

## Quality assurance and adverse event management in regenerative medicine for knee osteoarthritis: Current concepts



Maimuna Marenah<sup>a,\*</sup>, Jinjie Li<sup>a</sup>, Ashok Kumar<sup>a</sup>, William Murrell<sup>a, b, c</sup>

<sup>a</sup> Emirates Integra Medical & Surgery Centre, Dubai Healthcare City, Dubai, United Arab Emirates

<sup>b</sup> Emirates Healthcare Group, Dubai, United Arab Emirates

<sup>c</sup> Landstul Regional Medical Center (LRMC), Division of Surgery, Dept. Orthopaedic Surgery, Landstul, Germany

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### ABSTRACT

The economic and human cost of knee osteoarthritis is forecast to increase. This will impact not only aging individuals, but also the working age members of emerging economies. The current treatment pathways are often costly, time-consuming, and insufficient to manage the degeneration of the knee over the ever-increasing lifespan of patients around the world. In response to the shortcomings of a focus on symptom management, international and high-impact regulators, researchers, clinicians, and most importantly patients, are increasingly interested in the possible management of knee osteoarthritis with novel therapies in the field of regenerative medicine treatments. Regenerative medicine is an emerging discipline whose adherents aim to use the tools of the human body to address underlying dysfunction, leading to lasting repair of damaged tissues and structures. The evidence base lacks consensus on issues related to safety, efficacy, cost-efficiency, and treatment specifications. In this current concepts review, we describe the potential impact of regenerative medicine for knee osteoarthritis and evaluate literature of the past decade for elements related to the quality of clinical research. Finally, we discuss strategies for improving the evidence base for the future. The results of the review reveal that the typical follow-up period for most clinical research into the area is between 6 and 12 months; local ethics board approval is commonly reported, and that Platelet-Rich Plasma is the most common option explored. However, several quality elements were lacking in this cohort of recent literature: cost efficacy data, long-term follow-up, and detailed adverse event reporting. In order to address these weaknesses in the literature, patient outcomes registries are needed, in order to satisfy the need for longer follow-up for individuals receiving regenerative treatments, in addition to further clinical trials which address larger and more diverse patient populations. Transparency will be of utmost importance in further research and clinical translation of regenerative medicine for knee osteoarthritis.

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## 1. Introduction

### 1.1. Knee OA

Knee Osteoarthritis is a prevalent degenerative condition which affects populations.<sup>1</sup> Knee OA is characterized by damage of the knee cartilage, associated wear on nearby bone, degradation of local cellular structures, and inflammation. Disease progression in OA patients is a degenerative process resulting from decreased anabolic and increased catabolic activities in articular cartilage and

synovial membrane of the joint. Identifying the causes of Knee OA is complex and involves a mixture of local and systemic factors.<sup>2</sup> Typical symptoms include joint effusion, crepitus, stiffness, limited range of motion, and most significantly, pain.<sup>2–4</sup> Biomechanical factors impact the experience of Knee OA, as do diet and lifestyle overweight and obese and aging populations around the world are experiencing increasing burden.<sup>1,5,6</sup> Nguyen et al. report that BMI-adjusted knee pain and symptomatic Knee OA have increased 200% for men and tripled in women in a 20 year period. This data suggests that management of Knee OA must become a priority for all stakeholders. Yet current treatment protocols may lack the impact necessary to address growing populations of symptomatic patients.<sup>2,3</sup> (see Fig. 1).

\* Corresponding author.

E-mail address: [research@emiratesintegra.com](mailto:research@emiratesintegra.com) (M. Marenah).

## 1.2. Current treatment for knee OA

The usual treatment pathway ranges from self-management techniques: low-impact aerobic and strengthening exercises, includes weight loss, use of non-steroidal anti-inflammatory drugs or tramadol, to injective and operative interventions: hyaluronic acid and corticosteroid injections, arthroscopy with lavage and/or debridement to meniscectomy-although the latter has been identified as a probable risk factor for future osteoarthritis disease.<sup>2,7</sup> The ultimate step is often total knee arthroplasty (TKA), knee replacement; some observers predict that TKA rates will rise to 3.48 million procedures by 2030.<sup>8</sup> Current treatment pathways are often costly, time-consuming, and insufficient to manage the degeneration of the knee over the ever-increasing lifespan of patients around the world.<sup>9</sup>

## 1.3. Global health context

Social and economic factors may contribute to the current trends seen in knee OA. For example, female gender as well as the likelihood that an individual will experience disability related to the OA diagnosis.<sup>1,2,5</sup> Socioeconomic status, occupation and gender have been associated to increased disease burden; this growing imbalance is of increasing concern, particularly in economic terms.<sup>10</sup>

Knee OA is a disease of global relevance and significance for the future.<sup>11</sup> Globally, life expectancy and food access are improving; at the same time, the economic and human burden of neonatal, communicable and nutritional diseases decrease. This uplifting news is tempered by the fact that non-communicable conditions are quickly rising to take their place,<sup>5</sup> as the disease paradigm in global health shifts from a focus on communicable to chronic diseases, new populations will see an increase in the prevalence of degenerative musculoskeletal disease. One such chronic disease is osteoarthritis of the knee.

Regenerative Medicine treatments focus on replacing lost cartilage and bone as well as improving symptoms such as pain, loss of range of motion and function and reverse the trend of increased disability experienced by the aging global population.<sup>5,12,13</sup>

## 1.4. Regenerative medicine philosophy

Due to obstacles within current conventional treatment of knee osteoarthritis, a growing number of clinicians, scientists, and translational researchers seek to address degeneration and inflammation of Knee OA through the techniques and tools of regenerative medicine; furthermore, regulatory authorities are expressing optimism about potential applications (see Fig. 1).<sup>13–15</sup>

Regenerative Medicine is an emerging multidisciplinary field of researchers and clinicians that aim to solve the underlying dysfunction and cause the repair of affected tissues or structures, most often using the tools of the body itself to bring about healing, stop deterioration and ultimately to cure.<sup>12,14</sup>

## 1.5. Current concepts

In this current concepts review, we first investigate the global health challenges and opportunities and provide context for the significance of Knee OA in the near future. Second, we review current regulatory and expert guidelines diagnose features of research and clinical translation that are essential for advancement of regenerative medicine for Knee OA and identify areas of consensus and opportunities to improve quality assurance and adverse event management within the field. Finally, we execute a

brief review of the literature to assess quality assurance and adverse event management in published clinical research. The suggested measures will provide support for future research, clinical translation, and conformance to prevailing international regulatory guidance and best practice recommendations based on these identified features.

## 2. Global health context

A Swedish study reported that workers diagnosed with Knee OA were nearly twice as likely to take sick leave compared to the general population.<sup>16</sup> In the United States, OA-related absenteeism has an estimated annual cost of \$10.3 billion.<sup>17</sup> Indirect and direct health costs of osteoarthritis can include: inability to accomplish household chores, sick leave taken, the cost of caregivers, reduction in work efficiency, and disability related unemployment or under-employment according to one Canadian study.<sup>18</sup> Disability related to OA has increased more than 30% from 2006 to 2016, and worldwide, makes up approximately 2.8% of the years people spend living with a disability.<sup>5</sup> Nations which also must focus and devote resources to communicable diseases and to the project of development will surely feel the effects of growing rates of chronic musculoskeletal conditions such as Knee OA.<sup>5,13</sup> Furthermore, this disability is experienced disparately across groups; those individuals, communities, and nations with lower socioeconomic status, experience disability at younger ages. Disparity in the form of increased rates of disability among certain racial and ethnic populations and women should also be noted.

Regenerative treatments have been endorsed as an economically efficient method to confront the challenge of chronic disease in diverse economic landscapes.<sup>13</sup>

## 3. Regenerative medicine for knee OA

Surgical treatments are invasive, expensive, have their own complications and rely more on replacement than regeneration or restoration of the knee joints, yet demand remains high; indeed, total knee replacements are predicted to increase in number significantly, reaching 3.48 million per year in the US by the year 2030.<sup>8</sup> Because of these challenges related to current treatments, regenerative medicine has generated interest among the patients, physician, pharmaceutical industry and health regulatory authorities. A number of autologous (stem cells and platelet-rich plasma) and allogenic regenerative products have gained recognition as safe and promising alternatives to existing treatments. High patient-demand, minimal regulation and increased availability of regenerative products, techniques and practices, have led some to overrate their results and aggressively market these options. Despite research fabrication scandals and clinic closures by recent regulatory crackdowns, the field has managed to promote regenerative medicine as a permanent solution to many degenerative or structural disorders of joints, cartilage, tendons and ligaments.

The growing number of clinicians, scientists, and translational researchers who seek to address degeneration and inflammation of Knee OA, look to the techniques and tools of regenerative medicine; encouragingly, regulatory authorities are optimistic about the potential application.<sup>13–15</sup> Regenerative treatments focus on replacing lost cartilage and bone as well as improving symptoms such as pain, loss of range of motion and function and reverse the trend of increased disability experienced by the aging global population.

We chose to use the definition proposed by Daar et al., an 'Interdisciplinary field of research and clinical applications focused on repair, replacement or regeneration of cells, tissues or organs to restore impaired function resulting from any case'.<sup>12</sup> This definition suggests products such as platelet-rich plasma, a peripheral blood

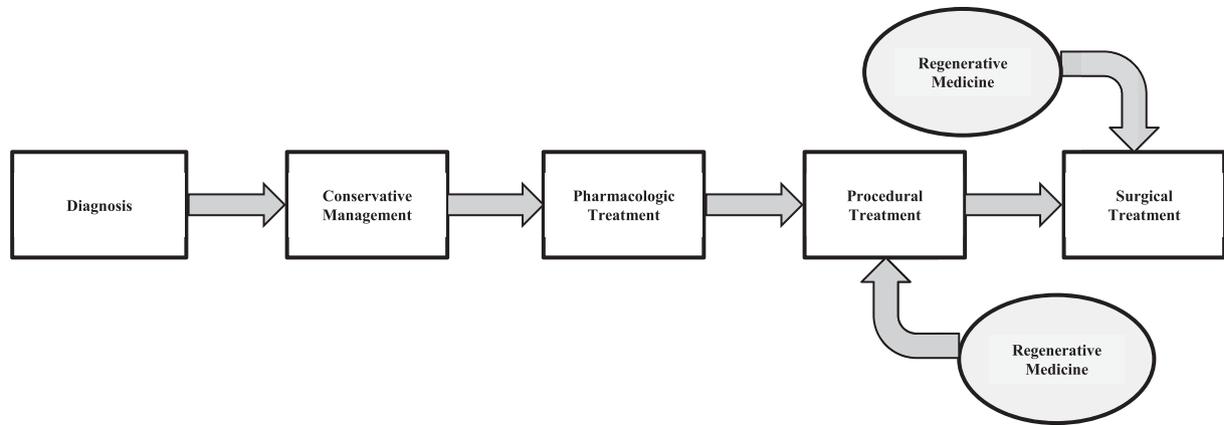


Fig. 1. Proposed Clinical flow for Regenerative Medicine for Knee OA<sup>7</sup>.

product containing higher platelet and growth factor concentrations relative to the whole blood; mesenchymal stem cells from various sources such as adipose and bone marrow, which have the capacity to differentiate in-vivo into bone, cartilage, and other tissues.<sup>20,21</sup> Surgical techniques such as microfracture of the knee, which theoretically produce controlled damage in order catalyze healing are also related to this definition.<sup>22,23</sup> Mixtures of techniques are also popular among clinicians and researchers for example, some researchers have applied PRP as an adjunct to Total Knee Arthroscopy.<sup>24</sup> However, current literature shows conflicting and debatable results regarding cost efficiency, treatment specification, efficacy and safety of these regenerative treatments.

#### 4. Quality assurance and adverse event management

##### 4.1. International guidance

The WHO, U.S. Food & Drug Administration, and others have called for the development of a rigorous evidence base for the treatment of Knee OA with regenerative products in order to guide regulatory decision-making and the development of safe, efficacious, and cost-effective products.<sup>19,25</sup>

Guidance for clinical research and translation of regenerative medicine is essential. Numerous convincing safety studies,<sup>20,26–28</sup> which often involves autologous products which do not pose the potential for disease transmission and host-donor rejection as do other transplantations, have brought about the emergence of a regulatory ‘gray area’ where many clinicians and clinical researchers find themselves today.<sup>29</sup>

In the clinical setting, providers often struggle due to sparse local guidance and an adolescent evidence-base, leading to sub-optimal monitoring of treatment outcomes and thus, claims. For example, in the United States, products which can be categorized as minimally manipulated and intended for use homologous to the original purpose in the body, such as autologous products such as platelet-rich plasma need not undergo preliminary review by the Food and Drug Administration (FDA) and approval in the same category as drugs, a process which is often costly in terms of time and human resources.<sup>30</sup> Indeed, the U.S. FDA recently asserted their intent to support the creative application of these technologies, yet with the same report, announced their intention to increase oversight and enforcement on the field.<sup>15</sup>

The guidelines for research involving human subjects from the World Medical Association outlines the concerns for research into regenerative medicine for Knee OA.<sup>31</sup>

An assessment of recent international guidance, as well as that

of the U.S. Food & Drug Administration, illustrates consensus with regard to reporting of adverse events, the importance of ethical approval by the local institutional review board (IRB), as well as the significance of cost efficiency and long-term follow up (see Table 1). Underreporting and a lack of transparency regarding lack of negative outcomes can be especially costly and harmful when emerging and hopeful cellular therapies are being evaluated.<sup>32</sup>

Long-term follow up is particularly emphasized for individuals conducting clinical projects using cell-based products, due to the tendency of these substances to persist in the body and potentially lead to malignancy (see Table 1).

##### 4.2. Current literature

In order to assess the quality of recent literature, four elements of quality clinical research were evaluated (see Fig. 2). Data collection consisted of an electronic literature search within the Medline database to collect a representative sample of the current clinical research and practice of the past 10 years in regenerative medicine techniques used for treatment of Knee OA. Papers included in this brief review were assessed according to their relevance, their level of evidence, as well as how they addressed elements of quality. The search was executed electronically and full text articles were obtained and reviewed for data extraction and screening according to the inclusion and exclusion criteria. The following MESH terms related to the definition of regenerative medicine adapted from Daar & Greenwood,<sup>5</sup> were utilized: platelet rich plasma, tissue therapy, bone marrow cell transplantation, peripheral stem cell transplantation, hematopoietic progenitor cell, adult stem cell, biologics, and mesenchymal progenitor cell in order to capture regenerative medicine used for treating Knee OA, in order to include full text studies about regenerative medicine used for treating Knee OA. The literature search yielded 152 studies using regenerative medicine for osteoarthritis of the knee joint. These identified studies were subsequently screened for selection based on the Preferred Reporting Items for Systematic Reviews (PRISM) flow diagram.<sup>33</sup> The focus of this review was clinical research; as such, pre-clinical data, editorials, and systematic reviews were removed from the data set. Papers discussing topics related to complementary and alternative medicine and those not directly related to knee cartilage characteristic features of Knee OA, and those that addressed osteoarthritis of other anatomical structures (e.g. hip and spine) were excluded. Studies not matching our inclusion criteria and duplicate studies were excluded. Exclusion criteria included papers discussing topics related to complementary and alternative medicine, those which focused on other

**Table 1**  
Recommended tools for quality clinical translation and research for regenerative medicine.

Organization	Recommended Tools for Quality Clinical Translation and Research for Regenerative Medicine
World Health Organization <sup>15,21</sup>	<ul style="list-style-type: none"> <li>- Adverse event reporting;</li> <li>- Analysis of cost efficiency;</li> <li>- Long-term follow-up and contact.</li> </ul>
International Society for Stem Cell Research <sup>22</sup>	<ul style="list-style-type: none"> <li>- Comparison to existing and widely accessible treatments;</li> <li>- Cost efficiency analysis;</li> <li>- Focus on easily accessible and feasible products such as autologous and minimally manipulated.</li> </ul>
United States Food & Drug Administration <sup>13,32</sup>	<ul style="list-style-type: none"> <li>- Adverse event reporting;</li> <li>- Long-term follow up and data monitoring;</li> <li>- IRB approval;</li> <li>- Comparison to current best therapeutic approaches and to those most commonly available;</li> <li>- Access-deliver value to healthcare systems including patients and payers.</li> </ul>
	<ul style="list-style-type: none"> <li>- Adverse event reporting;</li> <li>- Long-term follow up;</li> <li>- IRB approval;</li> <li>- Transparency in publishing, reporting both positive and negative outcomes.</li> </ul>

### Quality Elements in Current Literature Review of KOA

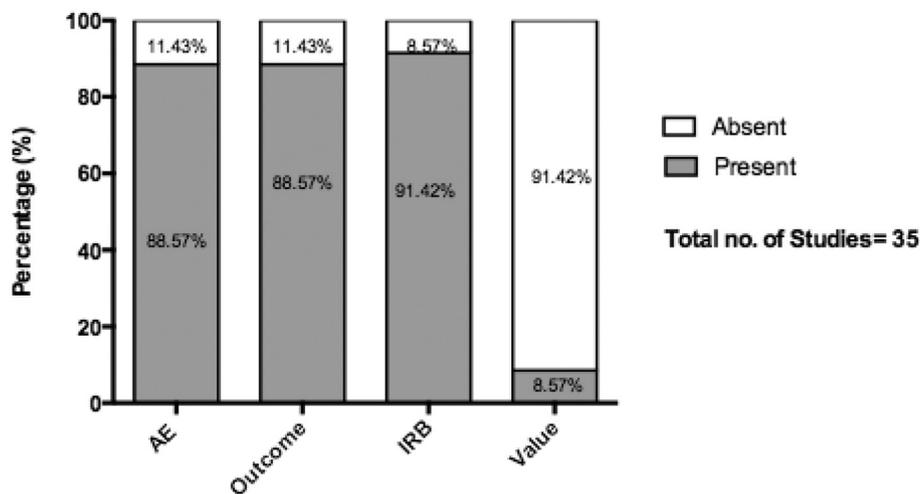


Fig. 2. The figure above represent the current status of quality elements found in literature review of regenerative medicine for knee osteoarthritis.

musculoskeletal disorders not directly related to the knee cartilage and other characteristic features of Knee OA,<sup>7</sup> and those that addressed osteoarthritis of other anatomical structures (e.g. hip and spine). Finally, out of 152, only 35 studies were selected for inclusion in this review.

These 35 selected clinical research papers were subsequently reviewed for features related to quality assurance and transparency in clinical research in human subjects and utilization of cell-based therapies in the clinical setting. This evaluation was based on a set of qualitative variables developed by the authors to assess the status of reporting in the literature (Fig. 2) of: reporting of Adverse Events (AE), Regulatory Approval (IRB), Outcome with regard to the regenerative medicine technology of interest (Outcome), reporting of Adverse Events (AE), mention of cost/benefit analysis and cost efficiency (Value).<sup>19,25,29</sup>

In 32 of the 35 papers evaluated, researchers reported that they had sought and received the approval of their local institutional review board (IRB). Data from prospective patient registries were found in four papers in our sample. Explicit consideration of cost efficiency was found in only three (8.6%) papers in our sample. Among those papers which reported cost efficacy, none reported

data supporting the cost over the period of treatment. Eleven had Level 1, 9 Level 2, three Level 3 and 9 had Level 4 evidence as evaluated by the Oxford Centre for Evidence-based medicine Levels of Evidence.<sup>34</sup> Three-thousand one-hundred and one patients participated in these 35 studies. Thirty-one (88.6%) clearly showed a favorable outcome of their treatment protocol. Thirty-one studies (88.6%) reported their adverse effects. Reported adverse effects included pain at the site of injection, swelling, increased local temperature, stiffness, infection. Exact number and character of these individual side effects were not reported in all the studies. Cost/Benefit analysis or cost efficiency was reported in only 3 (8.6%) papers. Prospective patient registries were used only in four studies.

This sample of clinical research was further evaluated for number of participants and length of follow-up. The average study in this review lasted scarcely longer than a year at 52.6 weeks. The longest-running study in our sample, with data from 5-year follow up of 3 patients.<sup>35</sup> The mean participant volume in our sample was 99 individuals, with one paper reporting as much as 681 participants, this sample gathered from a prospective patient registry.<sup>36</sup>

## 5. Conclusion

Knee osteoarthritis is a clinically complex disorder of the knee. Existing treatment options for knee OA target quality of life improvement, rather than recovery of lost tissues and function in the structure. For example, intra-articular hyaluronic acid and corticosteroids are the two most commonly used treatment for knee osteoarthritis but they also provide only short term pain relief.

This condition is associated with pain and disability among greater numbers of individuals worldwide. Costs associated with current treatment pathways and the growing area of regenerative medicine have and will continue to encourage research and development of cost effective therapies which potentially halt or reverse the degeneration of tissues in the knee. Health disparity found in prevalence of osteoarthritis of the knee and the experience of the disease itself -i.e. level of pain, rate of associated disability- may depend in part upon gender or socioeconomic status. In order to mediate disparities and increased economic and social burden of knee OA, cost-effective treatments should be prioritized. The governments of China, Japan, South Korea, India, and Brazil have reportedly launched research programs into stem cell and tissue engineering research, investing heavily in building the evidence to encourage the eventual use of these products.<sup>36</sup>

Transparency about safety and feasibility is important in a field where the risks and any complications are likely to be borne by the patient and the health care system.<sup>25</sup> Thus, reporting of adverse events and investigation and reporting of both affirmative and negative results during the course of administration of minimally manipulated products is a requirement. Long-term follow-up is essential to ensure the capture of this data.

While large studies are not the only option, access to transparent, well-controlled, representative populations will be key to the development of regenerative medicine for treatment of knee osteoarthritis. Challenges and costs of managing large and diverse patient populations can be mediated by tools like prospective patient registries. In this way, those who are using these technologies outside of clinical research under the investigational drug process of the FDA and analogous organizations, can maintain the long-term health monitoring and adverse event reporting that is essential in this field and improve their reporting of details of treatment details. Gaps in reporting can be supported by use of Patient Treatment Registries as they will provide a base level of data collection for each individual patient.

Regenerative medicine has the potential to make significant impact on the management of knee osteoarthritis, whose burdens are costly to nations, communities and individuals. In this current concepts review, both literature and guidance were briefly reviewed. Research conclusions are promising,<sup>37–41</sup> researchers are planning further clinical trials; and governments and other guiding organizations have signaled their support. In order to take advantage of this convergence, key factors emerge which will maximize the future benefit of regenerative medicine for the treatment of Knee OA: cost efficacy, long-term health surveillance, and transparency.

## Conflicts of interest

The authors have no relevant conflicts of interest to declare.

## Authors contributions

WM contributed paper concept and main objectives. Literature search and data extraction was executed by MM and JL. MM and AK contributed to manuscript development. Data analysis and revisions were contributed by WM and JL.

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