartilage proliferation, and joint remodelling. The combination of the above mentioned processes causes the pain and disability experienced by OA sufferers (Colledge et al., 2010).

2.1.2 Prevalence of osteoarthritis

The global prevalence of symptomatic OA in adults over 60 years is estimated to be about 12% of the population, with up to 33% showing signs of OA radiographically (Ickinger & Tikly, 2010). The prevalence of OA in South Africa has not been well researched. Most of the studies on OA have not been done using South African data specifically, but have suggested that the prevalence of OA was low in Sub-Saharan Africa compared to other countries (Parker & Jelsma, 2010). In the study done by Woolf and Pfleger (2003), it was reported that countries in the Sub-Saharan region had the lowest prevalence of OA of the knee compared to developed countries.

According to a study undertaken in Cape Town by Parker and Jelsma (2010), the prevalence of musculoskeletal conditions, including OA, is much higher in South Africa than previous studies have indicated. In the cross section taken over two primary health clinics, 36% of patients had non-injury related, musculoskeletal symptoms. Studies show that obesity has increased in developing countries, including South Africa (Kruger et al., 2005). As obesity is a significant risk factor for OA of the knee, it can therefore be inferred
that the prevalence of OA of the knee in South Africa has probably increased as well (Woolf & Pfleger, 2003).

2.1.3 Impact of osteoarthritis of the knee

OA not only impacts negatively on many areas of the patient’s personal life, but it also has a considerable impact on health care systems and results in a significant cost to the patient (Lapsley et al., 2001; Majani et al., 2005).

2.1.3.1 Impact of osteoarthritis on the patient

OA affects many areas of the patient’s life. The patient’s physical ability is reduced, impacting on their ability to travel, partake in daily living activities and perform household tasks (Majani et al., 2005). In the elderly, OA is one of the largest contributors to disability (Srikulmontree, 2012). OA can interfere with a patient’s sleep, lead to a decrease in socialising, and possibly contribute to depression (Majani et al., 2005). OA of the knee typically affects the patient’s ability to walk, bend and climb stairs (Weiner et al., 2007).

The cost to the patient suffering with OA can be considerable, and incorporates both the cost of treatment and potential loss of income.

Conventional treatment is expensive, is predominantly aimed at pain relief, and does not prevent further progression of the disease. Therefore the cost to the patient is increased over time due to more treatment being required (Gupta et al., 2005).

Loss of income is also a factor when considering the cost to the patient with OA. As a patient becomes more disabled, they may no longer be able to perform to the level that is required. This may lead to a decreased or complete loss of income. This aspect is often not included in the overall financial burden of OA on the patient (Gupta et al., 2005).
2.1.3.2 Impact of osteoarthritis on health systems

As discussed in section 2.1.2, the global prevalence of symptomatic OA is estimated at 12% of the population. This is a significant percentage of the population, and as a result, there is a great burden on health systems globally (Mobasher et al., 2012). The prevalence of OA of the knee in South Africa is expected to increase, therefore the financial burden on the country’s health system would also increase (Woolf & Pfleger, 2003). Conventional treatment is costly and normally aimed at relieving the symptoms through analgesics, NSAIDS and surgery. The cost of treatment increases over time as the OA progresses (Gupta et al., 2005).

In South Africa, about 80% of the population rely on public health care (WHO, 2012). Therefore an increase in treatment needed by the patient over time will affect the health system directly. Nutraceuticals and alternative treatments may prevent further progression of OA, thereby decreasing the amount of medication needed by the patient in the long-term (Handa & Singh, 2003).

2.1.4 Risk factors for osteoarthritis

Risk factors for OA of the knee include:

- Being over the age of 40 years;
- Genetics (65% genetic factor found in twin studies);
- Female gender;
- Shape and alignment of joints;
- Obesity;
- Lack of exercise;
- Repetitive use of the knee (for example weightlifting and running);
- Occupation (for example miners and cleaners); and / or
- Trauma (Luqmani et al., 2008; Schwellnus et al., 2010; Lozada, 2011).
2.1.5 Classification and aetiology of osteoarthritis

OA is usually classified as either primary or secondary to another condition. Both can be further classified as localised or generalised.

Primary OA, also referred to as idiopathic OA, is classified in cases where no other underlying cause for the articular deterioration is found (Samson et al., 2007). Localised primary OA can present in the hands and feet, knees, hips or spine. In cases where three or more joints are affected, it is classified as generalised primary OA (Luqmani et al., 2008).

The aetiology of secondary OA could include: injury to a joint; congenital conditions affecting the bones or other joint components; or an underlying disease, for example bone dysplasia or Paget’s disease. An injury would be classified as a localised secondary OA, while a more widespread condition such as Paget’s disease would result in a classification of generalised secondary OA (Samson et al., 2007, Luqmani et al., 2008).

2.2 Anatomy of a normal knee joint

The knee joint is composed of three bones and their respective articulations, articular cartilage, a joint capsule, ligaments and muscles (Scuderi & Tria, 2010).

2.2.1 The bones of the knee joint and their respective articulations

The femur, tibia and patella are the three bones that compose the knee joint (Scuderi & Tria, 2010).
The femur is the largest bone of the human skeleton and transmits weight from the hip bone to the tibia when standing. The distal femur consists of two protrusions: the lateral and medial femoral condyles. The medial and lateral femoral condyles articulate with the menisci and tibial condyles to form the knee joint (Monk, 2013). Anteriorly, the femoral condyles form the patellofemoral groove or trochlea, where the patella articulates with the femur (Moore & Dalley, 2006). Two projections on the femoral condyles form the proximal attachment points for the medial (MCL) and lateral (LCL) collateral ligaments (Monk, 2013).

The tibia is the second largest bone in the body. The proximal part of the tibia consists of the lateral and medial tibial condyles. The tibial condyles have a flat superior articulating surface, called the tibial plateau (Moore & Dalley, 2006). The tibial condyles are separated by an intercondylar eminence which has an attachment area for the anterior horns of medial and lateral menisci, and the anterior cruciate ligament (Scuderi & Tria, 2010). There are various attachment points on the tibia for the attachment of the fascia of the thigh, the patellar ligament, and the iliotibial band (ITB). The lateral tibial condyle also has a facet for articulation with the fibula (Scuderi & Tria, 2010; Monk, 2013).
The patella is a sesamoid bone, and articulates with the femur at the trochlea, as seen above in figure 2.1 (Moore & Dalley, 2006; Monk, 2013).

### 2.2.2 Articular cartilage

The type of cartilage found within joints is hyaline cartilage, and is referred to as articular cartilage (Rubin & Strayer, 2012). The main function of articular cartilage is to shield the bones underneath from impact, as well as to minimise friction between joint articulation surfaces during movement (Sharma & Berenbaum, 2007).

The major components of hyaline cartilage are:

1. Chondrocytes, which are cells responsible for maintaining the extracellular matrix;
2. Collagens (mainly type II), which gives the cartilage tensile strength;
3. Proteoglycans, which draw water into the cartilage to help with load bearing; and
4. Water, which minimises friction and contributes to the elasticity of cartilage (Kumar et al., 2010).

Three different zones can be identified in articular cartilage: a superficial zone, an intermediate zone, and a deep zone. Each zone consists of a layer of collagen orientated in a different direction. The different variations between the zones contribute to the strength of the cartilage. Deep to the three zones is a calcified cartilage layer. Subchondral bone is situated directly below the calcified cartilage layer (Pearle et al., 2005; Sharma & Berenbaum, 2007).

#### 2.2.2.1 Chondrocytes

Chondrocytes contribute 2-3% of the total tissue volume of articular cartilage in adults (Sharma & Berenbaum, 2007). Chondrocytes are surrounded by an extracellular matrix (Coetzee et al., 2003). The extracellular matrix is maintained by the chondrocytes through a process of anabolism and catabolism (Pearle et al., 2004). This is achieved by producing enzymes that can break down matrix components, as well as enzyme inhibitors which
prevent enzyme production. This process maintains the integrity of the joint cartilage, keeping the function of the joint optimal (Kumar et al., 2010).

### 2.2.2.2 Collagen

Various types of collagen make up 10-15% of articular cartilage, with Type II collagen contributing to about 80% of all collagens. Type II collagen creates a structural network of fibres (Bronner & Farach-Carson, 2007). This formation gives articular cartilage its tensile strength, and retains the shape and volume of the tissue (Sharma & Berenbaum, 2007). The distension of the extracellular matrix by water, which is discussed below (2.2.2.4), is restricted by the collagen fibres, which are rigid and protect the joint against compressive loads (Bronner & Farach-Carson, 2007).

### 2.2.2.3 Proteoglycans

Proteoglycans are also referred to as mucopolysaccharides, and form about 10-20% of articular cartilage. Proteoglycans consist of a core protein chain and carbohydrates. The carbohydrates are the larger portion, and are called glycosaminoglycans (GAG) (Coetzee et al., 2003).

Aggrecan is the most abundant of the proteoglycans found in cartilage (Sharma & Berenbaum, 2007). The GAG chains of aggrecan are predominantly chondroitin sulphate GAG chains. These GAG chains are negatively charged, which results in the molecule drawing water into the cartilage (Kiani et al., 2002). The water causes the extracellular matrix to swell when there is no load on the joint. However, when a load is applied, the compression forces the water out of the cartilage, and the cycle is repeated once the load has been removed. It is this process which facilitates the shock-absorbing properties of articular cartilage when weight or force is put on the joint (Bronner & Farach-Carson, 2007).
2.2.2.4 Water

As discussed in section 2.2.2.3, water contributes to the shock-absorbing properties of articular cartilage when a load is applied to the joint (Bronner & Farach-Carson, 2007). Water also contributes to the elasticity of cartilage and aids in minimising friction within the joint (Kumar et al., 2010).

2.2.3 Knee joint capsule

The knee joint capsule is composed of an outer fibrous layer (figure 2.2) and an inner synovial layer (Standring et al., 2008). The capsule is an important contributor to the functioning of the knee joint (Levange & Norkin, 2011).

![Figure 2.2 Fibrous layer of the knee joint capsule (Dixit et al., 2007).](image-url)
2.2.3.1 Structure of the knee joint capsule

The posterior attachments of the outer fibrous layer of the joint capsules are the femoral condyles, the intercondylar notch, and the posterior tibial condyle. Anteriorly, the fibrous layer is completed by the patella, the patellar ligament and the tendon formed by the quadriceps muscles (Standring et al., 2008). The extensor retinaculum completes the anterolateral and anteromedial parts of the fibrous layer of the joint capsule (Levangie & Norkin, 2011).

The inner synovial layer or membrane of the joint capsule is attached to the proximal part of the tibia and the distal part of the femur (Loeser, 2001). The posterior part of the synovial membrane extends between the two condyles of the femur, where it attaches to the anterior and posterior cruciate ligaments. Laterally and posteriorly, the synovial membrane envelopes between the lateral condyle of the femur and popliteus muscle. Posteromedially, the synovial membrane is located between the medial condyle of the femur, gastrocnemius muscle and semimembranosus muscle (Levangie & Norkin, 2011).

2.2.3.2 Function of the knee joint capsule

The knee joint capsule, in conjunction with its related ligaments, preserves the normal functioning of the joint. The capsule reduces the extent of movement made by the joint, thus providing passive stability. Active stability is achieved by the nerves in the joint preventing a person from overextending the joint (Levangie & Norkin, 2011).

The outer fibrous layer of the joint capsule provides a protective covering for the joint, closing off the joint space (Standring et al., 2008). The synovial membrane produces synovial fluid which moves into the joint space. The main purpose of synovial fluid is to decrease friction during motion by lubricating the synovial joint (Doan-Johnson, 2012).
2.2.3.3 Synovial fluid

Synovial fluid is produced by cells present in the synovial membrane, and is composed of hyaluronic acid, lubricin, proteinases and collagenases (Doan-Johnson, 2012).

Hyaluronic acid, also known as hyaluronan, is responsible for the viscosity and elasticity of the synovial fluid (Loeser, 2001). A unique characteristic of synovial fluid is its ability to increase in viscosity when pressure is applied to it. This aids in shock-absorption. Once pressure is removed, the synovial fluid thins out once again. Lubricin contributes to the lubricating quality of the fluid, thus reducing friction between articular cartilage surfaces. Proteinases and collagenases are enzymes that help clear the synovial fluid of any breakdown remnants produced during daily functioning of the joint (Doan-Johnson, 2012).

2.2.4 Ligaments and menisci of the knee

The ligaments and menisci found within the knee joint contribute to the stability of the knee joint. The ligaments are grouped into extra-capsular and intra-articular ligaments, while the menisci consist of the medial and lateral meniscus (Swan, 2006).

2.2.4.1 Extra-capsular ligaments of the knee

There are five external (extra-capsular) ligaments supporting the knee joint (Swan, 2006):

- The fibular collateral ligament, also known as the lateral collateral ligament (LCL);
- The tibial collateral ligament, also known as the medial collateral ligament (MCL);
- The patellar ligament;
- The arcuate popliteal ligament; and
- The oblique popliteal ligament (Scuderi & Tria, 2010).

The extra-capsular ligaments (figure 2.3) contribute to the stability of the knee joint during movement (Swan, 2006). The lateral and medial collateral ligaments also aid in knee joint stability when standing (Scuderi & Tria, 2010).
2.2.4.2 Intra-articular ligaments of the knee

There are two intra-articular ligaments, namely the anterior and posterior cruciate ligaments, found within the joint capsule. The intra-articular ligaments stabilise the joint by restricting movement posteriorly and anteriorly (Wilckens et al., 2003; Swan, 2006).

The anterior cruciate ligament (ACL) and posterior cruciate ligament (PCL) cross each other within the joint capsule, as seen in figure 2.4 (Moore & Dalley, 2006). The ACL limits excessive flexion of the knee joint, movement of the femur anteriorly on the tibia, as well as posterior movement of the tibia on femur. The PCL prevents the femur from being displaced posteriorly on the tibia, and hyperextension of the knee joint (Wilckens et al., 2003; Moore & Dalley, 2006; Agur & Dalley, 2008; Monk, 2013).
2.2.4.3 Menisci of the knee

There are two menisci that support the knee, namely the lateral meniscus and medial meniscus (Scuderi & Tria, 2010).

The lateral and medial menisci are formed from fibrocartilage, and cover the peripheral two-thirds of the tibial articular surface (Moore & Dalley, 2006). Due to their crescent shape, they are called menisci, which is a term derived from the Greek word *meniskos*, meaning “little moon” (Verma, 1999).

The external margins of the menisci, which are thicker and attached to the joint capsule, taper down to thinner unattached edges at the interior of the joint. This results in a wedge shaped structure (figure 2.4) on a transverse view (Moore & Dalley, 2006; Monk, 2013).
The main role of the menisci is to help with weight compression of the joint by increasing the associated articulating surface areas of the bones comprising the knee joint. The menisci prevent soft tissue impingement during movement, and also aid with synovial fluid movement (Scuderi & Tria, 2010).

2.2.5 Muscles facilitating movement of the knee joint

The muscles of the knee joint are usually classified into two groups, knee flexors and extensors. There are seven muscles that make up the flexor group and four muscles that make up the extensor group, as can be seen in Table 2.1. The knee flexor group help bend the leg at the knee, thereby decreasing the angle between the calf and back of the thigh. The knee extensor group straighten the leg at the knee, thereby increasing this angle (Levangie & Norkin, 2011).

<table>
<thead>
<tr>
<th>Muscle</th>
<th>Proximal attachment</th>
<th>Distal attachment</th>
<th>Action at the knee</th>
</tr>
</thead>
<tbody>
<tr>
<td>Knee flexor group</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>* Semi-membranosus</td>
<td>• Ischial tuberosity</td>
<td>• Posterior aspect of medial condyle of tibia</td>
</tr>
<tr>
<td>2</td>
<td>* Semitendinosus</td>
<td>• Ischial tuberosity</td>
<td>• Medial aspect of the superior part of tibia</td>
</tr>
<tr>
<td>3</td>
<td>* Biceps femoris</td>
<td>• Long head – ischial tuberosity</td>
<td>• Lateral aspect of the head of femur</td>
</tr>
<tr>
<td></td>
<td>* 1,2,3 =</td>
<td>• Short head – linea aspera and lateral supracondylar line of femur</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Sartorius</td>
<td>• Anterior superior iliac spine and</td>
<td>• Superior aspect of medial part of</td>
</tr>
<tr>
<td></td>
<td></td>
<td>superior part of notch inferior to it</td>
<td>tibia</td>
</tr>
<tr>
<td>---</td>
<td>---</td>
<td>--------------------------------------</td>
<td>-------</td>
</tr>
<tr>
<td>5</td>
<td><strong>Gracilis</strong></td>
<td>• Body and inferior ramus of pubis</td>
<td>• Superior aspect of medial part of tibia</td>
</tr>
<tr>
<td>6</td>
<td><strong>Popliteus</strong></td>
<td>• Lateral aspect of lateral condyle of femur • Lateral meniscus</td>
<td>• Posterior surface of tibia, superior to soleal line</td>
</tr>
<tr>
<td>7</td>
<td><strong>Gastrocnemius</strong></td>
<td>• Lateral head – lateral part of lateral condyle of femur • Medial head – popliteal surface of femur, superior to medial condyle</td>
<td>• Posterior surface of calcaneus</td>
</tr>
</tbody>
</table>

**Knee extensor group**

<table>
<thead>
<tr>
<th></th>
<th></th>
<th>Anterior inferior iliac spine • Ilium superior to acetabulum</th>
<th>Base of patella • Tibial tuberosity</th>
<th>Knee extension</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><strong>Rectus femoris</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td><strong>Vastus lateralis</strong></td>
<td>• Greater trochanter of femur • Lateral lip of linea aspera of femur</td>
<td>Base of patella • Tibial tuberosity</td>
<td>Knee extension</td>
</tr>
<tr>
<td>3</td>
<td><strong>Vastus medialis</strong></td>
<td>• Intertrochanteric line of femur • Medial lip of linea aspera of femur</td>
<td>Base of patella • Tibial tuberosity</td>
<td>Knee extension</td>
</tr>
<tr>
<td>4</td>
<td>Vastus intermedius</td>
<td>• Anterior and lateral surfaces of shaft of femur</td>
<td>• Base of patella</td>
<td>• Tibial tuberosity</td>
</tr>
</tbody>
</table>

Table 2.1 The muscles of the knee joint (McGinty & Irrgang, 2000; Moore & Dalley, 2006).

2.2.6. Movement and stability of the knee joint

The main function of the knee joint is to manage body weight and position during daily activities. In order to perform these activities, a large, three-dimensional range of motion is required: flexion and extension; internal and external rotation; and abduction and adduction (McGinty & Irrgang, 2000; Dixit et al., 2007). In addition to these movements, the joint also needs to oppose the large compressive forces applied to it. The supporting muscles of the joint, the intra and extra-capsular ligaments and the articulating surfaces all contribute to the above-mentioned mobility and stability features of the knee joint. However, as the articulating surfaces of the knee joint are not entirely congruent, the knee joint is naturally unstable (Standring et al., 2008).

2.2.7. Arterial supply and venous drainage of the knee joint

The arterial blood supply of the knee joint (figure 2.5) is provided by the genicular anastomoses, which are created by ten arteries, namely: the superior lateral and superior medial genicular arteries, the middle genicular artery, the inferior lateral genicular artery, the descending genicular artery, the lateral femoral circumflex artery, the anterior and posterior tibial arteries, the anterior tibial recurrent artery, and the popliteal artery (Moore & Dalley, 2006).
Figure 2.5 Arterial blood supply of the knee joint (Kelley, 2012).

The venous drainage of the knee joint is facilitated by the popliteal vein. The popliteal vein is a deep vein, and is formed by the anterior and posterior tibial veins and the posterior fibular veins. The small saphenous vein is a superficial vein, and joins the popliteal vein at the popliteal fossa. The popliteal vein develops into the femoral vein above the knee joint (Jones, 2013).

2.2.8 Innervation of the knee joint

Innervation of the knee joint consists of the branches from the obturator and femoral nerves, and the tibial and common peroneal nerves (Noyes, 2010).

The obturator and femoral nerves originate from the lumbar plexus (L2, L3 and L4). The tibial and the common peroneal nerves (figure 2.6) originate from the lumbo-sacral plexus (L4, L5, S1, S2 and S3) (Callaghan et al., 2003).
The posterior branch of the obturator nerve becomes an articular branch, which supplies the posterior part of the knee joint. The nerve penetrates the oblique popliteal ligament (Callaghan et al., 2003).

Three branches of the femoral nerve become articular. These branches supply the anterior aspect of joint capsule, the vastus medialis muscle and the medial side of knee joint (Callaghan et al., 2003; Noyes, 2010).

![Diagram of the knee joint with nerves labeled](image)

**Figure 2.6 The tibial and common peroneal nerves (Colton et al., 2008).**

The tibial and common peroneal nerves make up the sciatic nerve which supplies the muscles of the legs (Noyes, 2010). The three articular branches of the tibial nerve supply the posterior compartment of the leg, while the common peroneal nerve supplies the anterior and lateral compartments, and has one articular branch (Callaghan et al., 2003).
2.2.9 The bursae of the knee

Bursae are membranous, enclosed structures that contain synovial fluid. They are positioned in areas that are prone to friction, thereby reducing friction between the articulating structures of the joint during movement (Moore & Dalley, 2006; Bickley, 2009; Chatra, 2012).

Bursae can be situated between the overlying skin and the surface of the joint or the bone; between muscles and bone; or between ligaments and bone (Bickley, 2009). They may communicate directly with the synovial cavity or related muscles, or form an isolated sac (Moore & Dalley, 2006).

The eight main bursae associated with the knee joint (figure 2.7) are the:

- The suprapatellar bursa;
- The popliteus bursa;
- The anserine bursa / subsatorial bursa;
- The gastrocnemius bursa;
- The semimembranosus bursa;
- The subcutaneous prepatellar bursa;
- The subcutaneous infrapatellar bursa; and
- The deep infrapatellar bursa (Moore & Dalley, 2006; Chatra, 2012).

Of the eight above mentioned bursae, only four arise directly from the synovial cavity; namely the suprapatellar, the popliteus, the gastrocnemius and semimembranosus bursae (Moore & Dalley, 2006; Chatra, 2012).
2.3 Clinical considerations of osteoarthritis of the knee

2.3.1 Pathogenesis of osteoarthritis of the knee

The pathological process that leads to OA is a result of defective repair and remodelling of the joint after it has been damaged (Colledge et al., 2010).

There are four stages in the pathogenesis of OA:

1. Initial repair, which involves the increased production of chondrocytes, which manufacture the extracellular matrix;
2. Early-stage OA, characterised by the breakdown of the extracellular matrix of articular cartilage, due to the action of protease enzymes exceeding chondrocyte production;
3. Intermediate-stage OA, with the continued net loss of articular cartilage due to enzymatic activity; and
4. Late-stage OA, characterised by joint space narrowing, total cartilage loss, osteophyte formation and sclerosis of the adjoining bone, which commonly results in deformity of the joint (Walker & Whittlesea, 2012).

2.3.2. Signs and symptoms of osteoarthritis of the knee

The two main complaints, in patients suffering from OA of the knee, are knee pain and decreased daily functionality, such as walking (Samson et al., 2007).

The osteoarthritic process, which causes capsular swelling and pressure in subchondral bone, is theorised to be the main reason for the pain experienced (Samson et al., 2007). The pain experienced by patients with OA of the knee tends to:

- Increase gradually over time;
- Vary from day to day;
- Occur asymmetrically;
- Improve with rest; and
- Affect one or a few joints (College et al., 2010).

The functional restriction is caused by the capsular thickening and osteophyte formation (Colledge et al., 2010). OA is a common cause of decreased daily function and OA sufferers score significantly lower in functionality tests (Rahman et al., 2005). The patient typically experiences morning stiffness that lasts for less than 30 minutes. On examination, a coarse crepitus, osteophytes, muscle wasting and gait abnormalities may be observed (Colledge et al., 2010).

2.3.3 Diagnosis of osteoarthritis of the knee

OA of the knee can be diagnosed either on clinical findings, a combination of clinical and radiographic findings, or a combination of clinical findings and laboratory test results (NICE, 2008; ACR, 2011).
The clinical criteria for a diagnosis of OA of the knee is knee pain, with at least three out of the following six criteria:

- Being over the age of 50 years;
- Morning stiffness lasting for less than 30 minutes;
- Crepitus;
- Bony tenderness;
- Bony enlargement; and / or
- No palpable warmth (ACR, 2011; Domino, 2012).

The clinical and radiographic criteria for diagnosis of OA of the knee is the presence of knee pain, as well as radiographic evidence of osteophytes, with at least one of the following criteria:

- Being over the age of 50 years;
- Morning stiffness lasting for less than 30 minutes; and / or
- Crepitus (NICE, 2008; ACR, 2011).

The clinical and laboratory criteria for diagnosis of OA of the knee is knee pain, with at least five out of the following nine criteria:

- Being over the age of 50 years;
- Morning stiffness lasting for less than 30 minutes;
- Crepitus;
- Bony tenderness;
- Bony enlargement;
- No palpable warmth;
- Erythrocyte sedimentation rate (ESR) of less than 40mm/hour;
- Rheumatoid factor (RF) of less than 1:40 (to exclude a diagnosis of rheumatoid arthritis); and / or
- Clear synovial fluid (SF) consistent with OA (Zhang et al., 2008; ACR, 2011).
2.3.4 Differential diagnoses of osteoarthritis of the knee

2.3.4.1 Rheumatoid arthritis

Rheumatoid arthritis (RA) is an autoimmune disease that causes an inflammatory arthritis. Due to an often unknown trigger, the immune system of an individual with RA confuses the synovial membrane of a joint with a foreign body. The immune system therefore attacks the joint synovium, resulting in inflammation, pain and stiffness. Bone, cartilage and soft tissue are also destroyed in the process (Altman, 2012b).

According to the American Rheumatism Association, the diagnosis of rheumatoid arthritis is made on the presentation of four or more of the following:

- Morning stiffness that lasts for longer than an hour;
- Arthritis of more than two joints;
- Arthritis of the hand joints;
- Symmetrical arthritis;
- Rheumatoid nodules;
- The presence of rheumatoid factor (RF) in the blood above a certain level, designated by the laboratory utilised for the test;
- Radiological changes; and / or
- Symptoms that are experienced for more than six weeks (Colledge et al., 2010).

2.3.4.2 Ankylosing spondylitis

Ankylosing spondylitis (AS) is a type of arthritis, primarily of the spine and sacroiliac joints. The condition can cause the spine to fuse together, resulting in stiffness, decreased range of motion and pain. Most individuals affected by ankylosing spondylitis test positive for the genetic marker HLA-B27, although it is still not known what the cause of the condition is (Colledge et al., 2010). The condition is three times more prevalent in men than in women, and normally starts between the ages of 20 and 40 years (Altman, 2012a).
2.3.4.3 Reiter’s syndrome

Reiter’s syndrome is diagnosed on the presentation of three symptoms. These symptoms are referred to as the classic triad: non-specific urethritis, conjunctivitis, and reactive arthritis. The reactive arthritis of Reiter’s syndrome predominantly affects the joints of the lower limbs. The syndrome most commonly affects men between the ages of 16-35 years, and is normally triggered by a bacterial dysentery infection or a sexually transmitted infection of *Chlamydia trachomatis* (Colledge *et al*., 2010).

2.3.4.4 Gout

Gout is characterised by the deposition of monosodium urate monohydrate (MSU) crystals around synovial joints and in connective tissue. An increase in deposition of MSU crystals may correlate to a high concentration of uric acid (Colledge *et al*., 2010). The concentration of uric acid depends on the balance between its synthesis and its elimination by the kidneys (Schumacher, 2012). Most sufferers of gout have an inherited impaired ability to excrete excess uric acid in response to an increase in digestion of purine which is obtained from the diet (Colledge *et al*., 2010). Purine is found mainly in red meat, shellfish, alcohol and certain medications (Schumacher, 2012).

The joints of the lower limbs are more commonly affected, with the tarso-metatarsal joint of the first metatarsal (big toe) being the most common deposition site. The symptoms of an acute attack of gout are: severe pain and tenderness of the joint; swelling with red shining skin; and rapid onset of symptoms. Although an attack may be severe, it is self-limiting (Colledge *et al*., 2010). Gout can be diagnosed by the presence of high uric acid levels in the blood, or by identifying urate crystals in synovial fluid aspirated from affected joints (Schumacher, 2012).

2.3.4.5 Septic arthritis

Septic arthritis is a serious condition and a medical emergency, as it can be fatal. It can be caused by a bacterial, fungal or viral infection, but most often by an infection of
*Staphylococcus aureus* (Shiel & Stoppler, 2013b). Septic arthritis usually presents with an acute arthritis of one joint, together with a fever. The joint will appear hot, red and swollen. The lower limbs are most commonly affected, and it often presents in patients with existing arthritic conditions (Colledge *et al*., 2010). Septic arthritis can be diagnosed by the presence of microbes in synovial fluid, which is normally sterile (Shiel & Stoppler, 2013b).

### 2.3.4.6 Psoriatic arthritis

Psoriatic arthritis is a condition affecting the joints, the skin (in the form of psoriasis), and other systems of the body such as the eyes (Shiel & Stoppler, 2013a). Psoriatic arthritis can appear similar to some cases of osteoarthritis, i.e. the arthritis is asymmetrical, with a single joint affected, and presents with inflammation and effusions. In addition, it can also mimic the presentation of rheumatoid arthritis with many joints being affected symmetrically (Colledge *et al*., 2010).

### 2.3.5 Complications of osteoarthritis of the knee

#### 2.3.5.1 Calcium pyrophosphate deposition disease (CPPD)

Individuals with OA may be susceptible to calcium pyrophosphate deposition disease (CPPD). In CPPD, calcium crystals (calcium pyrophosphate dihydrate) form deposits in the joint cartilage of the knee. The term chondrocalcinosis refers to the radiographical presence of CPPD (Saadeh, 2012).

In conditions such as OA, where the cartilage matrix of a joint is altered, CPPD may result. This is due to the deposition of crystals favouring an environment of changing cartilage matrix. An acute attack of pseudogout (acute calcium pyrophosphate crystal arthritis) can result when the crystals break loose. The attack is very painful and the joint becomes swollen, mimicking an acute attack of gout (Arthritis Research UK, 2013). CPPD may also manifest as pseudo-osteoarthritis and therefore present with symptoms mimicking OA (Saadeh, 2012).
2.3.5.2 Baker’s cyst

A Baker’s cyst is a popliteal mass that occurs from a distension of the gastrocnemius or semimembranosus muscle bursi. Synovial fluid collects in the bursa, resulting in a cyst. A Baker’s cyst is a common complication of severe osteoarthritis and can often be missed on clinical examination. Further complications of a Baker’s cyst include cellulitis, deep vein thrombosis or pseudothrombophlebitis (Chiou et al., 2008).

2.3.6 Special investigations for osteoarthritis of the knee

Although a diagnosis of osteoarthritis can be made with relative certainty based on presenting symptoms and patient history, there are special investigations that can be performed to help confirm the diagnosis and exclude other pathology (ACR, 2011; Domino, 2012).

2.3.6.1 Blood tests

The first investigation used in diagnosing OA, is a blood test for rheumatoid factor (RF). This is used to exclude other pathologies, in particular rheumatoid arthritis. There are two types of rheumatoid factor blood tests performed, namely qualitative and quantitative RF. The qualitative test will only provide a positive or negative result, whereas the quantitative test will provide an exact level of rheumatoid factor present in the blood. Rheumatoid factor can also be positive in a variety of other conditions including scleroderma, systemic lupus erythematosus (SLE) and Sjögren syndrome (AACC, 2010).

Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) can be used to detect any inflammation in the body. Studies have shown a correlation between CRP levels and synovial membrane inflammation experienced in OA. Therefore CRP levels rise with severity of the condition (Pearle et al., 2004). A CRP level of above 3mg/L and below 10mg/L may be indicative of the inflammatory process associated with an acute phase of OA (Windgassen et al., 2011). ESR and CRP are non-specific and can reflect many
inflammatory conditions, including heart disease, so they cannot be used in isolation to
diagnose OA (Pearle et al., 2004).

2.3.6.2 Radiology

According to most research, X-rays are only useful in the exclusion of other pathologies of
the knee. X-rays are often non-specific in detecting OA of the knee, determining its severity
and predicting further progression (Handa & Singh, 2003).

The following findings on X-ray may suggest a possible diagnosis of OA of the knee:

- Osteophytes;
- Joint space narrowing;
- Subchondral sclerosis;
- Subchondral cysts; and
- Subluxation of the joint (Eustice, 2008).

2.3.6.3 Synovial fluid analysis

Fine needle aspiration of synovial fluid can be performed. Synovial analysis can be used to
exclude other diagnoses. The synovial fluid should be clear and slightly viscous, and this
appearance would also support a diagnosis of osteoarthritis. Cloudy synovial fluid may
indicate the presence of micro-organisms due to acute or chronic septic arthritis, or white
blood cells which could support a diagnosis of rheumatoid arthritis. Synovial fluid may also
appear pink or bloody due to haemarthrosis (AACC, 2012).

2.4 Evaluation tools for osteoarthritis

2.4.1 Effect of osteoarthritis on functional ability

OA of the knee may lead to disability in a patient. This is due to the degeneration in the
joint, a decrease in muscle strength, as well as a decrease in range of motion (ROM) of the
joint. Range of motion is measured using an instrument called a goniometer, and is recorded in degrees. The type of movement most severely affected by OA of the knee is flexion of the knee (Steultjens et al., 2000).

2.4.2 The Short Physical Performance Battery (SPPB) test

The Short Physical Performance Battery (SPPB) test is a functional assessment tool commonly used in research trials. The test consists of a chair stand test and a measured walk test (gait test). The participant is requested to stand and sit five times, and the time taken is recorded. The participant is then requested to walk a distance of 4m as they would normally, and this is repeated a second time. The fastest time is taken as the measurement. The speed at which the patient is requested to walk is controversial. All speeds have produced adequate results, however the most favourable speeds, are a slow walk or normal speed walk (Borjesson et al., 2007). The SPPB test has been used in numerous studies on osteoarthritis of the knee (Weiner et al., 2007).

The SPPB test was formulated during a study on geriatric participants by Guralnik et al., in 1994. The study assessed the correlation between severity of reported disability, and disability found during assessment. The SPPB test has been found to be a useful tool in determining lower extremity function (Puthoff, 2008). The tests are also safe and easy to perform in a home or clinic environment by a trained individual (Fun, 2011).

2.4.3 Pain and lifestyle scales

2.4.3.1 The measure of Intermittent and Constant Osteoarthritis Pain (ICOAP) scale: knee version

Osteoarthritis Research Society International (OARSI) has suggested certain indices to be utilised in evaluating patients with chronic musculoskeletal conditions. The measure of Intermittent and Constant Osteoarthritis Pain (ICOAP): knee version is an accepted scale for assessing osteoarthritic knee pain experienced by patients. It has been reported that
patients typically experience either constant or intermittent pain, or experience both types of pain (OARSI, 2007).

The ICOAP scale was utilised in a trial establishing the effectiveness of Diclofenac versus acetaminophen by Verkleij et al. (2010). The scale consists of two different sections related to the different types of pain experienced by osteoarthritic sufferers (constant or intermittent). The patient is asked certain questions related to the type of osteoarthritic knee pain they experience. The answers are recorded on a scale from 1 to 5, and totalled for an overall score (OARSI, 2007).

2.4.3.2 The Western Ontario and McMaster Universities Osteoarthritis index (WOMAC)

The Western Ontario and McMaster Universities Osteoarthritis index (WOMAC) is a scale commonly used to assess OA of the knee (OARSI, 2007). The index has 24 parts, further divided into three different areas: pain (5 parts), stiffness (2 parts) and physical function (17 parts). It is a reliable tool to evaluate the signs and symptoms of OA in the knee and hip, as well as the response of the patient to treatment (ACR, 2012).

2.4.3.3 Other scales and indices for evaluating osteoarthritis

The Short Form of the Arthritis Impact Measurement Scales 2 (AIM2SF) is a lifestyle questionnaire rating the overall impact of arthritis on the patient’s life. The questionnaire is divided into 10 different categories namely; mobility level, walking and bending, self-care tasks, household tasks, social activity, support from family and friends, work, level of tension, mood, and health. The AIM2SF index has been translated into numerous different languages, and various forms of the index exist (ACR, 1999).

The Visual Analogue Scale and Likert Scale are often utilised in assessing patients with OA. Both scales are effective in evaluating a patient’s response to treatment (Bolognese et al., 2003).
2.5 Treatment of osteoarthritis of the knee

Treatment of OA is multi-faceted and is mainly focused on relieving the symptoms experienced by the patient. There are three aims in the treatment of OA:

- Preventing further disease development;
- Maximising daily function; and
- Reducing pain experienced by the individual (Walker & Whittlesea, 2012).

The first line of treatment involves interventions aimed at preventing further decrease of daily function, such as empowering the patient with information about the disease, exercises to improve muscle strength, and weight loss programmes if necessary (Walker & Whittlesea, 2012). Research has shown significant improvement in patients with OA of the knee undergoing exercise and weight loss regimes. Braces, heel wedges and canes have also been shown to improve the symptoms of sufferers of OA of the knee, although they do not alter disease progression (Ringdahl & Pandit, 2011). Alternative treatments, such as nutraceuticals, are mainly aimed at preventing further disease progression (Ickinger & Tikly, 2010).

Reducing pain experienced by the individual is primarily achieved by conventional analgesics such as acetaminophen, paracetamol, tropical creams and non-steroidal anti-inflammatory drugs (NSAIDS). Inflammation may be reduced by conventional and alternative treatment (Ickinger & Tikly, 2010).

2.5.1 Conventional treatment

Pain relief should start with the use of safer analgesics, such as acetaminophen and paracetamol, or topical creams. Acetaminophen can cause side-effects, such as liver damage, if more than the suggested dose is taken, which is 650mg every four to six hours (FDA, 2011). Paracetamol is a preferred pain reliever as it has fewer potential side-effects (Day & Graham 2005). A review done by the Osteoarthritis Research Society International (OARSI) has resulted in the daily maximum dose of paracetamol to be decreased to 4g a
day. The review reported that there are potential side-effects, such as loss of renal function and upper gastrointestinal distress, associated with long term daily doses of paracetamol above 3g a day (Ickinger & Tikly, 2010).

If sufficient relief is not achieved by these drugs, then non-steroidal anti-inflammatory drugs (NSAIDs) are prescribed in low doses followed by higher doses if necessary, to relieve pain adequately (Handa & Singh, 2003). Acetaminophen is generally preferred to NSAIDs, although there is a debate about the efficacy of acetaminophen compared to NSAIDs, especially in mild to severe OA (Verkleij et al., 2010). All types of oral NSAIDS are equivalent in their effectiveness in managing pain in patients with OA, however they should all be prescribed in the lowest dose and for the shortest duration possible (Ickinger & Tikly, 2010).

NSAIDs have numerous reported side-effects including tinnitus, liver damage, kidney damage and more commonly gastric upsets (Day & Graham, 2005). NSAIDs are contraindicated in patients with a history of a peptic ulcer, stroke and renal dysfunction. Elderly patients and those presenting with risk factors for heart disease need to be carefully monitored (Ickinger & Tikly, 2010). Due to the many side-effects and contraindications of NSAIDs, safer alternatives should be explored first (Day & Graham, 2005).

If NSAIDs are ineffective, intra-articular corticosteroid injections may be considered (Samson et al., 2007). The treatment may provide quick pain relief for up to three months (Ickinger & Tikly, 2010). However, this treatment can lead to further cartilage damage, and cannot be administered more than a couple of times a year (Samson et al., 2007).

2.5.2 Surgery

Surgeries performed to treat OA of the knee include: arthroscopy, where the surgeon removes pieces of cartilage or bone which have become detached from the joint; osteotomy, where the bones are realigned; and arthroplasty, where the joint surface is repaired (NIAMS, 2010). Osteotomies are performed earlier than other surgeries, to prevent further progression of the disease. An arthroplasty can help the patient to achieve
normal functioning of the joint, and is one of the most common surgeries performed (Rahman et al., 2005). Although these surgeries are effective, there are risks associated, as with all surgeries, such as a reaction to the anaesthetic, thrombosis or infection (Eustice, 2011).

2.5.3 Alternative treatment

There are many alternative treatments for OA of the knee. These include herbal preparations, nutraceuticals, homoeopathy and other physical therapies (Handa & Singh, 2003).

2.5.3.1 Herbal preparations

Turmeric (Curcuma domestica / longa) may be beneficial in reducing pain and inflammation associated with OA. Curcumin is the active ingredient found in turmeric. The recommended dosage is 900mg daily (Ehrlich, 2012). Tumeric has been shown to be clinically comparable to Ibuprofen for pain relief in a study conducted on patients with OA of the knee. It illustrated similar improvements in pain relief and physical ability compared to Ibuprofen in a two-week study (Kuptniratsaikul et al., 2009). Although minimal side-effects of tumeric have been reported during research trials, this may be due to low bioavailability of the active ingredient. No research has been conducted to date on the safety level of curcumin or other active ingredients of tumeric (Mobasheri et al., 2012).

Devil’s claw (Harpagophytum procumbens) is an alternative treatment option for pain relief, at a dosage of 400mg daily (Chrubasik et al., 2007). A review conducted by Chrubasik et al. (2007), found that there was strong support for the use of Devil’s claw in the treatment of OA as an anti-inflammatory. Devil’s claw is contraindicated in patients taking certain diabetic medications and patients suffering with heart disease (Ehrlich, 2012).

The gum of the Boswellia serrata, also known as Indian Frankinscence tree, is an alternative treatment for OA. It produced clinically significant results in reducing knee pain, and improving range of motion and function of the joint. The daily recommended dosage of
Boswellia serrata is 1200mg. Minor side effects of Boswellia serrata have been reported, such as gastrointestinal distress (Kimmatkar et al., 2003).

Ginger (Zingiber officinale) may be beneficial in reducing pain and joint inflammation in OA sufferers, at a dosage of up to 2g per day. It is proposed that ginger extract prevents the release of COX-2, which is a pro-inflammatory chemical produced by the body, resulting in pain. Studies have shown that the evidence for the effectiveness of ginger extract in the treatment of OA was moderate (Chrubasik et al., 2007). Mild gastrointestinal side-effects may be experienced. Zingiber officinale is contra-indicated in pregnancy, breast-feeding, heart conditions and individuals on anti-coagulant therapy (Leach & Kumar, 2008).

2.5.3.2 Nutraceuticals

The definition of a nutraceutical has not been regulated and varies greatly between different sources. Palthur et al. (2010) presented a research article entitled “Nutraceuticals: a conceptual definition” about the variations in definitions. The article suggested the following definition: “A nutraceutical is a food or a part of a food for oral administration with demonstrated safety and health benefits beyond the basic nutritional functions to supplement diet, presented in a non food matrix or non conventional food formats, in such a quantity that exceeds those that could be obtained from normal foods and with such frequency as required to realise such properties” (Palthur et al., 2010).

S-adenosylmethionine (SAM-e) is a molecule formed from adenosine triphosphate (ATP) and methionine, and is mostly produced in the liver (Loenen, 2006). SAM-e is proposed to increase cartilage production, as well as reduce pain and inflammation. An initial dose of 1200mg a day for 21 days is recommended. The dose is then gradually decreased to 200mg a day (Thieme, 2000). SAM-e may be as effective as NSAIDs in relieving symptoms of OA. There are no reported toxic effects of SAM-e (Ringdahl & Pandit, 2011).

Potassium humate is derived from brown coal, and was found beneficial in reducing inflammation in patients suffering from OA of the knee in a study undertaken by Van Rensburg et al. (2010), from the University of Pretoria. A dosage of 600mg was
administered three times daily, and shown to be clinically significant on the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) and ultra-sensitive CRP. No significant side-effects were reported during the trial.

Intra-articular injections of hyaluronic acid, which is usually found in synovial fluid, may also be used in the treatment of OA. The therapy is costly, yet it may provide long-term pain relief (Ickinger & Tikly, 2010). The possible side-effects of intra-articular injections of hyaluronic acid include infection, pseudoseptic reactions, anaphylaxis and urticaria (Samson et al., 2007).

There have been numerous studies conducted on omega 3 fatty acids and OA. Omega 3 fatty acids are polyunsaturated fatty acids and are classified as essential nutrients. Essential nutrients are not produced by the human body, and therefore they need to be consumed within our diet (Sacks, 2013). A study by the University of Bristol, on a particular type of guinea pig prone to developing OA, produced results concluding that supplementation with high omega 3 fatty acids (about 2700mg a day in adults) prevented and decreased progression of the disease (Knott et al., 2011).

Methylsulfonylmethane (MSM) is a plant-derived or chemically produced compound. A 12-week study conducted by Kim et al. in 2006 produced positive results. MSM was shown to be safe to use at a dosage of 3g twice daily. It reduced severity of pain and improved overall function of the participants. Minor side effects such as nausea and headaches may be experienced (Kim et al., 2006).

Resveratrol is a compound found naturally in the seeds, grape skins, roots and leaves of grapevines. Resveratrol has anti-inflammatory effects, and is a potent anti-oxidant (Maddox, 2012). Research was conducted on a rabbit model of OA by Elmali et al. in 2005. The research concluded that intra-articular injections of resveratrol may reduce degeneration of articular cartilage and prevent further progression of OA (Mobasher et al, 2012). The recommended dose of resveratrol is 2g daily (Maddox, 2012). There have been no reported side-effects of resveratrol, however, very little research has been undertaken.
to investigate the safety limit (Mobasher et al., 2012). Resveratrol may interact with anticoagulant medications and NSAIDS (Maddox, 2012).

Glucosamine sulphate and chondroitin sulphate, two nutraceuticals commonly used in the treatment of OA, will be discussed under OsteoEze Gold™, as it forms part of the formulation.

2.5.3.3 Physical therapies

An alternative treatment for OA is periosteal stimulation therapy (PST). PST is a form of acupuncture, but electrical stimulation is applied to the acupuncture needles. PST, also known as osteopuncture, has shown significant results in the short-term pain relief in OA (Weiner et al., 2007).

Electrotherapy is a modality utilised by physiotherapists to relieve the pain associated with a variety of conditions, including OA. Ultrasound and transcutaneous electrical nerve stimulation (TENS) are the two types of electrotherapy used to treat OA of the knee. Ultrasound therapy aims to decrease pain by using sound waves to produce heat in a certain area where the pain is located. TENS is a therapy similar to PST mentioned above. These therapies differ in the distribution of the electrical stimulation. In TENS electrodes are placed directly onto the affected areas whereas in PST, the electrodes are placed on acupuncture points (Mascarin et al., 2012). A 12-week study conducted by Mascarin et al. in 2012 produced favourable results for ultrasound and TENS therapy in pain management of OA. The therapy was applied bi-weekly for the duration of the 12-week study.

2.5.3.4 Homoeopathy

In homoeopathy, a specific remedy is prescribed to a patient according to the individual symptoms expressed. The patient as a whole is considered when a remedy and treatment protocol is prescribed (Ernst, 2002).
A clinical evaluation conducted in India, over five years, showed positive results for the use of homoeopathy in managing patients with OA. Three research centres conducted the study, and 1,323 case studies were evaluated. The majority of the cases showed an improvement (1007), 274 cases dropped out, 40 cases showed no improvement and two cases worsened. The most effective remedy was *Rhus toxicodendron* which had 279 positive results, followed by *Lycopodium clavatum* with 168, and *Calcarea carbonica* with 92 (Kurup et al., 2005).

A trial was conducted on 184 participants with OA of the knee by Van Haselen & Fisher (2000). It compared the efficacy of a topical homoeopathic gel with a topical NSAID gel in relieving the pain associated with OA. The trial was a double-blind, placebo controlled, randomised study. The results of the trial demonstrated that the homoeopathic gel was as effective as the topical NSAID gel.

A homoeopathic complex was proven to be significantly better than the placebo in a study conducted by Mukansi (2011) at the University of Johannesburg on 30 participants with OA of the wrist. The homoeopathic complex contained *Apis mellifica*, *Arnica montana*, *Bryonia alba*, *Calcarea carbonica*, *Calcarea fluorica*, *Causticum*, *Pulsatilla pratensis* and *Rhus toxicodendron*, all in a 6cH potency. It was found that the complex improved the pain experienced by the participants, as well as overall function of the wrist.

### 2.6 OsteoEze Gold™

OsteoEze Gold™ is a commercially available nutraceutical product used in the treatment of OA of the knee. Each OsteoEze Gold™ capsule contains 500mg glucosamine sulphate, 267mg chondroitin sulphate, 50mg vitamin C and 1mg manganese. One capsule is taken three times a day with meals (Nativa (Pty) Ltd., 2012).

Leffler *et al.* (1999) conducted a 16-week, randomised, double blind study on the combined therapeutic benefit of glucosamine hydrochloride, chondroitin sulphate, manganese and vitamin C on OA of the knee. The daily dosage was 1500mg of glucosamine hydrochloride, 1200mg of chondroitin sulphate and 228mg of manganese and vitamin C. The trial
produced favourable results. The formula and dosage is similar to OsteoEze Gold™, with the exception of the glucosamine hydrochloride. OsteoEze Gold™ contains glucosamine sulphate instead, as studies have shown that it is more effective than glucosamine hydrochloride (Gregory et al., 2008).

### 2.6.1 Chondroitin sulphate

Chondroitin sulphate is a compound found naturally in joint cartilage. Chondroitin sulphate is composed of glycosaminoglycans and disaccharide polymers. As discussed in section 2.1.2.3, chondroitin sulphate contributes to the thickness and flexibility of cartilage by drawing water into the cartilage. This process allows the forces applied to the joint to be evenly distributed (Mason, 2007). It also maintains the balance of the cartilage matrix by stimulating chondrocyte metabolism and slowing down the production of the enzymes elastase and hyaluronidase (Wildi et al., 2010). The production of collagen and proteoglycan is also promoted. Chondroitin sulphate is therefore essential in preventing the overall breakdown of the cartilage and loss of joint function (Mason, 2007).

Wildi et al. (2010) conducted a randomised, double-blind study on 69 participants. The results showed that an 800mg daily dose of chondroitin sulphate significantly improved symptoms of OA of the knee. The chondroitin sulphate significantly decreased the amount of cartilage volume loss by the participants compared to the placebo.

Kahan et al. (2009) carried out a two year study to investigate the long term effects of chondroitin sulphate on OA of knee. The results were favourable, and showed that a daily dosage of 800mg of chondroitin sulphate was an effective treatment.

Studies have suggested that chondroitin sulphate has not produced any significant side effects (Samson et al., 2007). The observed safety limit (OSL) for chondroitin sulphate is 1200mg daily (Hathcock et al., 2006). The daily dosage of chondroitin sulphate in OsteoEze Gold™ is 801mg and therefore well within the OSL as well as within the effective range as shown in the Kahan et al. (2009) research study (Nativa (Pty) Ltd., 2012).
Recent studies have not illustrated the efficacy of chondroitin sulphate when used in isolation, but rather in combination with glucosamine sulphate and other nutraceuticals (Gregory et al., 2008).

### 2.6.2 Glucosamine sulphate

Glucosamine is one of the most well researched and widely utilised alternative treatments for OA. Glucosamine is an amino sugar found within the human body. It is vital for the production of glycosaminoglycans and proteoglycans (Gregory et al., 2008). In particular, it leads to the production of the proteoglycan, aggrecan. As mentioned in section 2.1.2.3, aggrecan plays an important role in the weight bearing properties of articular cartilage (Reginster et al., 2012).

Glucosamine can be found in the exoskeletons of marine animals, or it can be synthetically manufactured. The most common form of glucosamine used in supplements is glucosamine sulphate (Gregory et al., 2008). Glucosamine sulphate may have an anti-inflammatory effect due to its ability to decrease prostaglandin E2 production, which is a pro-inflammatory molecule. The use of glucosamine sulphate for longer than six months may prevent breakdown of articular cartilage, by preventing the action of catabolic enzymes (Reginster et al., 2012).

Bruyere et al. (2008) conducted a five year follow-up survey on previous participants of long-term glucosamine sulphate trials. Participants received 1500mg of glucosamine sulphate daily during the trials. Twice as many participants from the placebo groups, compared to the glucosamine sulphate groups, had subsequently undertaken a total knee replacement. This illustrated the long term, favourable effects of glucosamine sulphate in the treatment of OA of the knee.

A review of a wide range of research conducted on glucosamine on OA was done by Reginster et al. (2012). The review concluded that there is sufficient evidence to support the use of glucosamine sulphate in the treatment of OA. However, there was insufficient
evidence to support the use of other forms of glucosamine, such as glucosamine hydrochloride.

In most studies, glucosamine sulphate has shown no significant side effects (Samson et al., 2007). A systematic review was done on 12 trials to assess the safety of glucosamine sulphate. The trials had a collective number of 1 486 participants that were in the medication group, thus receiving glucosamine sulphate. Forty-eight participants reported side effects, and only seven of these participants were removed from the trial. Most of the side-effects experienced by the participants were mild, and mainly related to mild gastrointestinal symptoms (Reginster et al., 2012).

Glucosamine sulphate is derived from the shells of shellfish, therefore an allergic reaction is possible in shellfish allergy sufferers (Nativa (Pty) Ltd., 2012).

2.6.3 Vitamin C and manganese

Vitamin C is a powerful anti-oxidant. It is therefore theorised that vitamin C may aid in preventing the further progression of OA and decrease inflammation (Felson, 2007; UMMC, 2011).

The Framingham Osteoarthritis Cohort Study (2000-2007) found that vitamin C decreased the rate of osteoarthritic progression significantly. The average vitamin C intake was between 120 and 200mg a day. The study found that knee pain associated with OA was also decreased (Felson, 2007).

A double-blind, randomised trial, conducted in 2003, produced significantly positive results. The trial was conducted on 133 participants with OA of the knee or hip. The medication group received a combination of calcium and vitamin C (calcium ascorbate). The study concluded that the calcium ascorbate significantly decreased pain experienced by the participants (Jensen, 2003).
Manganese is an important trace mineral that can be found in the liver, pancreas and kidneys. It contributes to the formation of bones and connective tissue. Manganese is a constituent of superoxide dismutase (SOD), which is an anti-oxidant enzyme (Ehrlich, 2011). Anti-oxidants help eliminate free radicals from the body. Free radicals are molecules that result from normal process within the body and cause damage to cells. They are linked to degenerative processes in the body, including OA of the knee (UMMC, 2011).
CHAPTER THREE – METHODOLOGY

3.1 Research sample

Sixty seven participants, from a target group of males and females, between the age of 40 and 70 years, were recruited for the study. The participants had to present with a symptomatic osteoarthritis (OA) of the knee that could be clinically diagnosed. Participants were also screened for rheumatoid factor (RF) to exclude a diagnosis of rheumatoid arthritis. In order to be included in the study, the participants were required to have an RF of less than 11mg/mol. The study was approved by the Faculty of Health Sciences Higher Degrees and Ethics Committee: ethical clearance no. AEC23-01-2012.

3.2 Recruitment

Advertisements (Appendix A) were placed at the Health Centre at the University of Johannesburg, Doornfontein campus (DFC), the Biokinetic clinic at the University of Johannesburg, (Bunting Road campus) and old age homes in the area around DFC, with the relevant permission obtained.

3.3 Inclusion and exclusion criteria

The following criteria were used to include or exclude participants from the study.

3.3.1 Inclusion criteria

Participants were included in the study if they:

- Were male or female, between the age of 40 and 70 years; and
- Presented with symptomatic OA of the knee, i.e. knee pain with at least two of the following five criteria: morning stiffness lasting less than 30 minutes from rising, crepitus, bony tenderness, bony enlargement and no palpable warmth.
3.3.2 Exclusion criteria:

Participants were excluded from the study if they:

- Suffered from co-morbid conditions, including heart conditions, morbid obesity, or chronic liver or renal disease;
- Had conditions with similar presentation to OA of the knee such as rheumatoid arthritis, gout, septic arthritis, injury and systemic lupus erythematosus (SLE);
- Are allergic to shellfish;
- Were currently using OsteoEze Gold™ or any other herbal or nutritional supplementation for OA of the knee in the month leading up to the start of the study;
- Were regularly using or dependent on non-steroidal anti-inflammatory medication (NSAIDs);
- Had a blood test showing a positive result for RF above 11m/mol; and / or
- Had a blood test showing an ultra-sensitive CRP level below 1mg/L.

Participants were advised to take paracetamol or aspirin instead of NSAIDs for duration of the study.

3.4 Research design and procedure

This was a 16-week double-blind, placebo controlled study using matched pairs according to age, gender and severity of symptoms (Appendix I). This formed part of a group study with Romy Levy who, using the same sample, tested the effects of OsteoEze Gold™ in the treatment of OA of the knee using the Arthritis Impact Measurement Scales (AIMSF/AIM2SF) health survey to evaluate quality of life, and C-reactive protein, to assess level of inflammation. The research was conducted at the DFC Homoeopathy Health Clinic.

Prospective participants underwent a screening consultation (Appendix F) and were requested to sign a consent form to have phlebotomy performed for an assessment of rheumatoid factor (RF) and CRP levels (Appendix B). A nursing sister at the Health Clinic
on DFC performed the phlebotomy, and blood analysis was done by Contract Laboratory Service (CLS) and the National Health Laboratory Service (NHLS).

The prospective participants satisfying both the inclusion and exclusion criteria were invited to partake in the study. Participants were requested not to take any medication or supplements for OA of the knee for the duration of the study. Participants were allowed to take paracetamol (acetaminophen) for pain management, and the frequency and dosage was documented (Appendix D). Participants were advised not to take more than 650mg (two 325mg tablets) of paracetamol every four to six hours (FDA, 2011). The half-life of paracetamol is two to three hours for an adult. Therefore participants were also requested not to take any paracetamol on the days of consultation, as this may have interfered with the assessment results (McNeil Consumer Healthcare, 2012). In addition, participants were requested not to undergo any major dietary or lifestyle changes during the study.

The participants were divided equally using matched pairs, into a control and experimental group. The matched pairs were assigned into the two groups according to:

- The age of the participant;
- The gender of the participant; and
- The severity of symptoms presented by the participant at the screening consultation.

The study was undertaken over 16 weeks and the participants were requested to undergo three consultations at DFC homoeopathic health clinic:

- An initial consultation in the first week of the trial (week-0);
- A second consultation 8 weeks later (week-8); and
- A final consultation 16 weeks after the initial consultation (week-16).

The participant’s vital signs (blood pressure, respiratory rate, heart rate and temperature) were assessed at every consultation to monitor the participant’s overall health throughout the study (Appendix G).
At each consultation, a measure of Intermittent and Constant OA Pain (ICOAP) scale: Knee version (Appendix D) and a Short Physical Performance Battery (SPPB) test (Appendix E) were performed. Therefore, each test was performed three times.

The ICOAP scale (Appendix D) consisted of three sections:

- Section A – constant knee pain;
- Section B – intermittent knee pain; and
- Section C – paracetamol usage (OARSI, 2007).

In section A, the participants were asked five questions regarding their constant knee pain. Their answers were graded from zero to four. The five scores from each question were averaged for each participant. This resulted in an average score for section A (OARSI, 2007).

In section B, the participants were asked six questions regarding their intermittent knee pain. Their answers were graded from zero to four. The six scores from each question were averaged for each participant. This resulted in an average score for section B (OARSI, 2007).

In section C, the participants were asked how often they had utilised pain medication (paracetamol) for their knee pain in the previous week. Five options were given and graded one to five: never (1), rarely (2), sometimes (3), often (4) or every day (5). This resulted in one score for section C (OARSI, 2007).

The SPPB test (Appendix E) consists of two tests:

- A chair test – how fast the participant was able to rise from a sitting position five times; and
- A gait test – a four metre walk at normal walking speed (Guralnik et al., 1994).
The two tests of the SPPB assessment were measured in seconds and recorded. The gait test was performed twice and the fastest time was recorded (Guralnik et al., 1994).

The experimental group received the OsteoEze Gold™ capsules and the control group received the placebo capsules. The placebo capsules were identical in appearance to the OsteoEze Gold™. The participants each received a four month supply of either the OsteoEze Gold™ capsules or the placebo capsules. A two month supply of the capsules was distributed to the participants at the initial consultation (week-0), and a further two month supply at the second (week-8) consultation.

A participant medication record (Appendix C) was utilised to record how many capsules (OsteoEze Gold™ or placebo) were taken every day, any side-effects experienced, and the quantity of any other pain medication utilised by the participant.

At the initial (week-0) consultation the following tasks were performed:

- An initial case taking and assessment of the participant’s vital signs (Appendix F);
- An ICOAP scale (Appendix D);
- An SPPB test (Appendix E);
- Distribution of a participant medication record (Appendix C); and
- Distribution of a two month supply of placebo capsules to the control group, or OsteoEze Gold™ capsules to the experimental group.

At the second (week-8) consultation the following tasks were performed:

- A follow-up evaluation including an assessment of the participant’s vital signs (Appendix G);
- An ICOAP scale (Appendix D);
- An SPPB test (Appendix E);
- Collection of the participant medication record and distribution of a second participant medication record (Appendix C); and
• Distribution of a two month supply of placebo capsules to the control group, or OsteoEze Gold™ capsules to the experimental group.

At the final (week-16) consultation the following tasks were performed:

• A follow-up evaluation including an assessment of the participant’s vital signs (Appendix G);
• An ICOAP scale (Appendix D);
• An SPPB test (Appendix E); and
• Collection of the second participant medication record.

3.5 Medication administration

Each OsteoEze Gold™ capsule contained 500mg glucosamine sulphate, 267mg chondroitin sulphate, 50mg vitamin C and 1mg manganese. The placebo capsules contained microcrystalline cellulose PH101 (520mg), talc USP 24 (20mg) and emyral white corn starch 100025 (60mg), but look identical to the OsteoEze Gold™ capsules (Venter, 2012). The placebo and medicated capsules were bottled and labelled in the same manner. The medication was produced and randomised by Nativa (Pty) Ltd in accordance with Good Manufacturing Practice (GMP) as stipulated by the South African Medicines Control Council (MCC, 2003). One capsule was to be taken three times a day with meals. If one dose was missed, two capsules could be taken at the next dose (Venter, 2012).

3.6 Reliability and validity measures

The medication and placebo capsules were manufactured by Nativa (Pty) Ltd. according to GMP (MCC, 2003).

The ICOAP scale has been used in 12 different languages, in different locations, by different administrators, and proven to be an effective tool in assessing the pain experienced by patients suffering with OA of the knee (Maillefert et al., 2009). The SPPB
test has been used effectively in various research trials, and is suitable for the age group, as well as for the condition of OA (Lin et al., 2001).

The participants were requested to abstain from using any treatment for their OA, except paracetamol, during the trial, and only when necessary. This approach has been utilised in recent research trials as paracetamol should not interfere with the results (Van Rensburg et al., 2010).

Participants were advised not to take more than 650mg (two 325mg tablets) of paracetamol every four to six hours (FDA, 2011). The use of paracetamol itself was evaluated with the Participant Medication Record (Appendix C) to further assess the effectiveness of the treatment on pain during the 16-week period.

Phlebotomy was performed by a professional nursing sister in privacy at the University of Johannesburg, Doornfontein Homoeopathic Health Clinic. The participant’s blood was transported to Contract Laboratory Services (CLS), a registered laboratory, for analysis.

3.7 Data collection

The objective data was obtained from the Short Physical Performance Battery (SPPB) assessment (Appendix E). The subjective data was obtained from the measure of Intermittent and Constant OA Pain (ICOAP) scale: knee version (Appendix D).

3.8 Statistical analysis

The data was statistically analysed by a statistician at Statkon. Frequencies and descriptives were applied to the data. Crosstabs were used to analyse group and gender. A test for normality, the Shapiro-Wilk test, was applied. The next set of tests was used to compare between groups (inter-group analysis). If the Shapiro-Wilk test result was normal, this would have been done with a t-test, and if the result was abnormal, the Mann-Whitney U test would be utilised. Next, comparisons within groups over time (intra-group analysis), were carried out. This was done using the Friedman test. If differences over time within the
groups were found, a Wilcoxon signed rank test would be applied to find out where these differences occurred (Becker, 2013).

### 3.9 Ethics

Participation in this research was completely voluntary and participants were able to leave the study at any point. The eligible participants signed a participant information and consent form (Appendix B) before starting the study, which explained in detail all the procedures which would take place during the study. Participants were able to ask questions at any stage, and these were appropriately answered by the researcher.

Participants were allowed to use paracetamol for pain relief. If the pain experienced by the participant became too severe, requiring the participant to use an alternative medication such as NSAIDs or corticosteroid therapy, the participant was excluded from the study and referred for further treatment.

There were no anticipated risks or side effects expected in taking OsteoEze Gold™, as any persons with shellfish allergy had been excluded from the study at the outset. However, the participants were advised to discontinue the product immediately and contact the researcher if any adverse reactions occurred (Venter, 2012).

Confidentiality and anonymity were maintained, as identification details regarding participants have been excluded from the dissertation. This information and case files are limited to researchers’ access only. Privacy was maintained as all consultations took place in a private setting.

The results of the study and which group participants were allocated to, was made available to every participant. Participants that were allocated to the placebo group had the opportunity to receive a four month supply of OsteoEze Gold™ from Nativa (Pty) Ltd. once the study had ceased.
CHAPTER FOUR – RESULTS

4.1 Introduction

The aim of this study was to determine the efficacy of OsteoEze Gold™ on osteoarthritis (OA) of the knee. Sixty-seven participants, who fulfilled the inclusion and exclusion criteria, were recruited for the study. Forty-eight participants completed the study – 21 from the placebo group, and 27 from the treatment group. The sample consisted of male and females between the ages of 45 and 75 years old. Objective data was obtained utilising the Short Physical Performance Battery (SPPB) test. Subjective data was obtained utilising the measure of Intermittent and Constant Osteoarthritis Pain (ICOAP) scale: knee version.

4.2 Statistical tests

4.2.1 Cross tabulations and descriptives of variables

Cross tabulations (crosstabs) is a process used to evaluate the distribution of variables within and between related groups. Descriptives of variables are utilised to illustrate how different variables vary within and between groups (UCLA Statistical Consulting Group, 2013).

4.2.2 The p-value

The p-value represents the probability of producing the same results if the null hypothesis is true. A p-value of less than 0.05 (p < 0.05) is considered a significant result, with a 95% confidence level. A p-value of less than 0.01 (p < 0.01) is considered highly significant (Goodman, 2008).
4.2.3 Shapiro-Wilk and Kolmogorov-Smirnov tests

The Shapiro-Wilk and Kolmogorov-Smirnov tests are tests for normality. The tests were applied to the data to evaluate if the sample was derived from a normally distributed population. The Kolmogorov-Smirnov test is normally only utilised in studies with larger sample groups. In other statistical tests, a $p$-value less than 0.05 ($p < 0.05$) is considered significant, however, in a test for normality, a $p$-value greater than 0.05 ($p > 0.05$) is considered normal (Becker, 2013; Lund & Lund 2013).

4.2.4 Mann-Whitney U test and t-test

The Mann-Whitney U test and t-test are tests utilised in inter-group analysis. The tests are applied to the data to assess if there were any differences between groups at a specific time during the study. The Mann-Whitney U test is a non-parametric test and the t-test is a parametric test. The Mann-Whitney U test is utilised if the test for normality produces an abnormal $p$-value, as it is considered more robust than the t-test. The Mann-Whitney U test is also more suitable for smaller research samples. If the median value of the two groups is different at the onset of the study this may interfere with the results. The test may show that there is no significance difference between the groups over time even though there was a significant difference within the groups over time (Pallant, 2010; Jacobson, 2011; Becker, 2013).

4.2.5 Friedman test and Wilcoxon Signed Ranks test

The Friedman test is a non-parametric test which is used in an intra-group analysis. The test assessed if there were any significant differences over time within a group, i.e. from the initial consultation (week-0) to the final consultation (week-16). If there are any significant results, then the Wilcoxon Signed Ranks test is applied to assess where in time the differences occurred, i.e. from the initial to the second consultation or from the second consultation to the final consultation (Pallant 2010; Jacobson, 2011; Becker, 2013).  

51
4.2.6 Bonferroni adjustment

The Bonferroni adjustment is used when there are multiple comparisons, to ensure there are no false positive significant results (Bland, 2007; Becker, 2013).

4.3 Demographics

Cross tabulation (crosstabs) and descriptives were applied to the data collected to analyse gender and age (Appendix I).

4.3.1 Gender

Crosstabs showed that the gender was equally distributed between the placebo and treatment groups. There were:

- 19 female and two male participants in the placebo group; and
- 24 female and three male participants in the treatment group.

4.3.2 Age

The age of the participants was evenly distributed in the both groups. The mean value of age for the placebo and treatment group was 64 and 58 years old respectively.
The largest percentage of participants in the placebo group were between the ages of 66 and 75 years old (10 of the 21 participants in the placebo group = 48%). In the treatment group, the majority of participants were between the ages of 56 and 65 years (15 of the 27 participants in the treatment group = 55%).

<table>
<thead>
<tr>
<th>Age group</th>
<th>Placebo group</th>
<th>Treatment group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of</td>
<td>Number of</td>
</tr>
<tr>
<td></td>
<td>participants</td>
<td>participants</td>
</tr>
<tr>
<td>45 – 55 years</td>
<td>3</td>
<td>8</td>
</tr>
<tr>
<td>55 – 65 years</td>
<td>8</td>
<td>15</td>
</tr>
<tr>
<td>65 – 75 years</td>
<td>10</td>
<td>4</td>
</tr>
<tr>
<td>Total</td>
<td>21</td>
<td>27</td>
</tr>
</tbody>
</table>

Table 4.1 Tabulation of participants per age category and relevant percentage per study group
4.4 The measure of Intermittent and Constant Osteoarthritis Pain (ICOAP) scale: knee version results

Data from the measure of Intermittent and Constant Osteoarthritis Pain (ICOAP) scale: knee version was collected at the initial consultation (week-0), the second consultation (week-8), and the final consultation (week-16). A Mann-Whitney U test was applied to the data during inter-group analysis (Appendix J). The Friedman and Wilcoxon-Signed Ranks tests were applied during intra-group analysis (Appendix K). Descriptives of variables was applied (Appendix L).

The ICOAP scale consists of three sections which were analysed independently:

- Section A – constant pain;
- Section B – intermittent pain; and
- Section C – paracetamol usage.

The total of the combined scores of the three sections was also analysed. An increase in score indicates worsening of symptoms, and a decrease in score indicates an improvement of symptoms.

4.4.1 Section A – constant pain

The score for section A of the ICOAP scale indicated the severity of the constant osteoarthritic knee pain experienced by the participants.

<table>
<thead>
<tr>
<th>Consultation</th>
<th>Initial (week-0)</th>
<th>Second (week-8)</th>
<th>Third (week-16)</th>
<th>Mean difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment group</td>
<td>7.815</td>
<td>2.148</td>
<td>1.556</td>
<td>- 6.259</td>
</tr>
<tr>
<td>Placebo group</td>
<td>5.857</td>
<td>4.429</td>
<td>3.429</td>
<td>- 2.428</td>
</tr>
</tbody>
</table>

Table 4.2 Tabulation of the mean value (descriptives of variables), for section A (constant pain), at each consultation for each group and mean difference from initial to third consultation
The mean value of section A, for the treatment group, decreased from 7.815 to 1.556 (mean difference = -6.259). There was a bigger mean difference between the initial and second consultations (-5.667), than between the second and third consultations (-0.592), in this group.

The mean value of section A, for the placebo group, decreased from 5.857 to 3.429 (mean difference = -2.428). There was a larger decrease in the mean difference between the initial and second consultations (-1.428), than between the second and third consultations (-1.000), in this group.

![Bar graph representing the mean value, for section A (constant pain), of the placebo and treatment groups at each consultation](image_url)

**Figure 4.2** Bar graph representing the mean value, for section A (constant pain), of the placebo and treatment groups at each consultation

The Friedman test was applied to the data of section A (constant pain). The treatment group proved to have very significant results ($p = 0.001$), while the placebo group results were not significant ($p = 0.391$).

The Wilcoxon-Signed Ranks test was then utilised to assess where in time the significant results occurred for the treatment group. The test showed that the results were significant.
from the initial consultation to the second consultation \((p = 0.002)\) as well as from the second consultation to the third consultation \((p = 0.002)\).

### 4.4.2 Section B – intermittent pain

The score for section B of the ICOAP scale indicated the severity of the intermittent osteoarthritic knee pain experienced by the participants.

<table>
<thead>
<tr>
<th>Consultation</th>
<th>Initial (week-0)</th>
<th>Second (week-8)</th>
<th>Third (week-16)</th>
<th>Mean difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment group</td>
<td>12.296</td>
<td>7.667</td>
<td>3.857</td>
<td>-6.444</td>
</tr>
<tr>
<td>Placebo group</td>
<td>10.143</td>
<td>4.619</td>
<td>5.852</td>
<td>-6.286</td>
</tr>
</tbody>
</table>

**Table 4.3 Tabulation of the mean value (descriptives of variables), for section B (intermittent pain), at each consultation for each group, and mean difference from initial to third consultation**

The mean value of section B, for the treatment group, decreased from 12.296 to 3.857 (mean difference = -6.444). There was a decrease in the mean difference between the initial and second consultations (-4.629), and there was a decrease in the mean difference between the second and third consultations (-1.815), in this group.

The mean value of section B, for the placebo group, decreased overall from 10.143 to 3.857 (mean difference = -6.286). There was a decrease in the mean difference between the initial and second consultations (-5.524), and there was a decrease between the second and third consultations (-0.762) in this group.
Figure 4.3 Bar graph representing the mean value, for section B (intermittent pain), of the placebo and treatment groups at each consultation

The Friedman test was applied to the data of section B. The treatment and placebo group both demonstrated significant results, $p = 0.015$ and $p = 0.023$ respectively.

The Wilcoxon-Signed Ranks test was then utilised to assess where in time the significant results occurred for the treatment and placebo groups. The test showed that the results for the treatment group were significant from the initial consultation to the second consultation (0.015) and from the second consultation to the third consultation (0.000). The results for the placebo group were significant from the initial consultation to the second consultation (0.000) and from the second consultation to the third consultation (0.023).

4.4.3 Section C – paracetamol usage

The score for section C of the ICOAP scale indicated the quantity of paracetamol used by the participants for their osteoarthritic pain.
### Table 4.4 Tabulation of the mean value (descriptives of variables), for section C (paracetamol usage), at each consultation for each group, and mean difference from initial to third consultation

<table>
<thead>
<tr>
<th>Consultation</th>
<th>Initial (week-0)</th>
<th>Second (week-8)</th>
<th>Third (week-16)</th>
<th>Mean difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment group</td>
<td>2.370</td>
<td>1.519</td>
<td>.741</td>
<td>- 1.629</td>
</tr>
<tr>
<td>Placebo group</td>
<td>2.667</td>
<td>2.810</td>
<td>1.238</td>
<td>- 1.429</td>
</tr>
</tbody>
</table>

The mean value of section C, for the treatment group, decreased from 2.370 to 0.741 (mean difference = -1.629). There was a decrease in the mean difference between the initial and second consultations (-0.851), and a decrease in the mean difference between the second and third consultations (-0.778) in this group.

The mean value of section C, for the placebo group, decreased from 2.667 to 1.238 (mean difference = -1.429). There was an increase in the mean difference between the initial and second consultations (+0.143), and a decrease between the second and third consultations (-1.572) in this group.

**Figure 4.4** Bar graph representing the mean value, for section C (paracetamol usage), of the placebo and treatment groups at each consultation
The Friedman test was applied to the data of section C. The treatment and placebo group both demonstrated significant results, \( p = 0.000 \) and \( p = 0.010 \) respectively.

The Wilcoxon-Signed Ranks test was then utilised to assess where in time the significant results occurred for the treatment and placebo groups. The test showed that the results for the treatment group were significant from the initial consultation to the second consultation (0.000) and from the second consultation to the third consultation (0.000). The results for the placebo group were significant from the initial consultation to the second consultation (0.015) and from the second consultation to the third consultation (0.005).

### 4.4.4 Total score for the ICOAP scale

The score from all three sections of ICOAP scale were combined and analysed as a total score.

<table>
<thead>
<tr>
<th>Consultation</th>
<th>Initial (week-0)</th>
<th>Second (week-8)</th>
<th>Third (week-16)</th>
<th>Mean difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment group</td>
<td>22.481</td>
<td>11.333</td>
<td>8.148</td>
<td>-14.333</td>
</tr>
<tr>
<td>Placebo group</td>
<td>18.667</td>
<td>11.857</td>
<td>8.524</td>
<td>-10.143</td>
</tr>
</tbody>
</table>

**Table 4.5 Tabulation of the mean value (descriptives of variables), for the total score of the ICOAP scale, at each consultation for each group, and the mean difference from the initial to the third consultation**

The mean value of the total score of the ICOAP scale, for the treatment group, decreased from 22.481 to 8.148 (mean difference = -14.333). There was a decrease in the mean difference between the initial and second consultations (-11.148), and a decrease in the mean difference between the second and third consultations (-3.185) in this group.

The mean value of the total score of the ICOAP scale, for the placebo group, decreased from 18.667 to 8.524 (mean difference = -10.143). There was a decrease in the mean
difference between the initial and second consultations (-6.810), and a decrease between the second and third consultations (-3.333) in this group.

![Bar graph](image.png)

**Figure 4.5 Bar graph representing the mean value of the total score for the ICOAP scale, for the placebo and treatment groups, at each consultation**

The Friedman test was applied to the data, and the treatment and placebo group both demonstrated significant results, $p = 0.000$ and $p = 0.003$ respectively.

The Wilcoxon-Signed Ranks test was then utilised to assess where in time the significant results occurred for the treatment and placebo groups. The test showed that the results for the treatment group were significant from the initial consultation to the second consultation (0.000) and from the second consultation to the third consultation (0.000). The results for the placebo group were significant from the initial consultation to the second consultation (0.005) and from the second consultation to the third consultation (0.001).
4.5 The Short Physical Performance Battery (SPPB) test results

Data from the Short Physical Performance Battery (SPPB) test was collected at the initial consultation (week-0), second consultation (week-8) and final consultation (week-16). A Mann-Whitney U test was applied to the data during inter-group analysis (Appendix J). The test inflates the scores to decrease risk of error during the analysis. The Friedman and Wilcoxon-Signed Ranks tests were applied during intra-group analysis (Appendix K).

The SPPB test consists of two sections which were analysed independently:

- A chair test; and
- A gait test.

For both these tests an increase in score indicates a worsening of symptoms and a decrease in score, an improvement of symptoms.

4.5.1 The chair test

The score for the chair test represented the time in seconds for the participant to complete five repetitions of chair rises (standing from sitting position).

<table>
<thead>
<tr>
<th>Consultation</th>
<th>Initial (week-0)</th>
<th>Second (week-8)</th>
<th>Third (week-16)</th>
<th>Mean difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment group</td>
<td>17.9430</td>
<td>15.3926</td>
<td>13.6763</td>
<td>- 4.2667</td>
</tr>
<tr>
<td>Placebo group</td>
<td>14.9437</td>
<td>14.3124</td>
<td>14.0719</td>
<td>- 0.8718</td>
</tr>
</tbody>
</table>

Table 4.6 Tabulation of the mean value (descriptives of variables), for the chair test, at each consultation, for each group, and the mean difference from the initial to the third consultation

The mean value of the chair test, for the treatment group, decreased from 17.9430 to 15.3926 (mean difference = -4.2667). There was a decrease in the mean difference
between the initial and second consultations (-2.5504), and between the second and third consultations (-2.2563) for this group.

The mean value of the chair test, for the placebo group, decreased from 14.9437 to 14.0719 (mean difference = -0.8718). There was a decrease in the mean difference between the initial and second consultations (-0.6313), and between the second and third consultations (-0.2405) for this group.

Figure 4.6 Bar graph representing the mean value for the chair test, for the placebo and treatment groups, at each consultation

The Friedman test was applied to the data for the chair test. The treatment group proved to have very significant results \((p = 0.000)\), while the placebo group results were not significant \((p = 0.286)\).

The Wilcoxon-Signed Ranks test was then utilised to assess where in time the significant results occurred. The test showed that the results were significant for the treatment group from the initial consultation to the second consultation \((p = 0.009)\), as well as from the second consultation to the third consultation \((p = 0.000)\).
4.5.2 The gait test

The score for the gait test represented the time it took, in seconds, for the participant to complete a 4m walk.

<table>
<thead>
<tr>
<th>Consultation</th>
<th>Initial (week-0)</th>
<th>Second (week-8)</th>
<th>Third (week-16)</th>
<th>Mean difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment group</td>
<td>5.0937</td>
<td>4.6189</td>
<td>4.5933</td>
<td>- 0.5004</td>
</tr>
<tr>
<td>Placebo group</td>
<td>4.9924</td>
<td>4.8005</td>
<td>5.0248</td>
<td>+ 0.0324</td>
</tr>
</tbody>
</table>

Table 4.7 Tabulation of the mean value (descriptives of variables), for the gait test, at each consultation, for each group, and the mean difference from the initial to the third consultation

The mean value of the gait test, for the treatment group, decreased from 5.0937 to 4.5933 (mean difference = - 0.5004). There was a decrease in the mean difference between the initial and second consultations (- 0.4748) and between the second and third consultations (-0.0256) for this group.

The mean value of the gait test, for the placebo group, increased from 4.9924 to 5.0248 (mean difference = + 0.0324). There was a decrease in the mean difference between the initial and second consultations (-0.1919), and an increase between the second and third consultations (+0.2243) for this group.
Figure 4.7 Bar graph representing the mean value for the gait test, for the placebo and treatment groups, at each consultation

The Friedman test was applied to the data of the chair test. The treatment group proved to have significant results ($p = 0.032$), while the placebo group results were not significant ($p = 0.795$).

The Wilcoxon-Signed Ranks test was then utilised to assess where in time the significant results occurred for the treatment group. The test showed that the results were significant for the treatment group from the initial consultation to the second consultation ($p = 0.017$) as well as from the second consultation to the third consultation ($p = 0.025$).
CHAPTER FIVE – DISCUSSION

5.1 Introduction

Data was collected from all the participants in the placebo and treatment groups over three consultations (week-0, week-8 and week-16).

The subjective data was obtained from the measure of Intermittent and Constant Osteoarthritis Pain (ICOAP) scale: knee version which consisted of three sections:

- Section A – constant pain;
- Section B – intermittent pain; and
- Section C – paracetamol usage.

The objective data was obtained from the Short Physical Performance Battery (SPPB) test which consisted of two sections:

- A chair test; and
- A gait test.

Each component, from both the ICOAP and the SPPB assessment tools, was analysed independently, and the total score for the ICOAP scale was also analysed.

5.2 The measure of Intermittent and Constant Osteoarthritis Pain (ICOAP) scale: knee version

5.2.1 Section A – constant pain

Section A showed highly significant results ($p = 0.001$) according to the Friedman test for the treatment group. The placebo group did not produce significant results ($p = 0.391$). The Wilcoxon-Signed Ranks test demonstrated that the results for the treatment group were
significant from the first to the second consultation, as well as from the second to the third consultation.

According to the frequencies of measure the mean value of the treatment group decreased by 6.259, from the initial consultation (7.815), to the last consultation (1.556). The mean value of the placebo group decreased by 2.428 from the initial consultation (5.857), to the last consultation (3.429).

An increase in the mean value indicates an increase in the severity of symptoms and a decrease in mean value indicates a decrease in severity. Both the treatment and placebo groups showed a decrease in severity of symptoms. The results for the placebo were not significantly different according to the Friedman test therefore the treatment group outperformed the placebo group.

This demonstrates that the OsteoEze Gold™ was effective in reducing constant knee pain in individuals suffering from osteoarthritis of the knee.

5.2.2 Section B – intermittent pain

Section B showed significant results for both the placebo and treatment group when the Friedman test was applied. The Wilcoxon-Signed Ranks test found that the results for both the treatment group and placebo group were significant between the initial consultation and second consultation, as well as between the second consultation and third consultation.

According to the frequencies of measures the mean value of the treatment group decreased by 6.444, from the initial consultation (12.296), to the last consultation (5.852). The mean value of the placebo group decreased by 6.286 from the initial consultation (10.143), to the last consultation (3.857). The treatment group and placebo group showed equal reduction in severity of symptoms.
This indicates that the OsteoEze Gold™ did not demonstrate an efficacy over placebo in the management of intermittent knee pain in individuals suffering from osteoarthritis of the knee.

### 5.2.3 Section C – paracetamol usage

Section C showed significant results for both the placebo and treatment group when the Friedman test was applied. The Wilcoxon-Signed Ranks test found that the results for both the treatment group and placebo group were significant between the initial consultation and second consultation as well as between the second consultation and third consultation.

According to the frequencies of measures the mean value of the treatment group decreased by 1.629, from the initial consultation (2.370), to the last consultation (0.741). The mean value of the placebo group decreased by 1.429 from the initial consultation (2.667), to the last consultation (1.238). The treatment group slightly outperformed the placebo group however both had significant reductions.

This indicates that OsteoEze Gold™ was not significantly different to placebo in reducing the usage of paracetamol for relieving knee pain in individuals suffering from osteoarthritis of the knee.

### 5.2.4 Total ICOAP score

According to the Friedman test, the results for the total ICOAP scale illustrated that both the placebo and treatment group produced significant results. The treatment group produced more significant results ($p = 0.000$) as opposed to the placebo group ($p = 0.003$). The Wilcoxon-Signed Ranks test found that the results for the treatment group were highly significant ($p = 0.000$) between the initial consultation and second consultation, as well as between the second consultation and third consultation ($p = 0.000$).

When the frequency of measures was applied to the data the mean value of the treatment group decreased by 14.333, from the initial consultation (22.481), to the last consultation
(8.148). The mean value of the placebo group decreased by 10.143 from the initial consultation (18.667), to the last consultation (8.524). Therefore the total ICOAP score demonstrated that the treatment group outperformed the placebo group overall however both produced significant reductions.

This indicates that the OsteoEze Gold™ was not significantly different overall compared to placebo in treating knee pain experienced by individuals suffering with osteoarthritis of the knee.

5.3 The Short Physical Performance Battery (SPPB) test

5.3.1 The chair test

According to the Friedman test, the results from the chair test proved to be highly significant \( p = 0.000 \) when compared to the placebo group \( p = 0.286 \). The Wilcoxon-Signed Ranks test showed that the results for the treatment group were significant \( p = 0.009 \) between the initial consultation to the second consultation, and highly significant \( p = 0.000 \) between the second consultation and the third consultation.

When the frequency of measures was applied, the mean value of the treatment group decreased by 4.2667 from the initial consultation (17.9430), to the last consultation (13.6763). The mean value of the placebo group decreased by 0.8591 from the initial consultation (14.9431), to the last consultation (14.0719). Therefore the treatment group outperformed the placebo group in the chair test.

This indicates that the OsteoEze Gold was significantly effective in improving the ability of standing and sitting in individuals suffering from osteoarthritis of the knee.

5.3.2 The gait test

The results from the gait tests proved to be significant \( p = 0.032 \) when compared to the placebo group \( p = 0.795 \). The Wilcoxon-Signed Ranks test showed that the results were
significant between the initial consultation and the second consultation \((p = 0.017)\) and between the second consultation and third consultation \((p = 0.025)\).

When the frequency of measures was applied, the mean value of the treatment group decreased by 0.5004 from the initial consultation (5.0937), to the last consultation (4.5933). The mean value of the placebo group increased by 0.0324 from the initial consultation (4.9924), to the last consultation (5.0248). Therefore the treatment group outperformed the placebo group in the gait test.

This indicates that the OsteoEze Gold was significantly effective in improving the walking ability of individuals suffering from osteoarthritis of the knee.

5.4 Participant variance

5.4.1 Matching of participants

Participants were matched at the beginning of the study according to gender, age and severity of symptoms. Although this procedure was followed as accurately as possible, there was a difference in the mean values of the ICOAP and SPPB scores at the initial consultation. This may have occurred due to the number of participants that dropped out of the study (19 participants). This affected the accuracy of the matching process as most of the dropout participants originated from the placebo group.

The most prevalent reason for a participant dropping out of the study was the worsening, or non-improvement, of the participant’s symptoms. This may have contributed to the placebo group ultimately consisting of more participants with less severe symptoms.

5.4.2 Demographics of the participants

Five males and 43 females completed the research study. Gender was equally distributed between the two groups: two males and 19 females in the placebo group; and three males and 24 females in the treatment group. More females than males completed the study,
however this distribution reflects the prevalence of osteoarthritis (OA) of the knee in the general population (McKee, 2009).

The age of the participants was evenly distributed in the placebo and treatment group. The mean value of age for the placebo and treatment group was 64 and 58 years old respectively. The severity of OA increases with age and is more prevalent in the elderly (Lozada, 2011). As the mean age of the placebo group was higher than the treatment group, the results may have been influenced.

5.4.3 Participant subjectivity and compliance

The ICOAP scale is based on the participant’s analysis of the pain they experienced. Therefore there may have been discrepancies in the severity of pain reported by the participant and the actual pain experienced. Data from the scale was collected every eight weeks, however, the scale referred only to the pain experienced in the week leading up to the consultation. This may have resulted in a variation as the data only reflected one week out of the eight.

Participants were requested at the beginning of the study to use paracetamol instead of NSAIDs for pain, and to refrain from taking paracetamol on the day of the consultation. However, if participants did not comply with this request, both the ICOAP and SPPB assessment results might have been affected.
CHAPTER SIX – CONCLUSION AND RECOMMENDATIONS

6.1 Conclusion

The treatment group showed a statistically significant reduction in the constant pain (section A) associated with osteoarthritis of the knee according to the frequency of measures and Friedman test. However, a statistically significant reduction in intermittent knee pain, associated with OA of the knee, was not observed. A statistically significant reduction in paracetamol usage (section C) and an overall reduction in knee pain associated with OA of the knee (ICOAP total), was not demonstrated according to the Friedman test. The tests showed that the treatment group had an improvement in the functional ability of the participants, with regards to standing from a chair (chair test) and walking (gait test). Therefore the treatment group had a positive effect on the subjective data (ICOAP scale) and the objective data (SPPB test).

These results support the hypothesis that OsteoEze Gold™ is effective in the treatment of the symptoms and signs associated with osteoarthritis of the knee. No significant side-effects were reported during the study. This further supports the use of OsteoEze Gold™ as an alternative treatment for osteoarthritis of the knee.

6.2 Recommendations for future research

The research study could be improved upon when considering the following recommendations:

- The length of the study could be increased to six months, as most research studies on OA are conducted for six months or longer. This is due to the chronic nature of the condition.

- The participants were required to take a capsule orally three times a day. A participant medication record (Appendix C) was collected at the second (week-8) and final consultation (week-16) from each participant to ensure compliance.
However even with this measure in place, participant compliance may have still affected the results. In future research the dosage of the medication could be altered to three capsules once a day. This dosage has been utilised in other successful research trials on OA of the knee (Uelbelhart et al., 2004; Herrero-Beaumont et al., 2007).

- Future research could be conducted over multiple sites to reduce the number of dropouts. Some of the participants that dropped out of the study reported transport as the reason for doing so. Therefore increasing the sites involved with the study could prevent this from occurring.

- The ICOAP scale is subjective and the results may have been influenced by how the participant was feeling on that particular day or what occurred during that week. In future research two different options could be considered: the scale could be administered every week of the trial; or an alternative scale pertaining to the previous month as opposed to the previous week could be utilised.

- Matching of participants according to age, gender and severity of symptoms was followed at the beginning of the study. Although this process was undertaken, it became more difficult to follow as participants dropped out and new participants were required to join the study. In future research more rigorous matching could be followed. Due to the lower initial median values of the placebo group the Mann-Whitney U test showed that there was no difference between groups at the second and last consultations. As the placebo group started with lower median values they remained similar to the treatment group because the treatment group’s values decreased at a quicker rate.

- The study could be done exclusively on females as the incidence of OA of the knee in females is almost twice as great as in males (McKee, 2009). Only five males completed the study compared to 43 females. This was due to the poor response by potential male participants to the study’s advertisements.
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Are you suffering with osteoarthritis of the knee?
Are you a male or female and between the ages of 50-70 years suffering from knee pain and stiffness when trying to perform your everyday activities?

We are conducting a research study for the Department of Homoeopathy at the University of Johannesburg, Doornfontein campus on:

The effect of OsteoEze Gold™ on inflammatory marker CRP and quality of life in osteoarthritis of the knee.

AND

The effect of OsteoEze Gold™ on pain and functional ability in osteoarthritis of the knee.

This research study has been approved by the Faculty of Health Sciences Higher Degrees and Ethics Committee.

Ethical Clearance No:

If you are interested please contact:

ROMY: 072 107 6568 or KIM: 073 171 2060
Dear prospective participant

Our names are Kim MacQuilkan and Romy Levy. We are final year Homoeopathic students at the University of Johannesburg. We are inviting you to participate in this research study. We are undertaking this research study for our M Tech Homoeopathic qualification:

The effect of OsteoEze Gold™ on inflammatory marker CRP and quality of life in osteoarthritis of the knee - Romy Levy

The effect of OsteoEze Gold™ on pain and functional ability in osteoarthritis of the knee - Kim MacQuilkan

Osteoarthritis (OA) is a common condition which affects the joints of the body. A person with OA often has pain, morning stiffness and decreased movement in the joint. OsteoEze Gold™ is an alternative treatment option for OA which is currently available on the market. It contains glucosamine sulphate and chondroitin sulphate which are found in normal joints and aid in joint support. OsteoEze Gold™ also contains Vitamin C and manganese which are antioxidants which protect against effects of aging on the joint.

We warmly invite you to participate in our research study if you are or have the following:

- Knee pain with at least 3 of the following:
  - Over the age of fifty (but not older than seventy)
  - Morning stiffness less than thirty minutes
  - Crepitus (cracking of knee joint that you can hear and feel)
  - Bony tenderness
  - Bony enlargement
Please be aware of the following, which may exclude you from our research study:

- Individuals with signs, symptoms or diagnosis of any chronic disease
- Conditions that may appear similar to OA of the knee such as rheumatoid arthritis (excluded with rheumatoid factor), gout, septic arthritis or injury
- Individuals with suspected or known shellfish allergy
- Current use of OsteoEze Gold™ or any other herbal or nutritional supplementation in the month leading to the start of the study
- Regular use or dependency of anti-inflammatory medication such as NSAIDS e.g. ibuprofen
- Blood test with positive result for rheumatoid factor (RF) over 1:40
- Level of an inflammatory marker called c-reactive protein (CRP) below 3mg/L

Our research aims to assess your symptoms of OA for a period of 16 weeks, consisting of an initial consultation, a follow-up consultation at 8 weeks and final assessment consultation at 16 weeks. Once you have signed this consent form and agreed to participate in this research study you will be requested to be present at the University of Johannesburg, Doornfontein campus, Homoeopathic Health Centre for consultations.

There are certain criteria that need to be evaluated before we can invite you to participate in this study. Two factors have to be assessed through a blood test: Rheumatoid Factor (a positive test will show that you have rheumatoid arthritis and not OA) and C-reactive protein (CRP is a blood test that measures the inflammation in your body). This will be done by a qualified nursing sister at the University of Johannesburg Health Centre.

You will be randomly allocated to one of two groups, either the experimental group or the placebo group. The placebo group is referred to as the control group. This will ensure that the study is unbiased and the results will show if OsteoEze Gold™ proves more effective than the placebo. The experimental group will receive the OsteoEze Gold™ capsules. Each capsule of OsteoEze Gold™ 500mg glucosamine sulphate, 267mg chondroitin sulphate, 50mg vitamin C and 1mg manganese. The placebo group will be given unmedicated placebo capsules.
Capsules will be given at initial consultation, four weeks, eight weeks and twelve weeks and will be labelled and coded in such a way that neither you, nor we, will know who has received the treatment or who has received the unmedicated placebo. In addition you will receive a Participant Medication Record with which you are requested to record daily, number of capsules taken and any side-effects that may be experienced. You will be allowed to take paracetamol for severe pain, please record the amounts taken accurately in the Participant Medication Record. These records will be collected every four weeks. Honesty with regard to record taking is very important to the results of the study. If your osteoarthritic pain becomes too severe that it requires you to take other forms of medication such as non-steroidal anti-inflammatory drugs (NSAIDs) or corticosteroid therapy, you will be excluded from the study and referred for further treatment.

Each consultation (initial, eight week and sixteen week) will take place at the University of Johannesburg, Doornfontein Homoeopathic Health Clinic and consist of:

- Evaluation of their vital signs (blood pressure, heart rate, respiratory rate and temperature)
- Quality of life using a thirty-six question, lifestyle assessment known as the SF-36 short form health questionnaire
- A pain scale called the Intermittent and Constant Osteoarthritic Pain assessment
- A functional assessment known as the Short Physical Performance Battery
- Blood test tracking the inflammatory marker CRP

The benefit of partaking in this study is the possible improvement of symptoms of OA of the knee through the use of a natural supplement, with less potential side-effects than conventional medication. The participation in this study is on a voluntary basis and you are free to withdraw from this study at anytime. A signed copy of this consent form will be made available to you. Individuals who were allocated to the placebo group, and did not receive the medicated capsules, will have the opportunity to be provided with sixteen week supply of OsteoEze Gold™, at no cost to you, once the research study has ended.
We have fully explained the procedure and the purpose of this study. We have also asked if the participant has any other questions relating to any part of this study and have answered and will be able to further answer any future questions to the best of our abilities.

Date: __________________

Researcher: Kim MacQuilkan  Signature:______________________
Researcher: Romy Levy  Signature:______________________

I have read this patient information and consent form. I have been fully informed about the procedures to be conducted in this research study. If at any time, I have more questions about this study, I understand that they will be answered by the researchers. In signing this consent form, I agree to fully undertake the tasks that are requested of me and understand that I may withdraw my participation at anytime during the course of this study.

Date: __________________

Participant: __________________  Signature:______________________

Supervisor: Dr Caminsky  Signature:______________________

CONTACT DETAILS:

Researcher: Kim MacQuilkan  Supervisor: Dr. M. Caminsky
Cell No: 073 171 2060  Office No: 011 559 5000

Researcher: Romy Levy  Co-supervisor: Dr. G. Yutar
Cell No: 072 107 6568
APPENDIX C – PARTICIPANT MEDICATION RECORD

Month ________ Number ________
Name ___________________________ Participant Group ________

Please make a note of how many capsules you have taken each day, any side effects you may have experienced and if and how many paracetamol are taken each day for your osteoarthritic knee pain. Please include the dosage of paracetamol that you have taken (e.g. 500mg tablet).

<table>
<thead>
<tr>
<th>Week</th>
<th>Monday</th>
<th>Tuesday</th>
<th>Wednesday</th>
<th>Thursday</th>
<th>Friday</th>
<th>Saturday</th>
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<tbody>
<tr>
<td>1</td>
<td>Capsules</td>
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<td>2</td>
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<td>Side Effects</td>
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<td></td>
<td>Paracetamol</td>
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<td>Capsules</td>
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APPENDIX D – A MEASURE OF INTERMITTANT AND CONSTANT OSTEOARTHRITIC PAIN: ICOAP: KNEE VERSION

Participant name: ________________________________ Assessment number: ____
Participant group: _______ Tester’s signature ____________________ Date: ______

To get a better sense of the different types of knee pain you may experience, I would like to ask you about any “constant pain” (pain you have all the time) separately from any pain you may experience less often, that is, “pain that comes and goes”. The following questions will ask you about the pain that you have experienced in your knee in the past week.

A) CONSTANT PAIN

For each of the following questions tell me the response that best describes, on average, your constant knee pain in the past week.

1. In the past week, how intense has your constant knee pain been?

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<tr>
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<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not at all/ No constant knee pain</td>
<td>Mildly</td>
<td>Moderately</td>
<td>Severely</td>
<td>Extremely</td>
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</tbody>
</table>

2. In the past week, how much has your constant knee pain affected your sleep?

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<th>4</th>
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<tbody>
<tr>
<td>Not at all/ No constant knee pain</td>
<td>Mildly</td>
<td>Moderately</td>
<td>Severely</td>
<td>Extremely</td>
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</table>

3. In the past week, how much has your constant knee pain affected your overall quality of life?

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<tbody>
<tr>
<td>Not at all/ No constant knee pain</td>
<td>Mildly</td>
<td>Moderately</td>
<td>Severely</td>
<td>Extremely</td>
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</table>

4. In the past week, how frustrated or annoyed have you been by your constant knee pain?

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<th>3</th>
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<tbody>
<tr>
<td>Not at all/ No constant knee pain</td>
<td>Mildly</td>
<td>Moderately</td>
<td>Severely</td>
<td>Extremely</td>
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</table>
5. In the past week, how upset or worried have you been by your constant knee pain?

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<tbody>
<tr>
<td></td>
<td>Not at all/ No constant knee pain</td>
<td>Mildly</td>
<td>Moderately</td>
<td>Severely</td>
<td>Extremely</td>
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</table>

B) PAIN THAT COMES AND GOES

For each of the following questions, please tell me the response that best describes your knee pain that comes and goes, on average, in the past week.

6. In the past week, how intense has your most severe knee pain that comes and goes been?

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<tbody>
<tr>
<td></td>
<td>Not at all/ No constant knee pain</td>
<td>Mildly</td>
<td>Moderately</td>
<td>Severely</td>
<td>Extremely</td>
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7. In the past week, how frequently has your most severe knee pain that comes and goes been?

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<tbody>
<tr>
<td></td>
<td>Not at all/ No constant knee pain</td>
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<td>Moderately</td>
<td>Severely</td>
<td>Extremely</td>
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</table>

8. In the past week, how much has your knee pain that comes and goes affected your sleep?

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<tbody>
<tr>
<td></td>
<td>Not at all/ No constant knee pain</td>
<td>Mildly</td>
<td>Moderately</td>
<td>Severely</td>
<td>Extremely</td>
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</table>

9. In the past week, how much has your knee pain that comes and goes affected your overall quality of life?

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<tbody>
<tr>
<td></td>
<td>Not at all/ No constant knee pain</td>
<td>Mildly</td>
<td>Moderately</td>
<td>Severely</td>
<td>Extremely</td>
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10. In the past week, how frustrated or annoyed have you been by your knee pain that comes and goes?

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<tbody>
<tr>
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<td>Mildly</td>
<td>Moderately</td>
<td>Severely</td>
<td>Extremely</td>
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</table>

11. In the past week, how upset or worried have you been by your knee pain that comes and goes?

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<tbody>
<tr>
<td>Not at all/ No constant knee pain</td>
<td>Mildly</td>
<td>Moderately</td>
<td>Severely</td>
<td>Extremely</td>
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</tbody>
</table>

C) PARACETAMOL USAGE

12. In the past week, how often did you need to use paracetamol for your knee pain?

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<tbody>
<tr>
<td>Never</td>
<td>Rarely</td>
<td>Sometimes</td>
<td>Often</td>
<td>Everyday</td>
</tr>
</tbody>
</table>

TOTAL SCORE FOR CONSTANT PAIN /
DIVIDED BY 5 FOR AVERAGE SCORE

TOTAL SCORE FOR INTERMITTANT PAIN /
DIVIDED BY 6 FOR AVERAGE SCORE

SCORE FOR PARACETAMOL USAGE

With relevant permission from Gillian Hawker, MD, M.Sc author of this assessment tool (Available download from: http://www.oarsi.org/index2.cfm?section=OARSI_Initiatives&content=Pain_Radiological_Indexes (Accessed 07/07/11)
APPENDIX E – SHORT PHYSICAL PERFORMANCE BATTERY PROTOCOL AND SCORE SHEET

Participant name: _______________________________ Assessment number: ____
Participant group: ____ Tester’s signature __________________________ Date: ______

Scores for each participant will be recorded in seconds for both speed of gait and rising from a chair tests. Ensure that the participant knows exactly what is being asked of them.

1. GAIT SPEED TEST

I am going to observe how you walk normally. I would like you to walk between this and that point which is 4m long. If you use a cane or any other walking aid you can use it to help you. I would like you to walk at your normal walking speed. When I want you to start walking I will say: “Ready, begin.” We are going to do this test one more time once you are ready and I want you start walking when I say “Ready begin”.

Time of first 4m walk in seconds: ________________________________
Time of second 4m walk in seconds: ________________________________
Time of the faster of the two 4m walks: _____________________________ Able to complete test: YES/NO

2. REPEATED CHAIR STAND TEST

Do you think it would be safe for you to try to stand up from a chair without using your arms? This test measures the strength in your legs. First, fold your arms across your chest and sit so that your feet are on the floor; then stand up keeping your arms across your chest. Do you think it would be safe for you to try to stand up from a chair five times without using your arms?

Time of 5 chair stands in seconds: _____________________________ Able to complete test: YES/NO

APPENDIX F – CASE TAKING FORM – INITIAL CONSULTATION

Participant name: _______________________________ Assessment number: ____
Participant group: _______ Tester’s signature_________________________ Date: ______

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<thead>
<tr>
<th>PAST MEDICAL HISTORY:</th>
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<tr>
<th>FAMILY HISTORY:</th>
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<tr>
<th>CURRENT MEDICAL HISTORY:</th>
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Additional exams indicated:

<table>
<thead>
<tr>
<th>Allergy to Shellfish:</th>
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<table>
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<tr>
<th>Current use of NSAIDS or other pain medication :</th>
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<table>
<thead>
<tr>
<th>Supplements:</th>
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<table>
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<tr>
<th>Other medication:</th>
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<tr>
<th>SOCIAL HISTORY:</th>
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### PHYSICAL EXAMS:

#### VITALS:

<table>
<thead>
<tr>
<th></th>
<th>Result</th>
<th>Comments</th>
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<tbody>
<tr>
<td>Blood pressure</td>
<td></td>
<td></td>
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<tr>
<td>Respiratory rate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulse</td>
<td></td>
<td></td>
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<tr>
<td>Temperature</td>
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<tr>
<td>CAJCOLD</td>
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#### KNEE EXAM

<table>
<thead>
<tr>
<th></th>
<th>Comments</th>
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<tbody>
<tr>
<td>Observation and passive ROM</td>
<td></td>
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<tr>
<td>Palpation and active ROM (including effusion tests)</td>
<td></td>
</tr>
<tr>
<td>Manoeuvres</td>
<td></td>
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</tbody>
</table>

#### Diagnostic criteria for osteoarthritis of the knee:

- Knee pain with at least 3 out of the 6 following criteria:
- Over the age of 50
- Crepitus
- Morning stiffness less than 30 minutes
- No palpable warmth
- Bony enlargement
- Bony tenderness

| Total score | 6 |
### OTHER EXAMS INDICATED

<table>
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<tr>
<th>OTHER EXAMS INDICATED</th>
<th>COMMENTS</th>
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### Any signs or symptoms of:

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<th>Any signs or symptoms of:</th>
<th>Tick if +</th>
<th>Comment</th>
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<tbody>
<tr>
<td>Rheumatoid arthritis</td>
<td></td>
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<tr>
<td>Septic arthritis</td>
<td></td>
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<tr>
<td>Acute gouty arthritis</td>
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<tr>
<td>Systemic lupus erythematosus (SLE)</td>
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### Any further comments or observations:

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-
APPENDIX G – CASE TAKING FORM – FOLLOW UP CONSULTATION

Participant name:_________________________ Assessment number:_____
Participant group:_______ Tester’s signature_______________________ Date: ______

PHYSICAL EXAMS:

<table>
<thead>
<tr>
<th>VITALS:</th>
<th>Result</th>
<th>Comments</th>
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<tbody>
<tr>
<td>Blood pressure</td>
<td></td>
<td></td>
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<tr>
<td>Respiratory rate</td>
<td></td>
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<td>Pulse</td>
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<td>Temperature</td>
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<tr>
<td>CAJ/COLD</td>
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Any further comments or observations:

<table>
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<tr>
<th>Comment</th>
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APPENDIX H – RANDOMISATION AND PROCEDURE

Capsules for this research will be assigned into either a placebo group or an experimental group. The groups will be coded A or B. Information regarding whether group A or B is the experimental or placebo group will be kept by Nativa (Pty) Ltd.

A procedure will be performed to ensure that participants will be randomly allocated to either group A or B but be matched according to participant’s age, gender and severity of osteoarthritic symptoms (score out of 5).

Eight groups will be created according to age, gender and severity of osteoarthritic symptoms namely:

- Male, age 50 – 60 years, score of 2-3 out of 5
- Male, age 50 – 60 years, score of 4-5 out of 5
- Male, age 60 – 70 years, score of 2-3 out of 5
- Male, age 60 – 70 years, score of 4-5 out of 5
- Female, age 50 – 60 years, score of 2-3 out of 5
- Female, age 50 – 60 years, score of 4-5 out of 5
- Female, age 60 – 70 years, score of 2-3 out of 5
- Female, age 60 – 70 years, score of 4-5 out of 5

Randomisation will be done facilitated using 8 envelopes labelled with the respective groups. The letters A and B will be put in all the envelopes. Each participant will be required to pick a letter from the envelope which corresponds with the group they represent within the study. This will ensure that the participants are randomly and evenly distributed between groups A and B.
APPENDIX I – CROSS TABULATIONS AND DESCRIPTIVES FOR DEMOGRAPHICS

I.1 Gender of participants

<table>
<thead>
<tr>
<th></th>
<th>Placebo group</th>
<th>Treatment group</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>Number 19</td>
<td>Number 24</td>
<td>Number 43</td>
</tr>
<tr>
<td></td>
<td>Percentage 44.2%</td>
<td>Percentage 55.8%</td>
<td>Percentage 100%</td>
</tr>
<tr>
<td>Male</td>
<td>Number 2</td>
<td>Number 3</td>
<td>Number 5</td>
</tr>
<tr>
<td></td>
<td>Percentage 40%</td>
<td>Percentage 60%</td>
<td>Percentage 100%</td>
</tr>
<tr>
<td>Total</td>
<td>Number 21</td>
<td>Number 27</td>
<td>Number 48</td>
</tr>
<tr>
<td></td>
<td>Percentage 43.8%</td>
<td>Percentage 56.3%</td>
<td>Percentage 100%</td>
</tr>
</tbody>
</table>

Table I.1 Cross tabulations applied to gender of the participants.

<table>
<thead>
<tr>
<th></th>
<th>Kolmogorov-Smirnov</th>
<th>Shapiro-Wilk</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Statistic</td>
<td>df</td>
</tr>
<tr>
<td>Gender</td>
<td>Placebo group</td>
<td>.529</td>
</tr>
<tr>
<td></td>
<td>Treatment group</td>
<td>.252</td>
</tr>
</tbody>
</table>

Table I.2 Test for normality applied to gender of the participants.

I.2 Age of participants

<table>
<thead>
<tr>
<th>Age of participants</th>
<th>Statistic</th>
<th>Std. Error</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo group</td>
<td>Maximum age 74</td>
<td>Mean age 64.19</td>
</tr>
<tr>
<td></td>
<td>Minimum age 50</td>
<td></td>
</tr>
<tr>
<td>Treatment group</td>
<td>Maximum age 75</td>
<td>Mean age 58.33</td>
</tr>
<tr>
<td></td>
<td>Minimum age 43</td>
<td></td>
</tr>
</tbody>
</table>

Table I.3 Descriptives applied to ages of the participants.
<table>
<thead>
<tr>
<th></th>
<th>Kolmogorov-Smirnov</th>
<th>Shapiro-Wilk</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Statistic</td>
<td>df</td>
</tr>
<tr>
<td>Age</td>
<td>Placebo group</td>
<td>.116</td>
</tr>
<tr>
<td></td>
<td>Treatment group</td>
<td>.113</td>
</tr>
</tbody>
</table>

Table I.4 Test for normality applied to the ages of the participants.
APPENDIX J – INTER-GROUP COMPARISONS

J.1 The measure of Intermittent and Constant Osteoarthritis Pain (ICOAP) scale: knee version

<table>
<thead>
<tr>
<th>Section and week</th>
<th>Mean</th>
<th>Std. Deviation</th>
<th>Std. Error Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>Section A</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week-0</td>
<td>5.857</td>
<td>8.6850</td>
<td>1.8952</td>
</tr>
<tr>
<td>Week-8</td>
<td>4.429</td>
<td>4.9591</td>
<td>.9544</td>
</tr>
<tr>
<td>Week-16</td>
<td>3.429</td>
<td>7.2427</td>
<td>1.5805</td>
</tr>
<tr>
<td>Section B</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week-0</td>
<td>10.143</td>
<td>9.3074</td>
<td>2.0311</td>
</tr>
<tr>
<td>Week-8</td>
<td>4.619</td>
<td>5.6078</td>
<td>1.2237</td>
</tr>
<tr>
<td>Week-16</td>
<td>3.857</td>
<td>6.3741</td>
<td>1.3909</td>
</tr>
<tr>
<td>Section C</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week-0</td>
<td>2.667</td>
<td>2.1055</td>
<td>.4595</td>
</tr>
<tr>
<td>Week-8</td>
<td>2.810</td>
<td>4.8834</td>
<td>1.0547</td>
</tr>
<tr>
<td>Week-16</td>
<td>1.238</td>
<td>1.6705</td>
<td>.3645</td>
</tr>
<tr>
<td>ICOAP total</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week-0</td>
<td>18.667</td>
<td>8.5401</td>
<td>1.8636</td>
</tr>
<tr>
<td>Week-8</td>
<td>11.857</td>
<td>10.4225</td>
<td>2.2744</td>
</tr>
<tr>
<td>Week-16</td>
<td>8.524</td>
<td>9.2283</td>
<td>2.0138</td>
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</tbody>
</table>

Table J.1 Group statistics of the inter-group analysis of the placebo group for ICOAP scale.

<table>
<thead>
<tr>
<th>ICOAP Treatment group</th>
<th>Mean</th>
<th>Std. Deviation</th>
<th>Std. Error Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>Section A</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week-0</td>
<td>7.815</td>
<td>8.6025</td>
<td>1.6556</td>
</tr>
<tr>
<td>Week-8</td>
<td>2.148</td>
<td>4.9591</td>
<td>.9544</td>
</tr>
<tr>
<td>Week-16</td>
<td>1.556</td>
<td>4.1262</td>
<td>.7941</td>
</tr>
<tr>
<td>Section B</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week-0</td>
<td>12.296</td>
<td>10.0721</td>
<td>1.9384</td>
</tr>
<tr>
<td>Week-8</td>
<td>7.667</td>
<td>7.1897</td>
<td>1.3837</td>
</tr>
<tr>
<td>Week-16</td>
<td>5.852</td>
<td>7.3259</td>
<td>1.4099</td>
</tr>
<tr>
<td>Section C</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week-0</td>
<td>2.370</td>
<td>2.0597</td>
<td>.3964</td>
</tr>
<tr>
<td>Week-8</td>
<td>1.519</td>
<td>1.6260</td>
<td>.3129</td>
</tr>
<tr>
<td>Section and week</td>
<td>Group</td>
<td>Week-0</td>
<td>Placebo 22.48</td>
</tr>
<tr>
<td>-----------------</td>
<td>---------</td>
<td>--------</td>
<td>---------------</td>
</tr>
<tr>
<td>Week-0</td>
<td>Placebo</td>
<td>22.48</td>
<td>-.954</td>
</tr>
<tr>
<td>Treatment</td>
<td></td>
<td>26.07</td>
<td></td>
</tr>
<tr>
<td>Week-8</td>
<td>Placebo</td>
<td>25.19</td>
<td>-.375</td>
</tr>
<tr>
<td>Treatment</td>
<td></td>
<td>23.96</td>
<td></td>
</tr>
<tr>
<td>Week-16</td>
<td>Placebo</td>
<td>25.98</td>
<td>-.875</td>
</tr>
<tr>
<td>Treatment</td>
<td></td>
<td>23.35</td>
<td></td>
</tr>
<tr>
<td>ICOAP total</td>
<td>Week-0</td>
<td>Placebo 22.432</td>
<td>.365</td>
</tr>
<tr>
<td></td>
<td>Treatment</td>
<td>26.11</td>
<td></td>
</tr>
<tr>
<td>Week</td>
<td>Condition</td>
<td>ICOAP Score</td>
<td>Effect Size</td>
</tr>
<tr>
<td>-------</td>
<td>-----------</td>
<td>-------------</td>
<td>-------------</td>
</tr>
<tr>
<td>Week-8</td>
<td>Placebo</td>
<td>24.62</td>
<td>-.052</td>
</tr>
<tr>
<td></td>
<td>Treatment</td>
<td>24.41</td>
<td></td>
</tr>
<tr>
<td>Week-16</td>
<td>Placebo</td>
<td>23.93</td>
<td>-.252</td>
</tr>
<tr>
<td></td>
<td>Treatment</td>
<td>24.94</td>
<td></td>
</tr>
</tbody>
</table>

Table J.3 Inter-group analysis for the (ICOAP) scale, utilising the Kolmogorov-Smirnov and Mann-Whitney U tests.

J.2 The Short Physical Performance Battery (SPPB) assessment

<table>
<thead>
<tr>
<th>Section and week</th>
<th>Mean</th>
<th>Std. Deviation</th>
<th>Std. Error Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>The chair test</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week-0</td>
<td>14.9433</td>
<td>3.23640</td>
<td>.70624</td>
</tr>
<tr>
<td>Week-8</td>
<td>14.3124</td>
<td>3.28924</td>
<td>.71777</td>
</tr>
<tr>
<td>Week-16</td>
<td>14.0719</td>
<td>3.54292</td>
<td>.77313</td>
</tr>
<tr>
<td>The gait test</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week-0</td>
<td>4.9924</td>
<td>1.77118</td>
<td>.38650</td>
</tr>
<tr>
<td>Week-8</td>
<td>4.8005</td>
<td>1.81779</td>
<td>.39667</td>
</tr>
<tr>
<td>Week-16</td>
<td>5.0248</td>
<td>1.87756</td>
<td>.40972</td>
</tr>
</tbody>
</table>

Table J.4 Group statistics of the inter-group analysis of the placebo group for SPPB assessment.

<table>
<thead>
<tr>
<th>Section and week</th>
<th>Mean</th>
<th>Std. Deviation</th>
<th>Std. Error Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>The chair test</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week-0</td>
<td>17.9430</td>
<td>7.52094</td>
<td>1.44741</td>
</tr>
<tr>
<td>Week-8</td>
<td>15.3926</td>
<td>6.10302</td>
<td>1.17453</td>
</tr>
<tr>
<td>Week-16</td>
<td>13.6767</td>
<td>5.06830</td>
<td>.97540</td>
</tr>
<tr>
<td>The gait test</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week-0</td>
<td>5.0937</td>
<td>1.62974</td>
<td>.31364</td>
</tr>
<tr>
<td>Week-8</td>
<td>4.6189</td>
<td>1.54628</td>
<td>.29758</td>
</tr>
<tr>
<td>Week-16</td>
<td>4.5933</td>
<td>1.59352</td>
<td>.30667</td>
</tr>
</tbody>
</table>

Table J.5 Group statistics of the inter-group analysis of the treatment group for the SPPB assessment.
<table>
<thead>
<tr>
<th>Section and week</th>
<th>Group</th>
<th>Mean ranks</th>
<th>Kolmogorov-Smirnov (Z)</th>
<th>Asymp. Sig. (2 tailed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>The chair test</td>
<td>Week-0</td>
<td>Placebo 22.76</td>
<td>-.759</td>
<td>.448</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Treatment 25.85</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Week-8</td>
<td>Placebo 24.38</td>
<td>-.052</td>
<td>.959</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Treatment 24.59</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Week-16</td>
<td>Placebo 26.98</td>
<td>-1.081</td>
<td>.280</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Treatment 22.57</td>
<td></td>
<td></td>
</tr>
<tr>
<td>The gait test</td>
<td>Week-0</td>
<td>Placebo 23.71</td>
<td>-.343</td>
<td>.732</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Treatment 25.11</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Week-8</td>
<td>Placebo 24.43</td>
<td>-.405</td>
<td>.685</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Treatment 23.78</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Week-16</td>
<td>Placebo 26.52</td>
<td>-.883</td>
<td>.377</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Treatment 22.93</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table J.6 Inter-group analysis for the SPPB assessment, utilising the Kolmogorov-Smirnov and Mann-Whitney U tests.
APPENDIX K – INTRA-GROUP ANALYSIS

K.1 Friedman test results for the measure of Intermittent and Constant Osteoarthritis Pain (ICOAP) scale: knee version

K.1.1 Placebo group

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Chi-Square</th>
<th>df</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Section A</td>
<td>21</td>
<td>1.879</td>
<td>2</td>
<td>.391</td>
</tr>
<tr>
<td>Section B</td>
<td>21</td>
<td>7.538</td>
<td>2</td>
<td>.023</td>
</tr>
<tr>
<td>Section C</td>
<td>21</td>
<td>9.234</td>
<td>2</td>
<td>.010</td>
</tr>
<tr>
<td>ICOAP total</td>
<td>21</td>
<td>11.676</td>
<td>2</td>
<td>.003</td>
</tr>
</tbody>
</table>

Table K.1 Friedman test results for the placebo group for the ICOAP scale.

K.1.2 Treatment group

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Chi-Square</th>
<th>df</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Section A</td>
<td>27</td>
<td>14.379</td>
<td>2</td>
<td>.001</td>
</tr>
<tr>
<td>Section B</td>
<td>27</td>
<td>8.374</td>
<td>2</td>
<td>.15</td>
</tr>
<tr>
<td>Section C</td>
<td>27</td>
<td>22.557</td>
<td>2</td>
<td>.000</td>
</tr>
<tr>
<td>ICOAP total</td>
<td>27</td>
<td>23.906</td>
<td>2</td>
<td>.000</td>
</tr>
</tbody>
</table>

Table K.2 Friedman test results for the treatment group for the ICOAP scale.
K.2 Wilcoxon Signed Ranks test results for the measure of Intermittent and Constant Pain (ICOAP) scale: knee version

K.2.1 Placebo group

<table>
<thead>
<tr>
<th>Section</th>
<th>Time period</th>
<th>Kolmogorov-Smirnov (Z)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Week 0 – Week 8</td>
<td>-1.666</td>
<td>.244</td>
</tr>
<tr>
<td></td>
<td>Week 8 – Week 16</td>
<td>-1.536</td>
<td>.125</td>
</tr>
<tr>
<td>B</td>
<td>Week 0 – Week 8</td>
<td>-2.589</td>
<td>.030</td>
</tr>
<tr>
<td></td>
<td>Week 8 – Week 16</td>
<td>-2.485</td>
<td>.17</td>
</tr>
<tr>
<td>C</td>
<td>Week 0 – Week 8</td>
<td>-1.133</td>
<td>.257</td>
</tr>
<tr>
<td></td>
<td>Week 8 – Week 16</td>
<td>-.484</td>
<td>.628</td>
</tr>
<tr>
<td>ICOAP Total</td>
<td>Week 0 – Week 8</td>
<td>-2.789</td>
<td>.005</td>
</tr>
<tr>
<td></td>
<td>Week 8 – Week 16</td>
<td>-3.399</td>
<td>.001</td>
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</tbody>
</table>

Table K.3 Wilcoxon Signed Ranks test for the placebo group for the ICOAP scale.

K.2.2 Treatment group

<table>
<thead>
<tr>
<th>Section</th>
<th>Time period</th>
<th>Kolmogorov-Smirnov (Z)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Week 0 – Week 8</td>
<td>-3.068</td>
<td>.002</td>
</tr>
<tr>
<td></td>
<td>Week 8 – Week 16</td>
<td>-3.157</td>
<td>.002</td>
</tr>
<tr>
<td>B</td>
<td>Week 0 – Week 8</td>
<td>-2.436</td>
<td>.015</td>
</tr>
<tr>
<td></td>
<td>Week 8 – Week 16</td>
<td>-3.791</td>
<td>.000</td>
</tr>
<tr>
<td>C</td>
<td>Week 0 – Week 8</td>
<td>-2.078</td>
<td>.007</td>
</tr>
<tr>
<td></td>
<td>Week 8 – Week 16</td>
<td>-1.233</td>
<td>.218</td>
</tr>
<tr>
<td>ICOAP Total</td>
<td>Week 0 – Week 8</td>
<td>-3.835</td>
<td>.000</td>
</tr>
<tr>
<td></td>
<td>Week 8 – Week 16</td>
<td>-4.243</td>
<td>.000</td>
</tr>
</tbody>
</table>

Table K.4 Wilcoxon Signed Ranks test for the treatment group for the ICOAP scale.
K.3 Friedman test results for the Short Physical Performance Battery (SPPB) assessment

K.3.1 Placebo group

<table>
<thead>
<tr>
<th>N</th>
<th>Chi-Square</th>
<th>df</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>The chair test</td>
<td>21</td>
<td>.286</td>
<td>2</td>
</tr>
<tr>
<td>The gait test</td>
<td>21</td>
<td>.458</td>
<td>2</td>
</tr>
</tbody>
</table>

Table K.5 Friedman test results for the placebo group for the SPPB assessment.

K.3.2 Treatment group

<table>
<thead>
<tr>
<th>N</th>
<th>Chi-Square</th>
<th>Df</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>The chair test</td>
<td>27</td>
<td>33.556</td>
<td>2</td>
</tr>
<tr>
<td>The gait test</td>
<td>27</td>
<td>6.889</td>
<td>2</td>
</tr>
</tbody>
</table>

Table K.6 Friedman test results for the treatment group for the SPPB assessment.

K.4 Wilcoxon Signed Ranks test results for the SPPB assessment

K.4.1 Placebo group

<table>
<thead>
<tr>
<th>Time period</th>
<th>Kolmogorov-Smirnov (Z)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>The chair test</td>
<td>Week 0 – Week 8</td>
<td>-.886</td>
</tr>
<tr>
<td>Week 8 – Week 16</td>
<td>-1.408</td>
<td>.159</td>
</tr>
<tr>
<td>The gait test</td>
<td>Week 0 – Week 8</td>
<td>-.017</td>
</tr>
<tr>
<td>Week 8 – Week 16</td>
<td>-.243</td>
<td>.808</td>
</tr>
</tbody>
</table>

Table K.7 Wilcoxon Signed Ranks test for the placebo group for the SPPB assessment.
K.4.2 Treatment group

<table>
<thead>
<tr>
<th>Time period</th>
<th>Kolmogorov-Smirnov (Z)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>The chair test</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 0 – Week 8</td>
<td>-2.619</td>
<td>.009</td>
</tr>
<tr>
<td>Week 8 – Week 16</td>
<td>-4.324</td>
<td>.000</td>
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<tr>
<td>The gait test</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 0 – Week 8</td>
<td>-2.378</td>
<td>0.017</td>
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<td>Week 8 – Week 16</td>
<td>-2.234</td>
<td>0.025</td>
</tr>
</tbody>
</table>

Table K.8 Wilcoxon Signed Ranks test for the treatment group for the SPPB assessment.