



## ■ PROTOCOL

# The use of biologics in professional and Olympic sport: a scoping review protocol

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## Aims

The use of biologics in the treatment of musculoskeletal injuries in Olympic and professional athletes appears to be increasing. There are no studies which currently map the extent, range, and nature of existing literature concerning the use and efficacy of such therapies in this arena. The objective of this scoping review is to map the available evidence regarding the use of biologics in the treatment of musculoskeletal injuries in Olympic and professional sport.

## Methods

Best-practice methodological frameworks suggested by Arksey and O'Malley, Levac et al, and the Joanna Briggs Institute will be used. This scoping review will aim to firstly map the current extent, range, and nature of evidence for biologic strategies to treat injuries in professional and Olympic sport; secondly, to summarize and disseminate existing research findings; and thirdly, to identify gaps in existing literature. A three-step search strategy will identify peer reviewed and non-peer reviewed literature, including reviews, original research, and both published and unpublished ('grey') literature. An initial limited search will identify suitable search terms, followed by a search of five electronic databases (MEDLINE, EMBASE, Cochrane Database of Systematic Reviews, Web of Science, and Google Scholar) using keyword and index terms. Studies will be screened independently by two reviewers for final inclusion.

## Dissemination

We will chart key concepts and evidence, and disseminate existing research findings to practitioners and clinicians, through both peer reviewed and non-peer reviewed literature, on-line platforms (including social media), conference, and in-person communications. We will identify gaps in current literature and priorities for further study.

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## Introduction

Biologic therapies can be defined as strategies that seek to enhance musculoskeletal tissue healing and regeneration by modulating the biological environment at the site of injury.<sup>1,2</sup> Approaches include the delivery of purified growth factors, autologous and allogenic blood products, scaffolds, and cell therapies.<sup>3,4</sup> Biologics can be used in isolation, or to augment surgical procedures.<sup>5</sup>

Fuelled by celebrity athlete endorsements and the desire for novel treatments,<sup>6</sup> the use of biologics to treat sports-related musculoskeletal injuries has attracted considerable interest over recent years.<sup>7,8</sup> Biologic strategies are particularly attractive to athletes,

who are drawn by the promise of therapies with the potential to accelerate recovery and shorten time away from sport, through minimally-invasive techniques that harness the body's intrinsic healing responses.<sup>9</sup>

While there is a growing body of data demonstrating the value of biologic approaches to treat several specific musculoskeletal injuries,<sup>10,11</sup> there is not yet sufficient evidence to support the widespread use of these strategies.<sup>12</sup> As per the Olympic motto, athletes are becoming 'faster, higher, stronger', and the burden of acute injuries is increasing as forces across bones and joints increase.<sup>13</sup> In an era of year-round single sport training, even from a relatively young age,

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**Table 1.** Inclusion and exclusion criteria of the scoping review.

Inclusion criteria	Exclusion criteria
Research articles are not limited by geographical location, design, language or setting	Studies not explicitly referring to ‘professional’ or ‘Olympic’ athletes
All age groups and sexes of participants	Studies involving professional or elite persons not in sport
Specific population groups only – ‘professional’ or ‘Olympic’ athletes must be stated	Opinion pieces/opinions, commentaries and papers with no data
Any sport	Qualitative studies
Any biologic therapy	Studies not published in English language
Sources of information can include primary research studies, reviews (including but not limited to systematic reviews, scoping reviews, and meta-analyses), guidelines, case reports, and grey literature including unpublished and ongoing trials, dissertations, and conference proceedings	Treatments not by convention considered ‘biologics’ including steroids

the frequency of overuse injuries has also increased.<sup>14</sup> Professional and Olympic athletes represent unique populations, with distinct challenges relating to the physical demands of full-time sport and external financial pressures on performance.<sup>15</sup> Little is known about the use of biologic strategies within these populations. While there have been a small number of reports describing the effects of specific biologics in small numbers of professional or Olympic athletes, no study has yet provided an overview evaluating the extent, range, and overall ‘landscape’ of literature investigating the use of biologics in professional and Olympic sport.

The rationale for this scoping review is to conduct a methodologically-rigorous study providing this overview by mapping and summarizing all the available evidence across all biologics and all professional and Olympic sport. We will also identify significant gaps in the literature and inform further research strategies.

## Methods

The methodological framework for this study is based on that presented by Arksey and O’Malley,<sup>16</sup> and further modified by Levac et al<sup>17</sup> and the Joanna Briggs Institute.<sup>18</sup> We utilized the five-stage process described by Arksey and O’Malley.<sup>16,19</sup> This study is designed, and will be conducted in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analysis extension for Scoping Reviews (PRISMA-ScR) reporting guidelines.<sup>20</sup>

**Stage 1: Identify the research question.** The research question was developed through discussion and deliberation between the research team and in consultation with experts in the field of biologics and professional and Olympic sports medicine. The research question was derived from, and is in accordance with, the objectives and broad scope that characterize a scoping review:

What is known about the prevalence and effect of biologic therapies to treat musculoskeletal injuries in professional and Olympic athletes?

### Stage 2: Identifying relevant studies

**Eligibility criteria.** The authors collectively agreed on the following inclusion and exclusion criteria to guide

the search process and identification of relevant articles (Table 1).

## Search strategy and databases

**Step 1: An initial limited search.** An initial limited search of MEDLINE, EMBASE, Cochrane Database of Systematic Reviews, Web of Science, and Google Scholar for articles was conducted in October 2020. The search terms used were ‘biologic’ OR ‘cell therapy’ OR ‘platelet’ OR ‘growth factor’ OR ‘mesenchymal stem cell’ OR ‘mesenchymal signalling cell’ OR ‘mesenchymal stromal cell’ AND ‘professional’ OR ‘Olympic’ AND ‘sport’. In all, 122 studies resulted from this search. A search of ProQuest dissertations with the same search criteria applied to relevant abstracts revealed 74 dissertations. Thus, 196 studies resulted in total from these sources. De-duplicating resulted in 168 studies being identified as relevant for initial screening in our limited search. All 168 studies identified were reviewed. Overall, 34 studies in total proved relevant, with the references from these studies being reviewed for further relevant papers.

**Step 2: Identification of key words and index terms.** The title, abstract and index terms used to describe the articles identified in step 1 will be analyzed. From this, a more finely tuned search strategy of key words and index terms will be obtained, to maximize inclusivity. The final search strategy will include terms from our initial limited search supplemented with keywords and phrases from relevant articles retrieved from the initial limited search.

The following electronic databases will be searched:

1. MEDLINE (Ovid).
2. EMBASE (Ovid).
3. Cochrane Database of Systematic Reviews.
4. Web of Science.
5. Google Scholar.

A similar strategy as above will be applied to the grey literature to identify non-indexed papers including to include unpublished and ongoing trials, annual reports, dissertations and conference proceedings. The same

search terms used for the above databases will be applied to search for relevant theses in the ProQuest database, and also in the World Health Organization (WHO) International Clinical Trials Registry Platform.

**Step 3: Further searching of references and citations.** Bibliographies of eligible studies will be examined to identify any original studies not obtained through the above searches. Additionally, citation searching of these studies, using Google Scholar, will also be carried out. Authors of all relevant primary comprehensive systematic reviews will be contacted for further information. Scoping reviews are iterative in nature, thus as reviewers become increasingly familiar with the research and evidence, additional search terms may be identified and incorporated into the search strategy.<sup>16</sup> Search strategies will be documented, and the complete final search strategies will be made available from the corresponding author or in supplementary data. Relevant references will be incorporated into a bibliographical manager which will be used to store references and allow for duplicates to then be eliminated.

**Stage 3: Study Selection.** Titles and abstracts identified by the search strategy will be evaluated against the eligibility criteria by two reviewers independently (NM and IM). The reviewers will assess the title and abstracts independently, using the inclusion and exclusion criteria. The titles and abstract of eligible studies will be categorized as 'include', 'exclude', or 'uncertain'. If there is disagreement regarding the eligibility of a study, a third reviewer will evaluate to establish consensus. If consensus is not reached, the study will be included in the scoping review. The full text will subsequently be sourced for all included and 'uncertain' articles, and separately evaluated. If excluded, the reason for exclusion will be documented. The process of study selection will be reported using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart.<sup>21</sup>

#### **Stage 4: Charting the data**

**Extraction of results.** Charting tables similar to that by the Joanna Briggs Institute<sup>18</sup> will be used to document and assimilate extracted data from the included studies as described below. Appropriate data from the eligible studies will be extracted manually using a customised data extraction sheet designed using Microsoft Word. This will be in tabular form. The initial limited search strategy will allow the development of initial a priori categories. These categories will be piloted on several studies to ensure all relevant results are extracted, pertinent to the research questions. Two reviewers (NM and IM) will perform data extraction, with IM checking 10% of NM's data extractions for accuracy and consensus and vice versa. If any disagreement arises, this will be discussed between the authorship team. If necessary, the categories will be modified, and the extraction sheet revised. The following data will be extracted:

- A. Author.
- B. Journal/source of publication.
- C. Year of publication.
- D. Country where study was conducted or arises.
- E. Aims/purpose.
- F. Study population and sample size.
- G. Study design and level of evidence.
- H. Type of sport being studied.
- I. Performance level of athletes included in study.
- J. Type of biologic and characteristics (e.g. platelet-rich plasma, platelet-poor plasma, leucocyte rich/poor) if applicable.
- K. Type of injury being treated.
- L. Outcome of intervention and details of these (e.g. how measured).
- M. Key findings that relate to scoping review research questions.

In the context of scoping reviews data charting is typically an iterative process and so the above extraction categories may be adapted with additional categories added or modified depending on the included studies. Where full-text manuscripts cannot be obtained, access through the libraries of Stanford University, USA, and the University of Edinburgh, UK, will be sought as a hard or electronic copy. For papers that cannot be retrieved following this process, we will directly request this from the corresponding author by electronic and/or traditional mail. If the full paper still cannot be found, the study will not be included.

**Stage 5: Collating, summarizing, and reporting the results.** The methods we employ in this scoping review will enable us to assimilate existing knowledge on this subject. The data collected will address the following aims:

1. Chart the current extent, range, and nature of evidence for biologic strategies to treat injuries in professional and Olympic sport provide a concise overview of the breadth and depth of research.
2. Summarize and disseminate existing research findings.
3. Ascertain gaps in the existing literature to inform future research priorities.

The exact reporting format will not be able to be determined until the data is charted and will be informed by the literature included. The results will be reported using the PRISMA: Extension for Scoping Reviews guidelines.<sup>20</sup> There will be no assessment of quality or meta-analysis of data as it is beyond the scope of the review.

#### **Dissemination of results**

This scoping review will inform clinicians, policy makers and professional sports organisations on the current extent and depth of evidence regarding the use of biologics in professional and Olympic sport. We will

provide insights into the gaps in research in this field and thus inform the priority areas for further research. Scoping the existing literature will provide a foundation to inform our readership on the directions that need to be taken for further research. Furthermore, we will inform professional sports organisations on the extent of the current evidence base behind biological treatments for their athletes.

Findings will be summarized as a manuscript for peer reviewed publication. Furthermore, we aim to present our findings in a variety of conference settings, including to sports physicians, sports organisations, orthopaedic surgeons, and clinicians in musculoskeletal medicine. We will aim to further disseminate the findings of this scoping review through a multiplatform approach. We will generate tools to increase stakeholder understanding, including infographics and animations, and will share widely through social media and other online platforms. Relevant experts in the fields of biologics and sports medicine will be contacted to inform our findings and to help communicate key findings to the wider public. Scoping review methodology consists of reviewing and synthesizing already published data, and thus this part of the study is not subject to ethical approval.

In settings where the extent and scope of current evidence is not known, scoping reviews are particularly effective for addressing widely framed research questions. This article presents our protocol for a scoping review, which comprises comprehensive, rigorous, and transparent methodology. This review, which includes both peer reviewed and grey literature, will enable an overview of the wider picture of current research for the use of biologics in the management of musculoskeletal injuries in professional and Olympic level athletes. This review will also discern gaps in knowledge in this field, and thus provide recommendations for future research. Importantly, we will use the findings from this review of professional and Olympic athletes to inform treatment of the much larger population of active individuals with sports injuries.

## Twitter

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## References

1. Rodeo S, Haddad FS. Regenerative solutions: bridging the translational gap. *Bone Joint J*. 2019;101-B(9):1033–1034.
2. Rodeo SA. Cell therapy in orthopaedics: where are we in 2019? *Bone Joint J*. 2019;101-B(4):361–364.
3. LaPrade RF, Dragoo JL, Koh JL, et al. AAOS research Symposium updates and consensus: biologic treatment of orthopaedic injuries. *J Am Acad Orthop Surg*. 2016;24(7):e62–.
4. LaPrade RF, Geeslin AG, Murray IR, et al. Biologic treatments for sports injuries II think Tank—Current concepts, future research, and barriers to advancement,

part 1: biologics overview, ligament injury, tendinopathy. *Am J Sports Med*. 2016;44(12):3270–3283.

5. Murray IR, Geeslin AG, Goudie EB, Petrigliano FA, LaPrade RF. Minimum information for studies evaluating biologics in orthopaedics (MIBO): platelet-rich plasma and mesenchymal stem cells. *J Bone Joint Surg Am*. 2017;99(10):809–819.
6. Cox L. Tiger admits to platelet-rich plasma therapy, what's that? ABC news. 2010. <http://abcnews.go.com/Health/Technology/tiger-woods-admits-platelet-rich-plasma-therapy/story?id=10303312> (date last accessed 06 November 2020).
7. Zlotnicki JP, Geeslin AG, Murray IR, et al. Biologic treatments for sports injuries II think Tank—Current concepts, future research, and barriers to advancement, part 3. *Orthop J Sports Med*. 2016;4(4):232596711664243.
8. Murray IR, LaPrade RF, Musahl V, et al. Biologic treatments for sports injuries II think Tank—Current concepts, future research, and barriers to advancement, part 2. *Orthop J Sports Med*. 2016;4(3):232596711663658.
9. Murray IR, LaPrade RF. Platelet-Rich plasma: renewed scientific understanding must guide appropriate use. *Bone Joint Res*. 2016;5(3):92–94.
10. Belk JW, Kraeutler MJ, Houck DA, et al. Platelet-rich plasma versus hyaluronic acid for knee osteoarthritis: a systematic review and meta-analysis of randomized controlled trials. *Am J Sports Med*. 2020:036354652090939.
11. Tang S, Wang X, Wu P, et al. Platelet-Rich plasma vs autologous blood vs corticosteroid injections in the treatment of lateral epicondylitis: a systematic review, pairwise and network Meta-Analysis of randomized controlled trials. *PM&R*. 2020;12(4):397–409.
12. Abrams GD, Murray IR. Editorial commentary: please don't call it a mesenchymal stem cell. *Arthroscopy*. 2020;36(8):2134–2136.
13. Murray AD, Murray IR, Robson J. Rugby Union: faster, higher, stronger: keeping an evolving sport safe. *Br J Sports Med*. 2014;48(2):73–4.
14. Aicale R, Tarantino D, Maffulli N. Overuse injuries in sport: a comprehensive overview. *J Orthop Surg Res*. 2018;13(1):309.
15. Duralde X, Jones T, Griffith T. Challenges of medical care delivery in professional sports: lessons from professional baseball. *J Am Acad Orthop Surg*. 2018;26(24):872–880.
16. Arksey H, O'Malley L. Scoping studies: towards a methodological framework. *Int J Soc Res Methodol*. 2005;8(1):19–32.
17. Levac D, Colquhoun H, O'Brien KK. Scoping studies: advancing the methodology. *Implementation Sci*. 2010;5(1):69.
18. Peters MDJ, Godfrey CM, Khalil H, et al. Guidance for conducting systematic scoping reviews. *Int J Evid Based Healthc*. 2015;13(3):141–146.
19. Murray A, Daines L, Archibald D, et al. The relationship and effects of golf on physical and mental health: a scoping review protocol. *Br J Sports Med*. 2016;50(11):647–650.
20. Tricco AC, Lillie E, Zarin W, et al. PRISMA extension for scoping reviews (PRISMA-ScR): checklist and explanation. *Ann Intern Med*. 2018;169(7):467–473.
21. Moher D, Liberati A, Tetzlaff J, Altman DG, et al, for the PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ*. 2009;339(jul21 1):b2535.

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- S. A. Rodeo: Edited the protocol.
- S. L. Sherman: Edited the protocol.
- A. D. Murray: Edited the protocol.
- F. S. Haddad: Edited the protocol.
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- G. D. Abrams: Designed and edited the protocol.

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