REGENERATIVE TISSUE BASED JOINT INJECTION FOR

TREATMENT OF CHRONIC KNEE PAIN SECONDARY TO OSTEOARTHRITIS:

A QUALITY IMPROVEMENT STUDY AND DEVELOPMENT OF A STANDARDIZED ASSESSMENT TOOL  
by

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A DNP Project Submitted to the Faculty of the

SCHOOL OF NURSING

In Partial Fulfillment of the Requirements

For the Degree of

DOCTOR OF NURSING PRACTICE

At the

UNIVERSITY OF DETROIT MERCY

**Introduction**

Osteoarthritis (OA) is a progressive and degenerative joint condition affecting 30.8 million Americans and is estimated to affect 130 million people across the world by 2050. It is currently the 5th leading cause of disability worldwide; with earning losses greater than $80 billion per year (Maiese, 2016). Knee osteoarthritis (KOA) accounts for more than 80% of the condition’s total burden (Wallace et al., 2017). In addition to impacting quality of life, knee osteoarthritis is a major economic burden.

KOA has doubled in prevalence since the mid-20th century (Wallace et al., 2017). The cause of this is poorly understood but thought to be attributed to increases in life expectancy and body mass index (BMI) (Wallace et al.). Due to the progressive, degenerative process of OA, regression and restoration of the damaged structures is unlikely (Mora et. al., 2018). Thus, current management modalities are targeted towards symptom control unless the degree of severity necessitates surgical intervention with joint replacement. Within the last decade total knee replacements performed annually in the United States has also doubled, with disproportionate increases among younger adults (Weinstein et al., 2013).

Arthritis is inflammation of one or more joints. Pain, swelling, and stiffness are the primary symptoms of arthritis. Any joint in the body may be affected by the condition, but it is particularly common in the knee (American Academy of Orthopedic Surgeons, 2014). The knee is the largest synovial joint in humans and given the weight-bearing and high use and stress of this joint, it is a frequent site for painful conditions including OA (Mora et. al).

Osteoarthritis is an idiopathic disease characterized by a degeneration of articular cartilage. The breakdown of cartilage matrix leads to the development of fibrillation and fissures and decrease of the full thickness surface of the joint. This is accompanied by bone changes with osteophyte formation and thickening of the subchondral plate. Changes caused by OA involve not only the cartilage, but also the synovial membrane, where an inflammatory reaction is often observed (Martel-Pelletier, 2004). OA can range in severity and is categorized using the Kellgren and Lawrence system for classification of osteoarthritis. The Kellgren and Lawrence system uses five grades of classifying severity of osteoarthritis using radiographic imaging of the joint, an important factor to consider when evaluating treatment options. This scale is discussed in detail below.

To date, there is no cure for osteoarthritis, but there are a number of treatments recognized by the American Academy of Orthopedic Surgeons that may help relieve pain and disability for those suffering from KOA such as:

* Lifestyle modifications: minimizing activities that aggravate the condition, weight control, exercise (land and water based), smoking cessation, diet.
* Physical therapy: specific exercises aimed to help increase range of motion (ROM) and flexibility, as well as help strengthen the muscles around the affected joint
* Assistive devices: devices such as a cane, shock-absorbing shoes or inserts, or wearing a brace or knee sleeve to assist with stability and function
* Medication: over-the-counter, non-narcotic pain relievers and anti-inflammatory medications, corticosteroids injections into the joint, disease-modifying anti-rheumatic drugs (DMARDs), visco-supplementation (injecting substances into the joint that may improve quality of joint fluid), glucosamine and chondroitin sulfate supplements
* Alternative therapies: acupuncture, magnetic pulse therapy
* Other remedies: heat, ice, pain-relieving ointment or creams
* Surgical treatment: arthroscopy, cartilage grafting, synovectomy, osteotomy, partial or full joint replacements

As the prevalence of OA continues to rise, researchers have begun to look into treatments that may aide in regenerating a degenerative knee, a factor that can aide in controlling risk and progression of OA. Tissues derived from the umbilical cord and amniotic membrane, also referred to as regenerative based tissue joint injections, are hitting the spotlight in regenerative medicine. This regenerative based injection is a source of regenerative cells that secrete molecules that modulate the immune system, stimulate regeneration, reduce inflammation and induce new blood vessel growth (Atala et al., 2018; Kyurkchiev et al., 2014; Weiss et al., 2008; Sane et al., 2018).

In current practice, as well as literature and published research in the arena of regenerative based tissue joint injections, a lapse in practice and research exists regarding a validated assessment tool for evaluation of individuals undergoing regenerative based tissue joint injections. To date, there is no published or validated assessment tool that exists to aide the provider in tracking pre and post- regenerative based tissue joint injection outcomes, in the form of history and assessment data. Through a literature review, seven validated screening tools that relate to chronic musculoskeletal pain were found. These screening tools include psychological risk factors for the development or maintenance of pain, pain-related distress, and pain-related disability; many focused on chronic back pain (Vierman et. al., 2019). To date, there is no standardized assessment tool focused on subjective and objective measurements pre and post musculoskeletal injection of a substance (such as steroids, anti-inflammatory medications, Synvisc, or biological allografts) in evaluating the effectiveness of a joint injection, specifically in relation to pain relief and function. Although there are many tools evaluating joint dysfunction, there remains a need for advancing our assessment tool to specifically track specific measuresments in order to evaluate outcomes associated with this form of treatment.

**Background and Significance**

The knee is the largest synovial joint in humans, composed of osseous structures, cartilage, ligaments and a synovial membrane. The synovial membrane is in charge of the production of the synovial fluid, which provides lubrication and nutrients to the avascular cartilage. Knee arthritis, since involving a weight-bearing joint, can make it hard to do many everyday activities, such as walking or climbing stairs. It is a major cause of lost work time and serious disability for many people (American Academy of Orthopedic Surgeons).

OA is classified into two groups according to its etiology: primary (idiopathic or non-traumatic) or secondary (usually due to trauma or mechanical misalignment) (Mora et. al). It was previously believed that OA was exclusively a degenerative disease of the cartilage, however, latest evidence has proven that OA is a multifactorial entity, involving multiple causative factors such as trauma, mechanical forces, inflammation, biochemical reactions, and metabolic derangements. It is known that the cartilage tissue is not the only one involved (Mora et. al.). Given its lack of vasculature and innervation, the cartilage by itself is not capable of producing inflammation or pain, at least in early stages of the disease (Mora et. al.). The source of pain is mainly derived from changes to the non-cartilaginous components of the joint, such as the joint capsule, synovium, subchondral bone, ligaments, and peri-articular muscles. These structures are affected and change as the disease advances through bone remodeling, osteophyte formation, weakening of the periarticular muscles, laxity of ligaments, and synovial effusion (Mora et. al.).

The role of inflammation is not well understood and there continues to be many debates to determine if the inflammatory reaction triggers the OA changes, or if the inflammation is secondary to the OA changes. Inflammation in OA is chronic and low-grade inflammation, involving mainly innate immune mechanisms. Synovitis, which represents infiltration of inflammatory cells into the synovium, is a common finding in OA and can be present during early stages of the disease, but is most prevalent towards more advanced stages (Mora et al.) In the Journal of Pain research, *Knee osteoarthritis: pathophysiology and current treatment modalities,* Mora et. al. states:

In OA, the synovial fluid has been found to contain multiple inflammatory mediators including plasma proteins (C-reactive protein, proposed as a marker for development and progression of OA), prostaglandins (PGE2), leukotrienes (LKB4), cytokines (TNF, IL1β, IL6, IL15, IL17, IL18, IL21), growth factors (TGFβ, FGFs, VEGF, NGF), nitric oxide, and complement components. Locally, all of these components can induce matrix metalloproteinases and other hydrolytic enzymes (including cyclooxygenase two and prostaglandin E) resulting in cartilage breakdown secondary to proteoglycan and collagen destruction (p. 2190).

The regenerative tissue based joint injection, derived from umbilical cord tissue, contain molecules which include: cytokines, chemokines, RNAs, and prostanoids which are minimally manipulated from the donor in order to retain the relevant characteristics of the tissue source (Signature Biologics, 2019). Alternatives such as regenerative based tissue injections for chronic knee pain secondary to osteoarthritis have proven in its early stages to be useful in joint regeneration, subsequently reducing pain and improving mobility in individuals suffering from knee OA, but are not currently offered as standard practice (Signature Biologics). This is in part due to the fact that this offering is new to the market, and carries a different approach to typical treatment offerings in today’s society, as it’s focus in preventative and regenerative in focus.

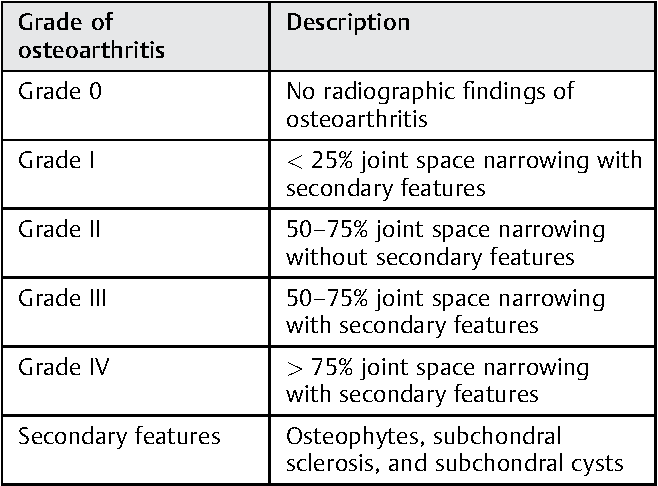
Currently, there has been no development of disease modifying pharmaceutical therapies for osteoarthritis. More than 50 modalities of pharmacological, non-pharmacological, and surgical treatment are reported in literature. However, the current most common treatment for osteoarthritis except for joint replacement have at best modest clinically relevant effects and can cause substantial adverse events or costs, or both (Jo et al., 2014). Debilitating knee pain and osteoarthritis continues to be an extremely relevant clinical issue, and costs associated continue to rise placing patients in financially unstable situations, contributing to work loss and disability, and often requiring revisions and complications secondary to surgery.

Today's accepted therapies include lifestyle modifications (nutrition and exercise programs, weight control), assistive devices, physical therapy, pain medications, steroids, acupuncture, and magnetic pulse therapy, none of these leading to the resolution of osteoarthritis or its associated burden (Weinstein et al., 2013). In the U.S., about 65% of patients with OA are prescribed NSAIDs aimed only at symptom control rather than disease prevention and progression (Weinstein). Recent NSAID use studies show no clinically or statistically significant changes in the progression of OA, particularly joint space narrowing, in participants with long-term NSAID use compared to those with no NSAID use (Lapane et. al., 2016).

Existing conservative management strategies often fail to alter disease progression and surgical intervention and management in the form of arthroscopy, cartilage grafting, synovectomy, osteotomy, total or partial knee placement are often times associated with significant complications and financial burden (Weinstein). Although knee replacement is a highly effective treatment for end-stage knee osteoarthritis, total knee replacement recipients can experience pain and severe complications, including infection and multiple surgical revisions. In turn, impacting finances, activities of daily living (ADL’s), quality of life, and the economy.

The American College of Rheumatology (ACR), Osteoarthritis Research Society International (OARSI), and American Academy of Orthopedic Surgeons (AAOS) have published clinical practice guidelines for the management of knee osteoarthritis. However, these guidelines do not consider costs and do not provide guidance on indications for TKA (Losina, 2016). The severity of OA can be graded according to the radiographical findings by the Kellgren–Lawrence (KL) system described in 1957 by the American academy of Orthopedic Surgeons.

FIGURE 1. Kellgren/Lawrence Grading Scale:

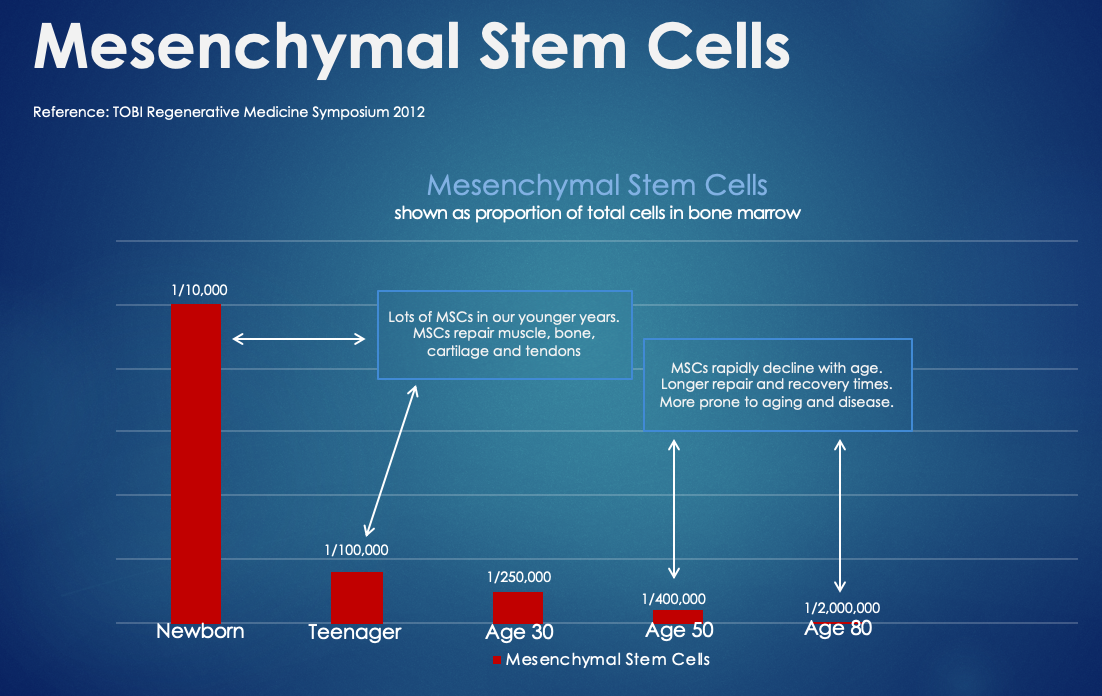
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Todays accepted therapies are generally intended to reduce pain, maintain or improve joint function, and minimize disability (Losina, 2016). However, when looking at a degenerative condition, finding a treatment that could aide in regeneration of the joint could be transformational for many individuals suffering from chronic knee pain secondary to osteoarthritis. There remains a gap in literature in exploring regenerative tissue based joint injection for treatment of knee pain secondary to osteoarthritis.

According to Liu et. al., (2014) a human cell and tissue product administered to a recipient can aide in repairing, reconstructing, replacing, or supplementing the same basic functions of the recipient’s cells or tissues, with peak healing effects seen at 4-6 months after injection. The use of regenerative tissue based product from umbilical cord blood provides greater benefit over using your own stem cell. As our bodies age, we experience longer healing time, increased inflammation, an ever-changing chemical environment, and cell exhaustion (cell aging) (Riordan, 2017).

When one is young, mesenchymal stem cells (MSCs) double every 20-24 hour. As an adult, MCSs double every 48 hours, at 65 years and older, MCSs double every 60 hours. To put things into perspective, a newborn MSC will create 1 billion cells in 30 days from one cell. An adult MSC will create 32,000 cells in 30 days from one cell. Persons age 65 and above will create 200 cells in 30 days from one cell (Riordan).

FIGURE 2. Proportion of Mesenchymal Stem Cells During Aging



While many of today’s treatments for osteoarthritis focus on pain management and temporary relief of symptoms, an alternative strategy utilizing regenerative based tissue joint injections has proven itself to be more appropriate in some circumstances (Jo et al., 2014). The umbilical cord cells, regenerative tissue based injection may be an ideal source of cells due to its accessibility, abundant resources, painless procedure for harvesting, and lack of ethical issues (Liu et. al., 2014). Many individuals suffering from KOA are appropriate candidates for this procedure, however, within the practice of West Coast RegenMed, patients who are classified as K/L stage 4 are advised that injection with regenerative based tissue joint injection may not be the most appropriate treatment option. In cases such as this, the individual is degenerated so severely, that a TKA would be the recommended treatment. However, there are individuals who will still choose treatment with regenerative based tissue joint injections, many times for the reason of avoiding surgery.

**Organization**

West Coast RegenMed evaluates many patients for concern of chronic knee pain secondary to osteoarthritis, from varying degrees of the condition. When a patient is deemed appropriate for a regenerative-based tissue joint injection, based on radiographic, subjective, and objective findings, the injection is performed. However, providers at West Coast RegenMed do not have a standardized process of assessing and monitoring a patient pre and post injection. This creates discrepancies between providers in assessments, data documented, and follow-up intervals for the patient.

**Clinical Question**

Will a quality improvement intervention of the development and implementation of a standardized assessment tool and monitoring process for individuals with KOA undergoing regenerative tissue based joint injections assist the provider in developing best practices for monitoring and evaluation of outcomes? Will data collected from this assessment tool for this project show improvement in knee pain and overall joint function and mobility?

**Purpose Statement**

Building on the current accepted treatments for chronic pain and KOA, the purpose of this quality improvement Doctor of Nursing Practice (DNP) project is to utilize current evidence and best practice to develop and implement a standardized provider assessment tool and monitoring process for patients receiving regenerative based tissue joint injections. This standaradized assessment tool will contain pertinent subjective and objective data including reported pain scores, daily activity tolerance (including stairs, walking), crepitus, range-of-motion (ROM), medication use related to KOA and overall reported quality of life in patients who have received regenerative based tissue joint injections. The monitoring process will be determined through quality improvement cycles utilizing a needs assessment and best current practice.

**Literature Review**

A literature review was performed using databases: PubMed, CINAHL, Cochrane, and Medline. Key words and phrases utilized in the search included: screening, assessments, knee, pain, osteoarthritis, chronic, regenerative, tissue based, treatment, management, cost, burden, total knee arthroplasty, mesenchymal were used individually and in combination of each other. The literature search yielded over 1,000 articles. Inclusion criteria for articles included: English language, full text articles, dated within the past 15 years. Exclusion criteria included: Non-English language, articles that were not available for full-text (without payment or membership), articles dated past 15 years old.

The common themes gathered from the literature include: burden of knee replacement, cost analysis related to KOA, new strategies against degenerative joint disease, and effectiveness of regenerative based tissue joint injections, treatment of chronic knee pain and osteoarthritis; and others of the like. Fourteen articles with the above criteria are used in the literature review below.

**Cost Analysis and Associated Outcomes of Knee Osteoarthritis**

OA is an inflammatory condition still lacking effective and fiscally sound treatments (Mancuso, Raman, Glynn, Barry & Murphy, 2019). Cost effectiveness of conservative management versus total knee arthroplasty (TKA) is a common investigated topic in this arena. A common measurement of disease burden can be seen through evaluating quality-adjusted life year (QALY) which is a generic measure of disease burden, including both the quality and quantity of life lived. It is used in economic evaluation to assess the value of medical interventions. One QALY equates to one year in perfect health (Sassi, 2006). In a study performed by Stan et al. (2015) the lowest reported QALY was within the TKA group. This study evaluated 30 patients treated for knee osteoarthritis with rehabilitation, 30 patients who underwent a unilateral TKA to a non-operated knee, and 30 patients who underwent a TKA following high tibial ostomy (HTO) for degenerative arthritis of the knee (2015).

**Cost Analysis of Total Knee Arthroplasty**

Stan, H. Orban & C. Orban recognize the total knee arthroplasty is an effective, but also cost-intensive health care procedure (2015). The TKA procedure itself, healing time, end results and complications are not uniformly excellent (2015). They go on to discuss that although total knee replacement is a highly effective treatment for end-stage knee osteoarthritis, total knee recipients can experience persistent pain and severe complications. According to Weinstein et al. (2013) “In the last decade, the number of total knee replacements performed annually in the United States doubled, with disproportionate increases among younger adults” (p. 385).

It was estimated that 4 million (95% confidence interval [CI] 3.6 million to 4.4 million) adults in the U.S. currently live with a total knee replacement, representing 4.2% (95% CI: 3.7% to 4.6%) of the population fifty years of age or older (2013). The lifetime risk of primary total knee replacement from age twenty-five years was 7.0% (95% CI: 6.1% to 7.8%) for males and 9.5% (95% CI: 8.5% to 10.5%) for females (2013). Over half of adults in the U.S. diagnosed with knee osteoarthritis will undergo a total knee replacement (Stan, H. Orban & C. Orban, 2013). In 2011, the Medicare program reimbursed U.S. hospitals $3.5 billion for total knee arthroplasty making it the program’s largest expenditure for a single procedure, with an average cost for a primary total knee arthroplasty (TKA) costing an average of $20,293 and each revision TKA costs an average of $26,388 (Losina, 2016).

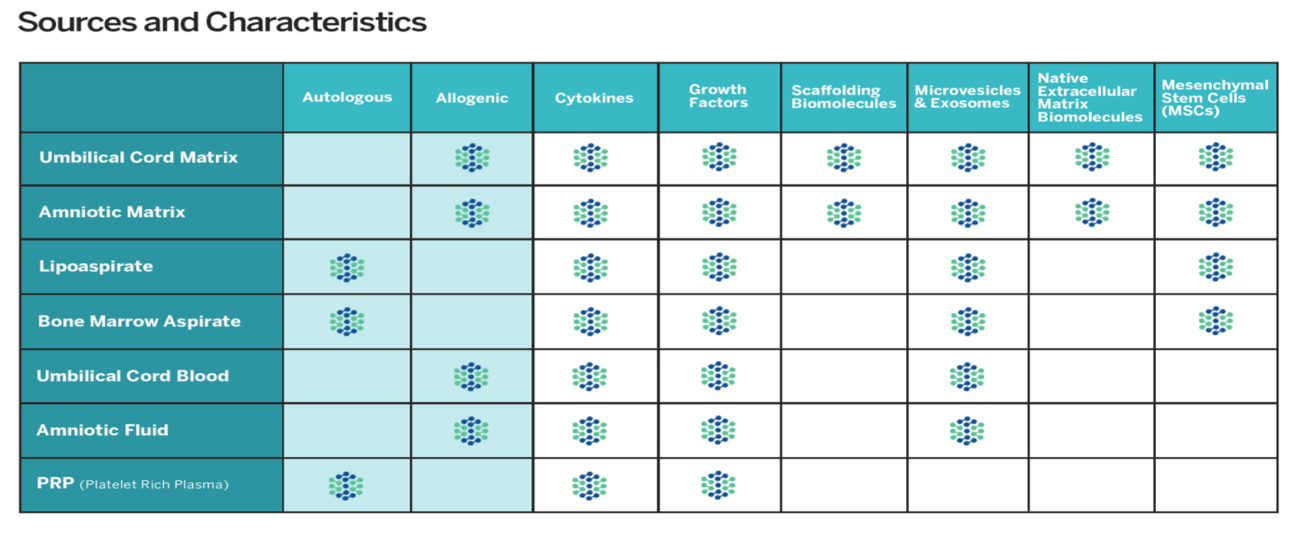
**Bankruptcy Associated with Medical Bills**

According to a Money article, financial experts say that medical bills, often unexpected and large, are a large factor in U.S. bankruptcy filings. “Bankruptcy filings in the United States dropped by half between 2010 to 2016, falling from 1,536,799 to 770,846” (Sisson, 2017, p. 2). According to experts, there are many factors that contribute to this decline in personal bankruptcy, including improvements in the economy, but “almost all agreed that expanded health coverage played a major role in the marked, recent decline.” (Sisson, 2017, p. 2).

**The Future State of Newborn Stem Cell Banking**

Mesenchymal stem cells (MSC) are stem cells traditionally found in bone marrow. However, mesenchymal stem cells can also be isolated from other tissue including cord blood (umbilical blood, umbilical matrix), peripheral blood (platelet rich alpha-2-macroglobin), placenta (amniotic membrane, amniotic matrix, amniotic fluid), bone marrow (bone marrow aspirate), and adipose (lipoaspirate) tissue (Ullah, Subbarao, & Rho, 2015) . When utilizing your own stem cells, the MSC is classified as autologous (2015). When utilizing an MSC from another source outside of the individual, the MSC is classified as allogenic (2015). Each source of mesenchymal stem cells encompasses different properties as shown on figure 4 below:

FIGURE 4. Mesenchymal Cell Sources and Characteristics



(Signature Biologics, 2019)

For reasons cited previously and shown above, West Coast RegenMed utilizes allogenic tissue, in which MSC are extracted from umbilical cord matrix for osteoarthritic joints. Newborn stem cell banking began more than 25 years ago with the establishment of cord blood banks. Over the course of almost three decades, there has been an evolution in the clinical application of stem cells isolated from newborn tissue. As personalized and regenerative medicine continues to advance, the osteoarthritis industry has reached an inflection point in evaluating alternative, regenerative options (Brown, Rao, & Brown, 2019).

Within the U.S., the health care system is critical to long-term economic stability. Health care coverage and costs associated with collection and cryopreservation of newborn tissues for future use and establishing insurance reimbursement once clinical efficacy and cost calculations are established in regenerative medicine would provide for economic incentives for all invested parties, as well as aide in the industry meeting the increased demand for precision in health care (Brown, Rao, & Brown, 2019).

Currently, mesenchymal stem cell therapy from cord tissue is Food and Drug Administration (FDA) approved, but not FDA regulated (Center for Biologics Evaluation and Research, 2019). FDA regulation is directly linked to insurance coverage and as it stands, mesenchymal stem cell therapy for chronic knee pain osteoarthritis is only available via out-of-pocket costs. Current costs of receiving allogenic mesenchymal stem cell therapy from cord tissue ranges from $3,000 all the way up to $30,000 per single injection (Cona, 2013). The number of injections needed vary per person, but on average consists of one single injection per joint being evaluated, however, some individuals may require or desire additional injections in hopes of furthering improvement in pain and mobility. Finding a cost-effective alternative, such as educating expecting families on storage of their own cord tissue, could allow for more opportunity to receive the therapy during the lifetime of themselves or a family member. It also could serve as a regenerative option for chronic pain caused from osteoarthritis, a degenerative disease.

**Effectiveness of Mesenchymal Stem Cell Therapy**

Mesenchymal stem cells have been successfully implemented in pre-clinical models aiming to resurface the degenerated cartilage (Mancuso et al., 2019). A systematic review with a meta-analysis performed by Iijima, Isho, Kuroki, Takahashi, & Aoyama aimed to summarize current evidence of the effectiveness of MSC treatment for KOA (2018). A literature search yielded 659 studies, of which 35 studies met the inclusion criteria (n = 2385 patients; mean age: 36.0-74.5 years). The meta-analysis suggests that MSC treatment through intra-articular injection or arthroscopic implantation significantly improved knee pain (standard mean differences [SMD]: -1.45, 95% confidence interval: 1.94-0.96), self-reported physical function (SMD: 1.50, 95% CI: 1.09, 1.92) and cartilage quality (SMD: -1.99; 95% CI: -3.51, -0.47) (2018, p. 1). Minor adverse events (knee pain or swelling) were reported with wide-ranging prevalence of 2-60%; however, there was no adverse symptoms or severe adverse events that occurred (Iijima et al., 2018).

Reports by Mancuso et al. (2019) summarizing mesenchymal stem cell therapy for osteoarthritis suggest significant potential for the use of MSC in OA. “*In vitro,* co-culture of OA chondrocytes with adipose-derived stem cells (ASC) MSC resulted in NF-kB-mediated cytoprotective effects via enhanced production of collagen II, inhibition of interleukin 6 (IL-6), TNF and various matrix melloproteinases (MMPs), as well as up-regulation of interleukin 10 (IL-10)” (p.5). The NF-kB target gene is involved in inflammation development and progression of inflammation. NF-kB has long been considered the “holy grail” as a target for new anti-inflammatory drugs (Lawerence, 2009). This data shows that administration of MSC creates NF-kB-mediated cytoprotective effects within the knee. These effects decrease the inflammatory processes within the knee, one of the primary symptoms and causes of pain in knee osteoarthritis (American Academy of Orthopedic Surgeons).

IL-6 is an interleukin that acts as both a pro-inflammatory cytokine and an anti-inflammatory myokine. IL-6 is promptly and transiently produced in response to infections and tissue injuries, and also contributes to host defense through the stimulation of acute phase responses, hematopoiesis, and immune reactions (Tanaka, Narazaki & Kishimoto, 2014). Injection of MSC dysregulates the continual synthesis of IL-6, a cytokine that contributes to inflammation. In turn, this results in an immediate halt of chronic inflammation associated with osteoarthritis, which in turn reduces pain experienced in the patient secondary from osteoarthritic changes. In addition, various clinical trials have shown exceptional efficacy of medications such as tocilizumab, a humanized anti-IL-6 receptor antibody, for various types of arthritis (Tanaka, Narazaki & Kishimoto).

**Complications Associated with Mesenchymal Stem Cell Therapy**

Though mesenchymal stem cells (MSCs) hold great potential in regenerative medicine, safety and complication reporting has only begun (Cento et. al., 2010). Cento et al. (2010) evaluated two groups of patients who were treated for orthopedic conditions with culture-expanded autologous, bone marrow derived MSCs. Group one consisted of 45 individuals and group two consisted of 182 individuals. “Cells were cultured in monolayer culture flasks using an autologous platelet lysate technique and re-injected into peripheral joints (n=213) or into intervertebral discs (n=13) with the use of c-arm fluoroscopy” (2010, p. 81). Surveillance for adverse events documented 7 cases of probable procedure-related complications and three cases of possible allograft complications, all of which were either self-limited or were remedied with simple therapeutic measures (2010).

**Methods**

The quality improvement initiative at West Coast RegenMed planned for this DNP project and innovation is to develop and implement a standardized assessment tool for providers to utilize while assessing and monitoring patients receiving regenerative based tissue joint injection therapy for chronic knee pain caused from KOA. This was created after a SWOT analysis of current practices of provider data collection for subjective and objective data was completed along with a review of the current evidence.

**Organizational Assessment**

A SWOT analysis was done to aide in identifying strategies for change specific to this quality improvement study. Key stakeholders of this project include the owner and operator of West Coast RegenMed, Dr. Ryan Bentley, providers and patients seeking regenerative based tissue joint injections at this facility, as well as providers across the United States. The vision at West Coast RegenMed is to create tools and resources to evaluate, treat and educate patients and providers on how to construct objective, quantifiable systems and protocols to achieve optimal health. The passion of the providers at West Coast RegenMed is to help those who are suffering with chronic and debilitating conditions that limit their ability to serve their purpose within their family, community, and beyond. This project proposal meets the vision of this practice as the aim is to create and implement a standardized assessment tool to assist in subjective and objective measures for individuals undergoing regenerative based tissue joint injections for chronic knee pain secondary to KOA, as well as evaluate MSC effectiveness in pain management within this population.

The alignment of this project with the vision at West Coast RegenMed is key in creating a common goal of evaluating treatment options and evaluations for chronic knee pain secondary to osteoarthritis to aide in relief of pain as well as empowering individuals to continue to live their lives without health and/or physical restraints. Other strengths include being a leader in this field in west Michigan as well as connections that lie between West Coast RegenMed and Signature Biologics (distributor of Mesenchymal stem cells) which was created during Ryan Bentley’s MD, PhD studies in biomedical science where he served as a pioneer in stem cell research.

The office at West Coast RegenMed is currently already set up and functioning to serve those seeking regenerative tissue based joint injection therapy for joint issues and pain secondary to osteoarthritis. Therefore, completing this project with the development and implementation of a standardized tool serves as an area of strength to add to an already established (material and financial wise) practice promoting quality improvement and impacting outcomes.

**Ethical Issues and Human Subject Consideration**

This quality improvement project aims to improve assessment and monitoring of patients with KOA receiving MSC therapy. The development of the standardized assessment tool and use of aggregate data poses no risk of harm to patients. Data collected in the process of the project does not contain patient identifiers and will be used for its intended purposes only and properly discarded in relation to laws and regulations.

There are no physical nor mental risks involved in this project. For this reason, the institutional review board at University of Detroit Mercy deemed this doctoral project exempt (Appendix C).

Approval was obtained from Dr. Bentley, owner and physician of West Coast RegenMed. Staff at West Coast RegenMed continued to schedule patients for regenerative based tissue joint injections per normal protocol. Patients undergoing regenerative based tissue joint injections were notified of this quality improvement study, and disclosure (appendix A) was given to each patient that data from their screening tool would be analyzed for the purpose of quality improvement, and all patient identifiers would be removed.

Patients will maintain autonomous in all treatment decision making as the provider ensures full and proper disclosure of treatment information including education, benefits, and risks of the procedure, as well as alternative treatment options. The provider will maintain bioethical standards, including nonmaleficence, beneficence and respect for patient autonomy.

**Setting & Sample**

The setting of this study is West Coast RegenMed, a regenerative medicine focused medical practice located in Holland, Michigan. West Coast RegenMed focuses on providing care to individuals from birth to death, through an integrative approach of combining traditional and holistic type care when appropriate, with an average of 300 patients total. The typical patient demographic is middle-aged individuals residing in west Michigan. However, the Amish population residing in the neighboring state of Indiana is the top demographic for regenerative based tissue joint injections.

Patients included in this practice innovation will be any individual suffering from chronic knee pain with radiographic imaging that shows osteoarthritic changes, who have been deemed a candidate for regenerative tissue based joint injection therapy at West Coast RegenMed. The assessment screening tool will be utilized in gathering subjective and objective information on 10 patients undergoing therapy, as well as used to evaluate outcomes and efficacy of the tool.

**Project TimelineA screenshot of a cell phone

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**Plan-Do-Study-Act (PDSA) Cycles:**

**PDSA 7/2019**

**Plan**

This project was implemented at West Coast Regenerative Medicine starting July, 2019. The project continued until ten patients underwent treatment and were assessed with the developed assessment tool. Each patient who undergoes the injection will be assessed at 3 weeks, 6 weeks, 3 months and 6 months utilizing a standardized assessment tool by the nurse practitioner or physician, and the data was then extracted for collection, assessment and improvement purposes. Mesenchymal peak healing effects are at 3-6 months (Riordan, 2017), therefore, the final standardized screening and potential for repeat imaging will be done at or after 6 months post-injection with a goal of 10 re-evaluations by June of 2020. These evaluations will also give key, real-time data for work loss, costs spent on over the counter (OTC) and prescription medications, etc. This will give the team a more accurate picture of the estimated costs above taking into account real patients that are being evaluated and treated with this therapy.

The medical director, Dr. Ryan Bentley, at West Coast Regenerative Medicine is supportive of this innovation. In the future, we hope to be able to receive grant funds to continue our studies in regenerative tissue based joint injections for chronic knee pain secondary to osteoarthritis and aide on lowering overall health care expenditure and disability related to this prevalent and debilitating disease.

A team was formed for this quality improvement project. The team consisted of two health care providers including one physician and one nurse practitioner, and one support staff/receptionist. Staff education was done regarding the project being implemented at West Coast RegenMed. Meetings were held monthly, starting June of 2019, at WCRM, where the team gathered to review the assessment tool, review the data collected and associated processes, and discuss lapses or improvement ideas based on results and feedback.

During the team meetings, a process was created for filing standardized assessment tools after patient appointments, which consisted of a handoff of paperwork to receptionist, and scanning into each patients chart for tracking and charting purposes. The physical copy was then shredded. Team members successfully ensured that each patient included in this quality improvement project was scheduled with the same provider, whether in office or phone call assessments, to ensure interrater consistency of the newly implemented assessment tool.

**Do**

At the start of July, 2019, the first developed standardized assessment tool was implemented (Appendix B) in patient appointments who were seeking MSC for chronic knee pain secondary to osteoarthritis. Verbal disclosure was given to each patient that data from their screening tool would be analyzed for the purpose of quality improvement, and all patient identifiers would be removed.

**Study**

With each patient encounter and hands-on usage of the tool, feedback was obtained from providers and small changes were made to the standardized screening tool in order to improve the efficacy of the tool. After each change, the revised tool was then implemented immediately following it’s revision. The initial evaluation of the assessment tool was for the usage of mesenchymal stem cells and focused on pain improvement. With time and hands-on usage of the tool, there was a shift to focus on the assessment of the tool, outcomes, and ensuring that all subjective and objective assessment points relevant to the monitoring and treatment were being obtained.

**Act**

The tool was revised to include flexion and extension measurements utilizing a goniometer to ensure accuracy and consistency of range of motion changes (Appendix C). A screenshot of a cell phone

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**PDSA 6/2020**

**Plan**

In evaluating individuals with this assessment tool, it was noted that mobility was a large factor in suffering from and treating KOA. In review of the standardized process at this time, mobility needed to be further evaluated in patients receiving treatment through expanded standardized screening tool assessment.

**Do**

While evaluating the current process and what evaluation methods were available to assess mobility, the KOOS screening tool was noted for it’s thoroughness and validation in evaluating knee mobility. The KOOS screening tool (Figure 5) is a questionnaire which was designed to assess short and long-term patient-relevant outcomes following knee injury, was added to the standardized assessment tool after evaluation of all 10 participants, therefore no data is available (Rosa et. al., 1998). This measurement was added to provide more concrete, consistent evidence in mobility changes as reported by patients and will be utilized within the standardized assessment tool moving forward. The KOOS is self-administered and assesses five outcomes: pain, symptoms, activities of daily living, sport and recreation function, and knee-related quality of life. The KOOS can be used to evaluate the course of knee injury as well as treatment outcomes. KOOS can be patient-administered, in English, at a 5th grade reading level, and takes about 10 minutes to complete (Roos et. al.).

The KOOS’s five patient-relevant dimensions are scored separately: pain (nine items); symptoms (seven items); ADL function (17 items); sport and recreation function (five items); quality of life (four items). A likert scale is used and all five possible answer options scored from 0 (no problems) to 4 (extreme problems) and each of the five scores is calculated as the sum of the items included. Scores are transformed to a 0-100 scale, with zero representing extreme knee problems and 100 representing no knee problems (Roos et. al.).

**Study**

The questions represented in the assessment tool were chosen by the team in relation to trends seen in literature surrounding KOA and treatments, as well as previous evaluations of patients seeking treatment for KOA at West Coast RegenMed. Dysfunction is a common symptom in all persons suffering from KOA, therefore various methods to measure dysfunction at each interval was included. Other objective measurements including pain rating, quality of life, medication usage, and cost associated with the condition were included base on relevance of each topic throughout literature review and professional experience. All objective measurements were read to patient in-person or via phone (depending on check-up interval, listed below) and the answer from the patient was noted on the assessment tool by the healthcare provider.

Objective measurements including flexion, extension, crepitus, drawer sign, lateral instability, swelling and radiographic imaging was included with understanding that each individual receiving the joint injection was seeking treatment for chronic knee pain and dysfunction secondary to osteoarthritis. These measurements also gave objective data points which were able to be assessed and compared at various intervals (listed below) to assess effectiveness of treatment and changes in the knee joint. All objective measurements were done in office and noted on the assessment tool by the healthcare provider.

**Act**

Moving forward, the KOOS tool will be added to the assessment tool for patients seeking regenerative based tissue joint injections for chronic knee pain secondary to osteoarthritis as means to track outcome measures related to functional status, mobility and pain.

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**FIGURE 5. Knee Injury and Osteoarthritis Outcome Score (KOOS)**

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Variables included in the *Regenerative Tissue Based Joint Injection Standardized Assessment* *Tool* aim to target assessment of pain, ROM and mobility before and after injection at timed intervals of pre-injection (in-person evaluation), 3 weeks (phone), 6 weeks (phone), 3 months (in-person), and 6 months (in-person) post-injection; keeping in mind that peak healing effects take place at 4-6 months (Figure 6). Questions 1-7 of assessment data will be collected during office visits, and questions 8-15 will be asked at all phone calls and office visits.

**FIGURE 6*. Regenerative Tissue Based Joint Injection Standardized Assessment* *Tool***

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Pt Name:** | **Pre-Injection**  **(office visit)** | **3 week**  **(phone call)** | **6 week (phone call)** | **3 month (phone call)** | **6 month (office visit)** |
| **1:Radiographic Imaging Findings\*** |  |  |  |  |  |
| **2: Flexion (degree measurement)** |  |  |  |  |  |
| **3: Extension (degree measurement)** |  |  |  |  |  |
| **4: Joint Crepitus Degree (mild, moderate, severe) & Location** |  |  |  |  |  |
| **5: Lateral Instability (+/-)** |  |  |  |  |  |
| **6: Drawer Sign (+/-)** |  |  |  |  |  |
| **7: Swelling (mild, moderate, severe) & Location** |  |  |  |  |  |
| **8: Walking Time** |  |  |  |  |  |
| **9: # of Steps** |  |  |  |  |  |
| **10: Onset of Pain (Date)** |  |  |  |  |  |
| **11: VAS Pain Rating** |  |  |  |  |  |
| **12: Current Pain Medications** |  |  |  |  |  |
| **13: KOOS Total Score** |  |  |  |  |  |
| **14: Post-Injection Goal of Patient & Evaluation of Goal** |  |  |  |  |  |
| **15: Improvements in Lifestyle Modifications Since Injection** |  |  |  |  |  |
| **16: Total cost associated with treatment & after treatment (injection cost, medications, functional support such as braces, PT/OT)** |  |  |  |  |  |

**Analysis**

**Profile of Sample**

This sample included 10 completed assessment tools on individuals ranging from 52 to 81 years of age, with 6 males and 4 females. All individuals were suffering from chronic knee pain, had positive radiographic imaging for osteoarthritis, and received a single injection of 1mL. regenerative based tissue joint injection from Signature Biologics, into one knee joint.

**Results of Standardized Screening Tool**

**Pain**

Of the 10 completed assessment tools analyzed, all had reported decreases in pain level from pre-injection to 6 months post-injection. The average pain rating pre-injection was 6.8/10. The average pain rating 6 months post injection was 2.2/10; a 4.6 point decrease from pre-injection average. The overall average decrease in pain rating utilizing the VAS pain scale from pre-injection to post-injection was 5.1.

**Objective Mobility Measurements**

The range of flexion between all participants, which was measured while lying face down on exam table with a goniometer varied from 95-148 degrees. The average degree of flexion at pre-injection was 122.7 degrees. The range of flexion between all participants at post-injection varied from 95-155 degrees. The average degree of flexion at 6 months post-injection was 131.8; a 9.1 degree increase from pre-injection average; an overall improvement in flexion.

**Subjective Mobility**

Of the 10 completed assessment tools analyzed, all participants reported increase in mobility from pre-injection to 6 months post-injection.

**Medication Usage**

Of the 10 completed assessment tools analyzed, all participants reported a decrease in over-the-counter and prescription medication usage from pre-injection to 6 months post-injection; with a 80% average decrease in medication usage reported.

**Total Cost Associated**

Of the 10 completed assessment tools analyzed, all participants average total cost spent associated with treatment was $2,850. All participants received a single 1mL regenerative based tissue joint injection (cost reflected above). All participants did not report any other major associated costs except for one participant who opted to begin physical therapy shortly after receiving treatment. Exact cost was not able to be obtained as it was covered by insurance, however, no additional out-of-pocket costs were reported from the patient.

**Evaluation Methods**

Evaluation was done at intervals and data for each variable was evaluated through descriptive statistics, as seen above. The descriptive statistics provided an objective way to determine if the intervention results in improvement (tracked in various variables listed in Figure 6) over time. These measurements were done through self-reports will be measured by self-reports and will continue as long as we are able to follow the patient post injection.

**Limitations**

  Although there were many studies involving treatment of OA, KOA and chronic knee pain, there was limited data on treatment of KOA and chronic pain through usage of regenerative based tissue joint injections. There also remained a gap in literature regarding utilizing a standardized assessment tool to track these types of treatment, which in turn presented an opportunity for this Doctoral project. With the information available, evidence does not suggest whether one intervention is superior to another intervention in reducing chronic pain, costs, and overall feasibility and success of the treatment.

Limitations involved in this particular project include time. It is not yet known how long a single injection of regenerative based tissue joint injections will provide aide to the individual receiving it, since they have only been offered for a total of 7 years and have not been followed closely with a standardized assessment tool at interval times.

**Recommendations**

All aspects evaluated in the treatment of chronic knee pain secondary to osteoarthritis with the usage of regenerative based tissue joint injections demonstrate merit and warrant continuation of monitoring. Particularly in evaluation of chronic knee pain, regenerative based tissue joint injections prove to provide pain relief. Given the regeneration in nature, it is hopeful that results are long-term. However, the question remains on how long term results can be seen. It is our hope to continue to collect data to determine this, as long as patients will allow and comply.

It would be my recommendation that we continue to implement measures in order to evaluate the effectiveness of this treatment in terms of patients treatment and overall costs associated. It would also be my recommendation that insurance companies evaluate and consider this treatment as a part of regular insurance coverage for individuals deemed appropriate for treatment. Lastly, I highly recommend that studies continue in relation to validating the standardized assessment tool for evaluation of outcomes related this treatment to further literature related to regerenative based tissue joint injections and outcomes for those with KOA or OA; as well as standardized offering of this treatment as a treatment option.

**Discussion & Dissemenation**

It is planned to continue to follow these patients as long as they comply and make themselves available to obtain long-term data on the effectiveness of regenerative based tissue joint injections. The process and results of this quality improvement project and program evaluation shall provide the foundation for ongoing assessments and monitoring of individuals undergoing regenerative based tissue joint injections. Dissemination of the findings and recommendations of this quality improvement project will include a presentation to the staff at West Coast RegenMed, as well as other healthcare providers administering regenerative based tissue joint injections. A manuscript will be developed for publication in order to disseminate the findings through a peer-reviewed nursing journal in efforts to expand the available knowledge on the importance of implementing a standardized screening tool in patients receiving this treatment.

The development of this standardized assessment tool for use in patients receiving regenerative based tissue joint injections serves as the first known assessment tool in this area. This tool has been shared with Signature Biologics in hopes of integration of this tool in the usage of all MSC injections that are supplied from this company as a form of standardized assessments, and data sharing to advocate for the usage of regenerative based tissue joint injections.

To date, this tool continues to be used in practice at West Coast RegenMed as well as Wellness Co., a west MI based office offering this service. It will continue to undergo PDSA cycles as additional data and learning occurs. The process and results of this quality improvement project and program evaluation shall provide the foundation for ongoing assessments and monitoring of individuals undergoing regenerative based tissue joint injections, as well as creating a process for monitoring outcomes for quality improvement in patient care.

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**Appendix A**

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**Patient Disclosure**

A quality improvement study is currently being performed within West Coast RegenMed in relation to regenerative based tissue joint injections. This quality improvement study includes the development of a screening tool and assessment of the data collected from this screening tool. This disclosure it to notify you that your results from this screening tool may be utilized for purposes of this quality improvement. Please be aware that all patient identifiers will be removed.

Kindly,

Staff of West Coast RegenMed

**Appendix B**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Pt Name:** | **Pre-Injection**  **(office visit)** | **3 week**  **(phone call)** | **6 week (phone call)** | **3 month (phone call)** | **6 month (office visit)** |
| **1:Radiographic Imaging Findings\*** |  |  |  |  |  |
| **2: Flexion (non-restricted or restricted)** |  |  |  |  |  |
| **3: Extension (non-restricted or restricted)** |  |  |  |  |  |
| **4: Joint Crepitus Degree (mild, moderate, severe) & Location** |  |  |  |  |  |
| **5: Lateral Instability (+/-)** |  |  |  |  |  |
| **6: Drawer Sign (+/-)** |  |  |  |  |  |
| **7: Swelling (mild, moderate, severe) & Location** |  |  |  |  |  |
| **8: Walking Time** |  |  |  |  |  |
| **9: # of Steps** |  |  |  |  |  |
| **10: Onset of Pain (Date)** |  |  |  |  |  |
| **11: VAS Pain Rating** |  |  |  |  |  |
| **12: Current Pain Medications** |  |  |  |  |  |
| **13: KOOS Total Score** |  |  |  |  |  |
| **14: Post-Injection Goal of Patient & Evaluation of Goal** |  |  |  |  |  |
| **15: Improvements in Lifestyle Modifications Since Injection** |  |  |  |  |  |
| **16: Total cost associated with treatment & after treatment (injection cost, medications, functional support such as braces, PT/OT)** |  |  |  |  |  |

**Appendix C**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Pt Name: | Pre-Injection  (office visit) | 3 week  (phone call) | 6 week (phone call) | 3 month (phone call) | 6 month (office visit) |
| Radiographic Imaging Findings\* |  |  |  |  |  |
| Onset of Pain (Date)\* |  |  |  |  |  |
| VAS Pain Rating |  |  |  |  |  |
| Walking Time |  |  |  |  |  |
| # of Steps |  |  |  |  |  |
| Flexion (degree measurement)\* |  |  |  |  |  |
| Extension (degree measurement)\* |  |  |  |  |  |
| Joint Crepitus Degree (mild, moderate, severe) & Location\* |  |  |  |  |  |
| Lateral Instability (+/-)\* |  |  |  |  |  |
| Drawer Sign (+/-)\* |  |  |  |  |  |
| Swelling (mild, moderate, severe) & Location\* |  |  |  |  |  |
| Current Pain Medications & Pain Relief Costs |  |  |  |  |  |
| Lifestyle Modifications Made Since Pain Started |  |  |  |  |  |
| Improvements in Lifestyle Modifications Since Injection |  |  |  |  |  |
| Post-Injection Goal of Patient & Evaluation of Goal\* |  |  |  |  |  |
| Likelihood of Recommending Procedure to Others? (1-5, 1 being not likely, 5 being very likely) |  |  |  |  |  |

**Appendix D**

