Evidence-based Guidelines for the use of Stem Cell Therapy

Orthopedic Conditions

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DISCLAIMER

The Evidence-based Guidelines for the use of Stem Cell Therapy published by the MoHFW/DHR-DGHS provides recommendations made after careful consideration of the available evidence. This evidence has been synthesized by collation of systematic reviews (SR) and meta-analysis (MA) of the existing randomized controlled trials (RCTs) on well-defined review questions on the subject matter. The guideline reflects the best available data as per the criteria laid down for the study inclusion set by the guideline development group. Considerable care has been taken to ensure that the information contained in these guidelines is accurate, evidence-based and up-to-date at the time of publication. However, there is a possibility that new studies may have been published too late during the guideline development process or after publication and are not incorporated into the guideline.

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MESSAGE

In this evolving and promising landscape of modern medicine, stem cell therapy stands as one of the most dynamic areas of scientific enquiry. Its potential to revolutionize the treatment of a wide array of conditions, from degenerative diseases to traumatic injuries, has generated the immense excitement and hope. Keeping the highest quality of evidence as the foundational base for formulating the recommendations is of utmost importance.

The Evidence-based guidelines for the use of stem cell therapy represent a comprehensive synthesis of the best available evidence providing a framework for clinicians, researchers, and policymakers alike. Devised to support the responsible integration of stem cell treatment into clinical practice, these guidelines offer clear and transparent evidence-based recommendations that are based upon latest scientific knowledge backed by a rigorous methodology.

As we navigate the complexities of stem cell therapy, it is imperative that we balance innovation with caution. The guidelines aim to address this balance by emphasizing the importance of rigorous clinical trials, ethical considerations, and patient safety. In closing, we commend the contributors for their dedication in creating these evidence-based guidelines for the use of stem cell therapy and look forward to more such guidelines in the future.

Dr. Rajiv Bahl
Secretary DHR & DG, ICMR

Dr. Atul Goel
DGHS

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ACKNOWLEDGEMENTS

These Evidence-based Guidelines have come into existence due to the vision of MoHFW to develop one comprehensive guideline for the entire country based on the best available evidence. The current Evidence-based Guidelines on the use of Stem Cell Therapy were taken up by the DHR and DGHS to resolve the uncertainty associated with the effectiveness of stem cell therapy and help the practitioners in making informed decisions about the use of this intervention. The secretariat thanks the members of the Steering Group for spearheading the process of guideline development. We wish to extend our heartfelt gratitude to the members of the Guideline Development Group for being the driving force behind the recommendations formulated in these guidelines. The secretariat would also like to thank the systematic review teams for being the most vital pillar of this guideline by synthesizing evidence which formed the basis of the recommendations. The secretariat is also indebted to the guideline methodologists Dr. Kameshwar Prasad, Dr. Rakesh Lodha and Dr. M. Jeeva Sankar for their untiring inputs and efforts throughout the guideline development process.

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ABBREVIATIONS

ACI	:	Autologous Chondrocyte Implantation
ADL	:	Activities of Daily Living
ADMSCs	:	Adipose tissue-Derived Mesenchymal Stem Cells
AEs	:	Adverse Events
ARCO	:	Association Research Circulation Osseous
ASES	:	American Shoulder and Elbow Surgeon
AVN	:	Avascular Necrosis
BMA	:	Bone Marrow Aspiration
BMAC	:	Bone Marrow Aspirate Concentrate
BMMNC	:	Bone Marrow Mono Nuclear Cell
BMMSC	:	Bone Marrow Mesenchymal Stem Cell
CD	:	Core Decompression
CI	:	Confidence Interval
CPGA	:	Collagen/ Polyglycolic Acid
DoI	:	Declaration of Interest
EtD	:	Evidence to Decision
FCD	:	Focal Cartilage Defect
FDA	:	Food and Drug Administration
GDG	:	Guideline Development Group
GDT	:	Guideline Development Tool
GRADE	:	Grading of Recommendations, Assessment, Development and Evaluation
HA	:	Hyaluronic Acid
HHS	:	Harris Hip Score
hMSCs	:	Human Mesenchymal Stem Cells
HSCs	:	Hematopoietic Stem Cells
IKDC	:	International Knee Documentation Committee
KL	:	Kellgren–Lawrence
KOOS	:	Knee Injury and Osteoarthritis Outcome Score
LKSS	:	Lysholm Knee Scale Score
MA	:	Meta-Analysis
MCID	:	Minimally Clinical Important Difference
MD	:	Mean Difference
MSCs	:	Mesenchymal Stem Cells
MWS	:	Mayo Wrist Score
NICE	:	National Institute for Health and Care Excellence
OA	:	Osteoarthritis
OIS	:	Optimal Information Size
ON	:	Osteonecrosis
PBMSCs	:	Peripheral Blood Mononuclear Cells
PBSCs	:	Peripheral Blood Stem Cells
PICO	:	Population Intervention Comparator Outcome
PRP	:	Platelet Rich Plasma
QDASH	:	Quick Disabilities of Arm, Shoulder & Hand
QoL	:	Quality of Life
RCT	:	Randomized Control Trial
REM	:	Random Effects Model

RoB	:	Risk of Bias
RR	:	Relative Risk
SAEs	:	Severe Adverse Events
SCT	:	Stem Cell Therapy
SD	:	Standard Deviation
SDSC	:	Synovium Derived Stem Cell
SE	:	Standard Error
SMD	:	Standardized Mean Difference
SPR	:	Sports and Physical Recreation
SR	:	Systematic Review
SVF	:	Stromal Vascular Fraction
THR	:	Total Hip Replacement
UCMSCs	:	Umbilical Cord-Derived Mesenchymal Stem Cells
VAS	:	Visual Analog Scale
WHO	:	World Health Organization
WOMAC	:	Western Ontario and Macmaster Universities Arthritis Index
YLD	:	Years Lived with Disability

EXECUTIVE SUMMARY

1. Background & Rationale:

Orthopedic injuries and conditions have a massive economic impact on the healthcare system. Chronic orthopedic conditions like osteoarthritis are a significant contributor to years lived with disability (YLD) and affect a patient's quality of life. For such diseases, current curative treatment options are limited to joint replacement therapy. Stem cell therapy is an upcoming novel therapeutic approach that utilizes the unique properties of self-renewal and differentiation of stem cells, to regenerate or replace damaged cells and tissues in the human body. Stem cell therapy is lately being offered as a potential solution for a variety of orthopedic conditions. It is quintessential to take an evidence-based approach during the development of such regenerative therapies, with the best quality evidence being sought to determine the true effectiveness and efficacy of such approaches. The overall goal of these guidelines is to provide guidance and evidence-based recommendations for the use of stem cell therapy in six orthopedic conditions namely osteoarthritis, avascular necrosis of hip, cartilage defects, tendinopathy, non-union of bone fracture, and meniscal tear/meniscopathy.

2. Target audience:

The recommendations in this guideline are intended to inform the policymakers, patients, health care professionals, especially orthopedic surgeons practicing in secondary and tertiary care centers as well as the researchers and scientists working in the field of regenerative medicine regarding the efficacy and safety of stem cell therapy in the aforementioned orthopedic conditions.

3. Guideline Development Methods:

The guideline was developed using standard methodology as described by international agencies like the WHO and NICE. This involved the creation of a steering group, a guideline development group and a systematic review teams. Briefly, the process involved: (i) Identifying priority review questions (PICOs), (ii) Evidence synthesis by systematic review (SR) & meta-analysis (MA), (iii) Review of evidence profiles and grading the certainty of evidence (iv) Formulation of recommendations using the Evidence to Decision (EtD) framework (v) Drafting the guideline (vi) External review and (vii) Dissemination of guidelines. The GRADE approach (Grading of Recommendations Assessment, Development and Evaluation) was used to assess the certainty of evidence for each review question. The evidence generated was analyzed by the GDG to make judgments and formulate the recommendations based on the EtD Framework in the GRADEpro GDT software. This included assessment of the effects (benefits to harms ratio) of the intervention, values and preferences of the patients, resources required, cost effectiveness, acceptability and feasibility of the intervention and equity considerations. In brief, the GDG members examined the evidence, made judgments on the EtD framework for each disease condition, and formulated the wordings of the final recommendations. This was followed by external peer review before the final release of guidelines.

4. Summary of Recommendations*:

S. No.	Key Question	Recommendation	Rationale/Justification
1.	In patients with osteoarthritis (OA), what is the efficacy and safety of stem cell therapy compared to usual care?	Stem cell therapy is **not recommended** in routine clinical practice for the treatment of osteoarthritis. Strength: Conditional# Certainty of Evidence: Very Low *#It may be used only in the context of rigorously conducted randomized controlled trials.*	There is very low certainty evidence of trivial reduction in pain and trivial improvement in function. The undesirable effects are variable and heterogenous.
2.	In patients with avascular necrosis (AVN) of hip, what is the efficacy and safety of stem cell therapy compared to usual care?	Stem cell therapy is **not recommended** in routine clinical practice for the treatment of avascular necrosis of hip. Strength: Conditional# Certainty of Evidence: Very Low *#It may be used only in the context of rigorously conducted randomized controlled trials.*	There is very low certainty evidence of trivial reduction in pain and no improvement in function. There is little or no difference in undesirable effects between stem cell therapy and usual care.
3.	In patients with cartilage defects (CD), what is the efficacy and safety of stem cell therapy compared to usual care?	Stem cell therapy is **not recommended** in routine clinical practice for the treatment of cartilage defects. Strength: Conditional# Certainty of Evidence: Very Low *#It may be used only in the context of rigorously conducted randomized controlled trials.*	There is very low certainty evidence of trivial reduction in pain and no improvement in function. There is little or no difference in undesirable effects between stem cell therapy and usual care.
4.	In patients with tendinopathy, what is the efficacy and safety of stem cell therapy compared to usual care?	Stem cell therapy is **not recommended** in routine clinical practice for the treatment of tendinopathy. Strength: Conditional# Certainty of Evidence: Very Low *#It may be used only in the context of rigorously conducted randomized controlled trials.*	There is very low certainty evidence of trivial reduction in pain and no improvement in function. There is little or no difference in undesirable effects between stem cell therapy and usual care.

5.	In patients with non-union of bone fracture, what is the efficacy and safety of stem cell therapy compared to usual care?	Stem cell therapy is **not recommended** in routine clinical practice for the treatment of non-union of bone fracture. Strength: Conditional[#] Certainty of Evidence: Very Low *[#]It may be used only in the context of rigorously conducted randomized controlled trials.*	The evidence is inadequate in quantity and quality to determine the safety and efficacy of stem cell therapy in patients with non-union of bone fracture.
6.	In patients with meniscopathy/ meniscal tear, what is the efficacy and safety of stem cell therapy compared to usual care?	Stem cell therapy is **not recommended** in routine clinical practice for the treatment of meniscopathy/ meniscal tear. Strength: Conditional[#] Certainty of Evidence: Very Low *[#]It may be used only in the context of rigorously conducted randomized controlled trials.*	There is very low certainty evidence of trivial reduction in pain and no improvement in function. The undesirable effects are variable and heterogenous.

*Platelet rich plasma (PRP) is not considered here, as it is not stem cell therapy.

I. GUIDELINE DEVELOPMENT PROCESS

1. Introduction:

A new process has been established in the MoHFW wherein one comprehensive evidence-based guidelines have been jointly developed by DoHFW, DGHS and DHR using a rigorous and robust scientific process to bring clarity among stakeholders i.e., patients, clinicians, and the society in general. The generation of such evidence included collation of evidence from SR and MA of existing literature on well-defined review questions (PICOs). Finally, the evidence obtained from SR & MA was graded for its certainty using the GRADE Approach. This grading was done to assess the certainty of evidence and formulate the recommendations using the EtD framework. Such rigorously developed evidence-based guidelines have the potential to address the research to policy gap by translating the best available evidence of any healthcare intervention into practice (Figure 1).

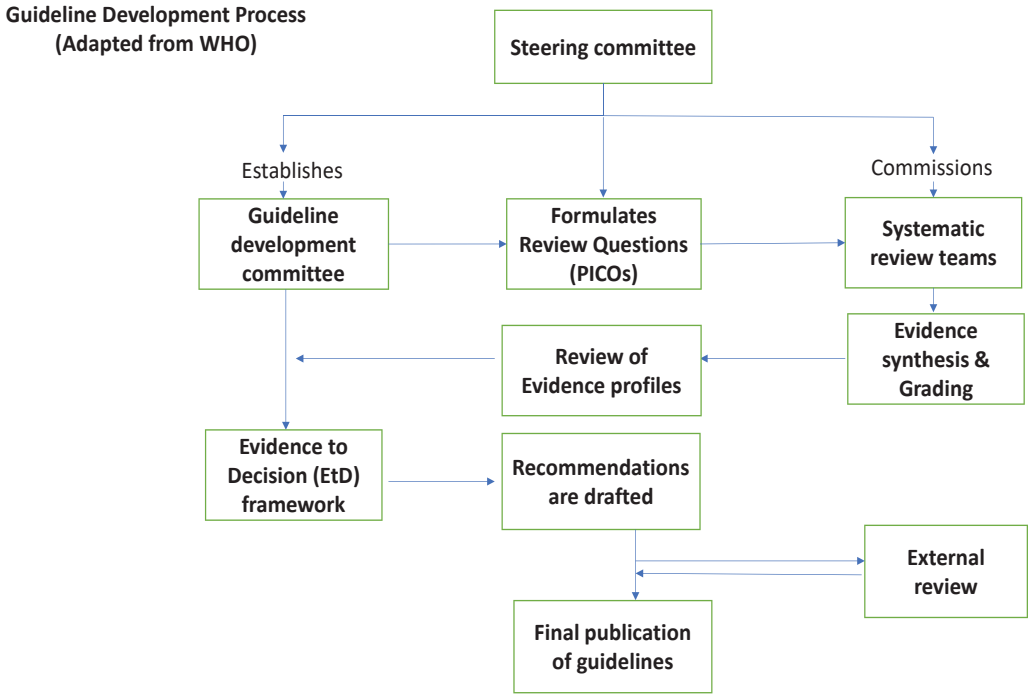


Figure 1: Guideline Development Process –adapted from WHO[1]

2. Rationale/ Scope:

The rapid advances in stem cell research have created high expectations in the field of cell-based therapies. Because of its regenerative potential, stem cell therapy has garnered significant interest among patients and practitioners. As a result, there has been rampant use of this experimental therapy despite limited knowledge of its safety and efficacy. Realizing that therapeutic applications

need to be based on rational and ethical premises, these guidelines aim to summarize the evidence available on the efficacy and safety of stem cell therapy to guide the informed decisions.

Majority of the orthopedic conditions often have a chronic disease course with limited curative treatment options. The disease conditions included for review in the present guidelines are Osteoarthritis, Avascular Necrosis of Hip, Tendinopathy, and Cartilage Defects, Non-Union of Bone Fracture and Meniscal Tear /Meniscopathy. These were selected based on the directives from the MoHFW and a review of literature on the therapeutic use of stem cell therapy in orthopedic diseases/conditions. The guidelines aim to provide guidance for the responsible, safe, and effective use of stem cell therapy and highlight the research gaps at which future endeavors need to be targeted.

3. Target audience:

The recommendations in this guideline are intended to inform the policymakers, patients and health care professionals especially orthopedic surgeons practicing in secondary and tertiary care centers as well as researchers and scientists working in the field of regenerative medicine regarding the safety and efficacy of stem cell therapy in the aforementioned orthopedic conditions.

4. Contributors:

The guideline was developed using standard methodology as described by international agencies like WHO and NICE.[1,2] This involved the creation of a steering group, a guideline development group and systematic review teams (Annexure-1):

Steering Group: This group was jointly chaired by the Secretary, DHR & DG, ICMR and DGHS in overseeing the entire process of guideline development. The steering group identified priority disease conditions, helped in the formulation of GDG, reviewed the declaration of interest of members, reviewed the draft guidelines and managed the guideline publication and dissemination.

Guideline Development Group: This group was constituted to formulate review questions relevant to the guidelines for conducting SRs for addressing the question, to decide on the critical outcomes and formulate recommendations based upon evidence generated by the systemic review teams. It is a multi-disciplinary group composed of methodologists, stem cell experts, subject experts, ethics expert, public health expert, pharmacologist, social scientist as well as patient group representatives. Potential members of the GDG were identified by the steering group based on requisite technical skills and diverse perspectives needed for the formulation of the guidelines. These members were free from any conflict of interest in order to formulate unbiased recommendations. The subject experts, stem cell experts and methodologists provided critical inputs on the formulation of review questions in the PICO format. After completion of the SRs, the evidence profiles were reviewed by the DHR secretariat and guideline methodologists with the help

of subject experts. Finally, the GDG examined and interpreted the whole body of evidence and made judgments in the EtD meetings using the GRADEpro GDT EtD framework.

Systematic Review Teams: These teams were commissioned to review and evaluate all available evidence in the form of randomized controlled trials (RCTs). The certainty of this evidence was assessed by the established GRADE criteria on the basis of risk of bias, imprecision, inconsistency, indirectness and publication bias.

External Reviewers: Relevant subject experts were identified to review the final guideline document and to comment upon the clarity of the recommendations, validity of the justification provided for each recommendation and the completeness of evidence.

ICMR-DHR Secretariat: The secretariat was responsible for providing the technical and administrative support in the entire process of guideline development.

5. Management of Conflict of interests:

All the GDG members must be free from any conflict of interest in order to formulate the unbiased recommendations. A conflict of interest is a set of circumstances that creates a risk that professional judgment given regarding a primary interest will be unduly influenced by a secondary interest. The primary interest in developing guidelines is improving quality of clinical care while secondary interests include all other interests that could be affected or potentially affected by a recommendation in the guideline and may be either financial or non-financial. Any kind of conflict of interest is an important source of bias in the development of guidelines.

All the potential GDG members had filled the Declaration of Interest (DoIs) form adapted from the WHO.[1] These declarations were then reviewed by the steering group and managed appropriately. A summary of the DoIs and how they were managed is provided in Annexure-2.

6. Defining the Scope and Key Questions:

The steering group held a meeting with the potential GDG members to identify the priority disease conditions on which the efficacy and safety of stem cell therapy need to be reviewed. A list of 10 broad disease groups was finalized including a total of 28 conditions. The group of orthopedic conditions included six diseases-osteoarthritis, avascular necrosis of hip cartilage defects, tendinopathy, non-union of bone fracture and meniscal tear/meniscopathy.

Thereafter, a meeting was held by the GDG to decide on the key review questions relevant for the selected diseases in the PICO format i.e., Population Intervention, Comparator and Outcome. The outcomes that matter most to the concerned population were carefully selected and specified as critical outcomes for the guideline development. *These questions were formulated without keeping the literature in mind in order to obviate bias. Considering the scarcity of evidence for this experimental intervention, it was decided to keep the PICO question as broad as possible and do a*

subsequent subgroup analysis for relevant subgroups as needed. These PICO questions are available in the respective disease section.

7. Systematic Review methods:

Commissioning of Systematic Reviews: Once the review questions were identified, the ICMR-DHR secretariat floated an Expression of Interest inviting experts in the field from all over the country to conduct SRs and MA. Out of received 130 applications, 28 were selected to conduct SRs and MA. The criteria for evaluation included were methodological expertise, subject expertise, quality of SRs published, database access, strength of team and conflict of interests, if any. The SRs were thus commissioned and all the teams were provided with the review questions in PICO format as finalized by the GDG. The ICMR-DHR secretariat and the methodologists provided oversight, including assessment and feedback on each systematic review protocol. The data extraction was checked to ensure the uniformity and transparency in the entire process of guideline development.

Literature search strategy: To maintain a uniform methodology, all the SR teams were instructed to design the literature searches on the following databases: PubMed, Embase, Web of Science, and Cochrane CENTRAL. **Only randomized controlled trials were included in the systematic review.** No grey literature was included. However, hand-searching of references to find relevant review articles was carried out. Non-English articles were excluded only if translation was not possible. Regarding 'Population,' for any disease condition, all the grades of severity were included, and subgroup analyses (if mentioned apriori in the protocol) was done wherever needed. All interventions with well characterized stem cells or stem cell-derived products were included.

In addition, following conditions precluded the trial from being included in the final body of evidence in the Evidence to Decision (EtD) framework:

- Flawed process of random sequence generation and/or concealment of allocation
- More than 30% of enrolled patients deviated from allocated intervention post-randomization
- Absence of stem cell characterization (flow cytometry or immuno- phenotyping or culture)

Therefore, the systematic review teams were asked to do a meta-analysis excluding such trials and the evidence produced thereafter was presented to the GDG.

Data extraction methods: Data extraction was conducted by the SR teams and reviewed by the ICMR-DHR secretariat and the methodologists. The teams were advised to use plot digitizer wherever feasible, if values were not available in the text. Imputations and assumptions were best to be avoided. All methodological queries were resolved with the help of guideline methodologists and the teams were also advised to refer to the *Cochrane Handbook for Systematic Reviews of Interventions* to resolve any methodological queries.[3] While doing the meta-analysis, the use of standardized mean difference (SMD) had minimized, as it is easier to compare mean difference (MD) with the minimal clinically important difference (MCID).

Risk of Bias Assessment: Risk of bias for each study outcome was assessed using the Revised Cochrane Risk of Bias-2 tool. For assessment, the GDG had agreed upon the following terms of reference and provided to all the systematic review teams:

- Use only the RoB-2 Tool for assessment of the risk of bias of RCTs and mention the reasons for the risk of bias judgments for all the domains of the RoB-2 Tool.
- The downgrading of evidence due to the risk of bias judgment should be decided by the following criteria:
    i. If >2/3rd (by weight in the pooled analysis) of RCTs are at low risk of bias (green), then label the overall risk of bias for that outcome as not serious in the GRADE Table.
    ii. If 2/3rd - 1/3rd (by weight in the pooled analysis) of RCTs are at low risk of bias (green), then label the overall risk of bias for that outcome as serious in the GRADE Table.
    iii. If <1/3rd (by weight in the pooled analysis) of RCTs are at low risk of bias (green), then label the overall risk of bias for that outcome as very serious in the GRADE Table.
- The teams were asked to review the RCTs with extreme results in the pooled analysis cautiously, to search for any major methodological discrepancy.

The progress of the SR teams was monitored monthly and queries were resolved by the secretariat after discussion with the methodologists.

8. Determination of Minimal Clinically Important Difference (MCID):

It is defined as the smallest change in any outcome that is considered as clinically meaningful or important by the patient and the health care providers. It is the difference at which a large set of clinicians will be willing to change their practice for this benefit and the certainty of evidence is rated in relation to this threshold. A thorough literature search was done to identify the MCIDs for each critical outcome. If multiple references were available for one outcome, the GDG deliberately finalized one threshold for each outcome. In cases, where the MCID was not found in the literature, the thresholds were defined by the GDG. The criteria used for deciding the MCID were as follows: severity of the condition, maximum potential of improvement in the condition, how meaningful are the consequences of the improvement, risks associated with the treatment and costs as well as feasibility of the treatment.

9. GRADing of the certainty of the evidence:

The GRADE approach was used to access the certainty of evidence using the GRADEpro GDT software (https://www.gradepro.org/). At baseline, RCTs start with high certainty of evidence and this certainty could be downgraded based on pre-defined criteria like the risk of bias, inconsistency, imprecision, indirectness, and publication bias. Publication bias was evaluated only if the number of studies for a particular meta-analysis were more than 10. For number of studies less than 10, it was considered inevaluable. The systematic review teams completed their reviews and shared the

evidence profiles with the guideline secretariat. The secretariat then reviewed the evidence profiles with the help of guideline methodologists and any discrepancies in the review were resolved through discussion with the systematic review teams. The table below highlights the significance of the certainty of evidence as per GRADE.[4]

Certainty level	Significance
High	We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low	Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very Low	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

10. Drafting of Evidence to Decision frameworks:

The guideline secretariat prepared the draft EtD framework. The EtD framework available on the GRADEpro GDT software was used to draft recommendations. It consists of a set of criteria that determine the strength and direction of a recommendation to bring about transparency in the formulation of recommendations. These criteria include the certainty of evidence, the balance between benefits and harms, the acceptability and feasibility of the intervention, patient values and preferences, equity considerations, resource use and cost effectiveness. Prior to drafting recommendations, all the GDG members were apprised of this framework and every criterion was explained in detail. The secretariat presented these frameworks along with a review of evidence profile and forest plots provided by the systematic review teams to the GDG.

11. Formulation of Recommendations:

The GDG members were asked to make judgments on each of the domains of the EtD framework based on the evidence presented to them. The judgments on the desirable and undesirable effects were based on the findings of the systematic reviews and meta-analysis. Review of literature/ research evidence as well as the experience of the GDG members was used to inform the discussions pertaining to patient values and preferences, resource use and cost effectiveness, acceptability, feasibility of the intervention along with equity considerations. Wherever research evidence was unavailable, the opinion of the GDG was recorded in additional considerations. The entire body of evidence was put into the GRADE EtD framework for drafting the final recommendation for each review question.

The voting for each domain was done through a Whatsapp poll. Thorough discussion and deliberation were held on each of the domains with an aim to reach consensus on each judgment. Based on the voting for judgments for each domain, final voting was done to determine the strength and direction of the recommendation. The final recommendation for each disease condition was made by consensus, defined as the agreement by 75% or more of the GDG members. A consensus was reached for all recommendations in this guideline and there were no strong disagreements. The GDG also identified caveats in the existing evidence and highlighted areas for future research.

12. Strength of Recommendations:

The strength of a recommendation is the extent to which the GDG is confident in the balance between the desirable and undesirable effects of the intervention, across the range of patients for whom the recommendations are intended. When a GDG was very certain about this balance (for example the desirable effects clearly outweighing the undesirable effects), a strong recommendation in favor of an intervention or against the intervention was issued and vice versa. However, when the GDG was uncertain about this balance, a conditional recommendation was issued. Owing to the experimental nature of the stem cell therapy, a separate column of *"may be used only in the context of rigorously conducted randomized controlled trials*" was added by the GDG in the Evidence to Decision framework of these guidelines.[5]

13. Document preparation and peer review:

After the completion of the EtD meetings, the ICMR-DHR secretariat prepared a draft of the guideline document to accurately reflect the deliberations and decisions taken by the GDG. This draft was reviewed by the guideline methodologists followed by the external review group. The external reviewers were requested to comment upon the clarity of the recommendations so that there is no ambiguity about the decision among the end-users, validity of the justification provided for each recommendation, accuracy and completeness of the evidence (RCTs only). The steering group carefully evaluated the input of the GDG members and the comments by the external reviewers. Revisions to the draft document were done as needed, to rectify any factual errors and the document was finalized, thereafter.

REFERENCES:

1. WHO handbook for guideline development, second edition. Geneva: World Health Organization; 2014 https://iris.who.int/bitstream/handle/10665/145714/9789241548960_eng.pdf?sequence=1 accessed 28 August 2024.
2. Developing NICE guidelines: the manual. https://www.nice.org.uk/process/pmg20/chapter/introduction. accessed 28 August 2024.
3. Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions.
4. Balshem H, Helfand M, Schünemann HJ, Oxman AD, Kunz R, Brozek J, Vist GE, Falck-Ytter Y, Meerpohl J, Norris S, Guyatt GH. GRADE guidelines: 3. Rating the quality of evidence. J Clin Epidemiol. 2011 Apr;64(4):401-6. doi: 10.1016/j.jclinepi.2010.07.015. Epub 2011 Jan 5. PMID: 21208779.
5. Andrews J, Guyatt G, Oxman AD, Alderson P, Dahm P, Falck-Ytter Y, Nasser M, Meerpohl J, Post PN, Kunz R, Brozek J, Vist G, Rind D, Akl EA, Schünemann HJ. GRADE guidelines: 14. Going from evidence to recommendations: the significance and presentation of recommendations. J Clin Epidemiol. 2013 Jul;66(7):719-25.

II. RECOMMENDATIONS

1. OSTEOARTHRITIS

A. BACKGROUND:

Osteoarthritis (OA) is one of the most common causes of pain and disability and is a significant contributor to years lived with disability (YLD). The knee is one of the common among all joint sites affected by OA. With ageing populations and increasing rates of obesity and injury, the prevalence of osteoarthritis is expected to continue to increase globally. As per GBD estimates, the age-standardized prevalence of OA in India has increased from 4,895 (95% uncertainty interval (UI): 4,420-5,447) in 1990 to 5313 (95%UI: 4,799-5,898) in 2019, per 100,000 persons.[1]

B. RECOMMENDATIONS:

Stem cell therapy is **not recommended** in routine clinical practice for the treatment of osteoarthritis.
Strength: Conditional#
Certainty of Evidence: Very Low

#*It may be used only in the context of rigorously conducted randomized controlled trials.*

Rationale/Justification
This recommendation has been made as there is very low certainty evidence of trivial reduction in pain and trivial improvement in function. The undesirable effects are variable and heterogenous. In addition, the follow up period is limited to comment on the long-term safety of stem cell therapy. Results should be interpreted with caution, in view of various study limitations like small number of participants and/or events, risk of bias, use of active co-intervention along with stem cell therapy, different sources and varying dose of stem cell used.

C. SUMMARY OF EVIDENCE:

Key question: In patients with osteoarthritis, what is the efficacy and safety of stem cell therapy as compared to usual care?

Included studies: Four databases were searched from inception to September 2023 for randomized controlled trials assessing the efficacy and safety of stem cell therapy in people with osteoarthritis. 2159 studies were identified and 39 studies met the inclusion criteria.[2-40] Out of these 39 RCTs, 26 trials met the 'reliable body of evidence' criteria, as specified by the GDG and were used for synthesizing evidence.

The included studies had participants with mean age ranging from 18 to 90 years with all grades of severity of osteoarthritis. The source of stem cells included bone marrow, adipose tissue, SVF and umbilical cord; that were either autologous or allogenic in nature.

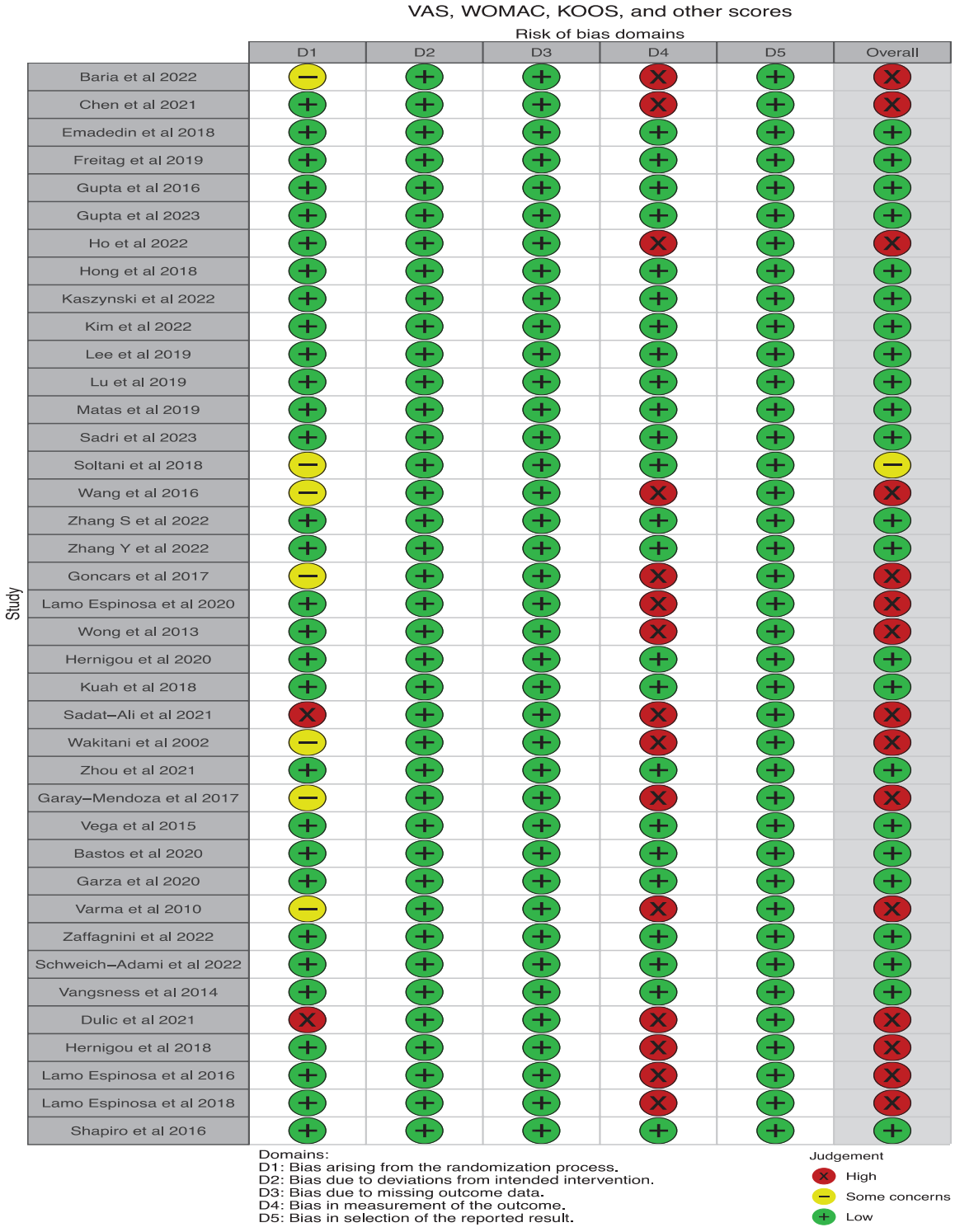
Below mentioned studies were excluded from the meta-analysis as they did not meet the criteria for "reliable body of evidence":

S. No.	Author	Reason for exclusion
1.	Dulic et al. 2021[32]	Flawed process of random sequence generation and concealment of allocation
2.	Baria et al. 2022[15]	Absence of stem cell characterization
3.	Garay Mendoza et al. 2017[13]	Flawed process of random sequence generation and concealment of allocation
4.	Carvalho Schweich-Adami et al. 2022[35]	Flawed process of random sequence generation and concealment of allocation
5.	Varma et al. 2010[36]	Absence of stem cell characterization
6.	Zhang et al. 2022[24]	Absence of stem cell characterization
7.	Sadat Ali et al. 2021[37]	Flawed process of random sequence generation and concealment of allocation
8.	Wang et al. 2016[11]	Flawed process of random sequence generation and concealment of allocation
9.	Hong et al. 2019[34]	Absence of stem cell characterization
10.	Hernigou et al. 2018[10]	Population not of interest
11.	Hernigou et al. 2020[38]	Wrong unit of randomization
12.	Wakitani et al. 2002[8]	Outcome not of interest
13.	Vangsness et al. 2014[40]	Population not of interest

Critical outcomes reviewed and their MCID:

S. No.	Outcome reviewed	What does it measure?	MCID (wherever decided by the GDG)
1.	Visual Analog Scale (VAS) Range: 0-10 Higher score is worse	Validated measure for measuring intensity of pain.	Absolute change of VAS score by 2 points
2.	Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)- Overall Range: 0-100 Higher score is worse	Self-administered questionnaire that is used to assess pain, stiffness, and function in patients with OA of the hip or knee.	Absolute change of WOMAC score by 20 points
3.	Knee Injury and Osteoarthritis Outcome Score (KOOS) • Pain • Symptom • Quality of Life • Activities of Daily living • Sports and Recreation Range: 0-100 for each of the subscales Higher score is better	Self-reported outcome measure assessing the patient's opinion about the health, symptoms, and functionality of their knee.	Absolute change of KOOS by 20
4.	SAEs	Serious adverse events	-

Risk of bias assessment:

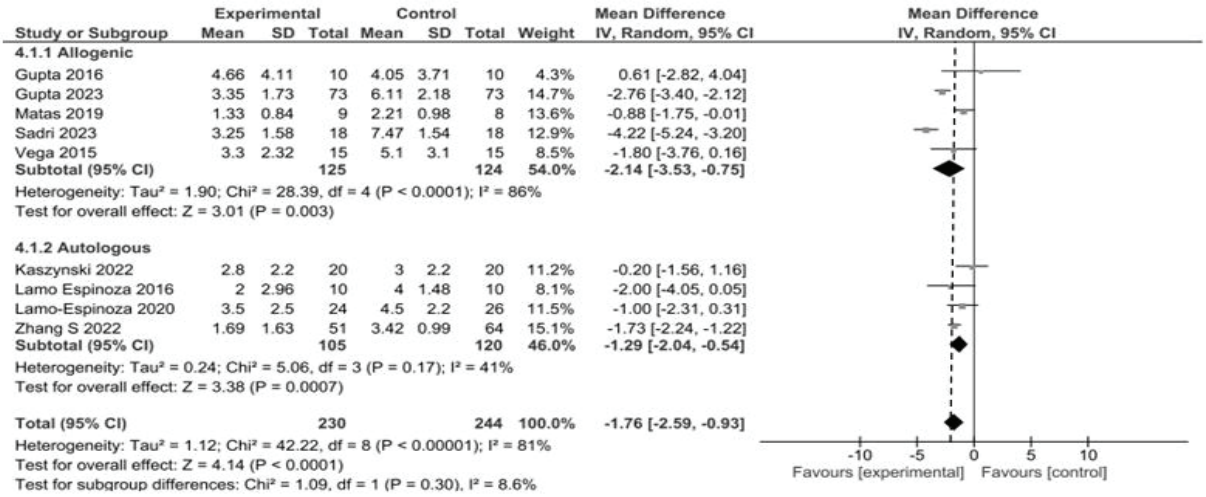


Desirable Effects (Dotted line represents MCID)**:**

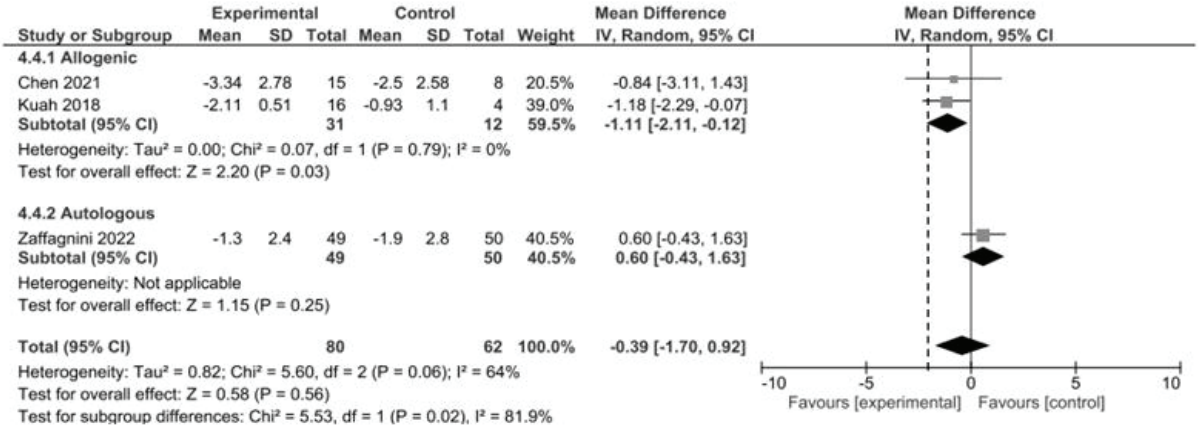
1. VAS at 12 months:

Nine trials with 474 participants reported post score of VAS at the end of 12 months. The mean difference was -1.76 (95% CI: -2.59 to -0.93) between the stem cell and the usual care arm. The difference was statistically significant but less than the MCID of 2, hence unimportant clinically. Four trials with 142 participants reported the absolute change in VAS score at the end of 12 months. The mean difference was -0.39 (95% CI: -1.70 to 0.92) between the stem cell and the usual care arm. The difference was statistically non-significant.

1.1. Forest plot showing the effect of stem cell therapy on VAS-post score as compared to usual care: 12 months

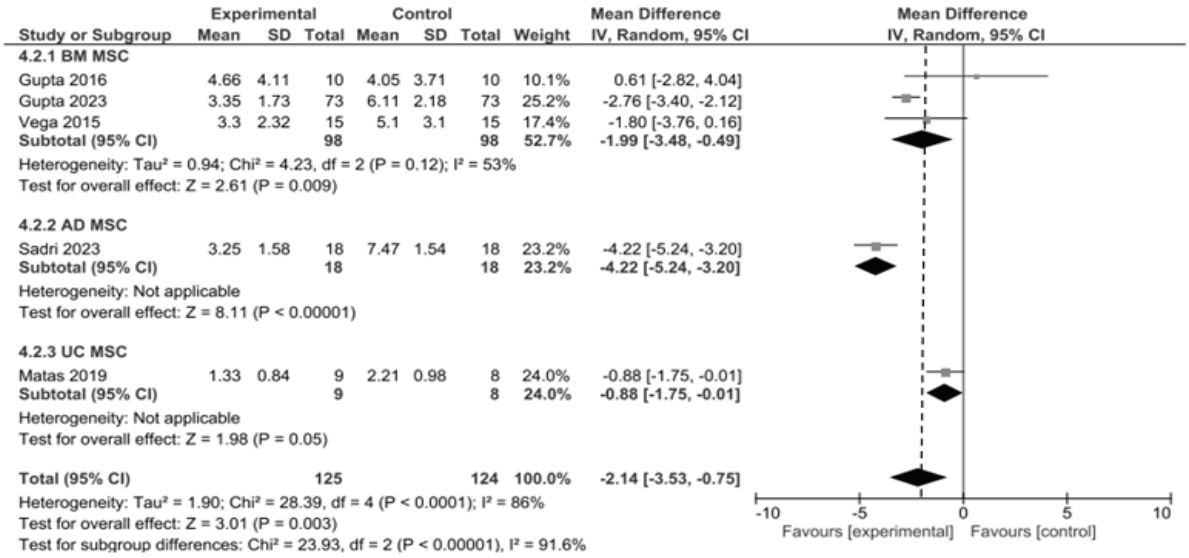


1.2. Forest plot showing the effect of stem cell therapy on absolute change in VAS from baseline as compared to usual care: 12 months

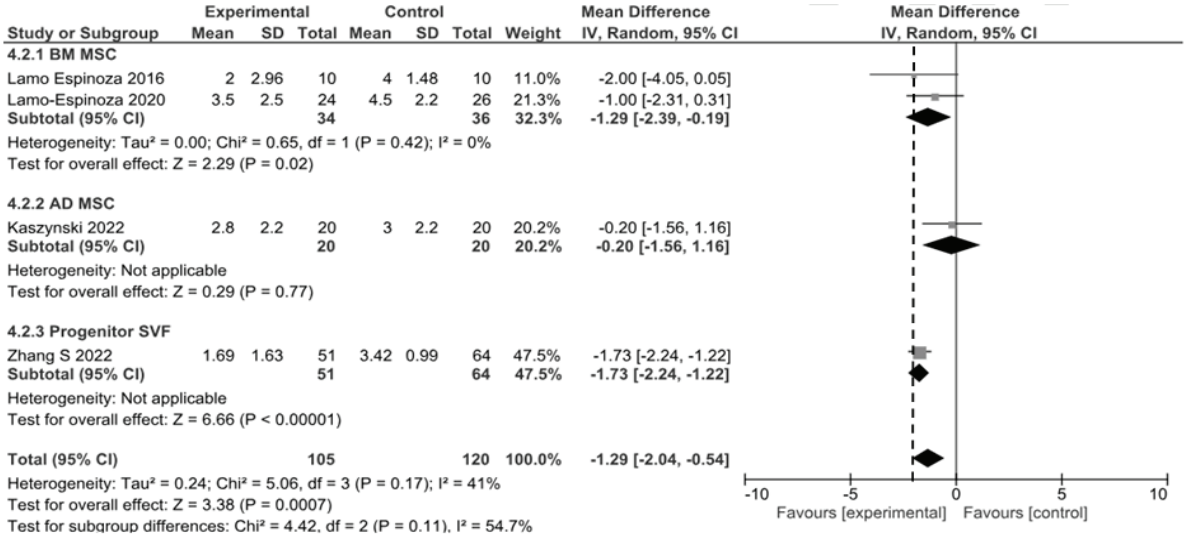


Subgroup analysis

1.3. VAS-post score at 12 months: Allogenic subgroup



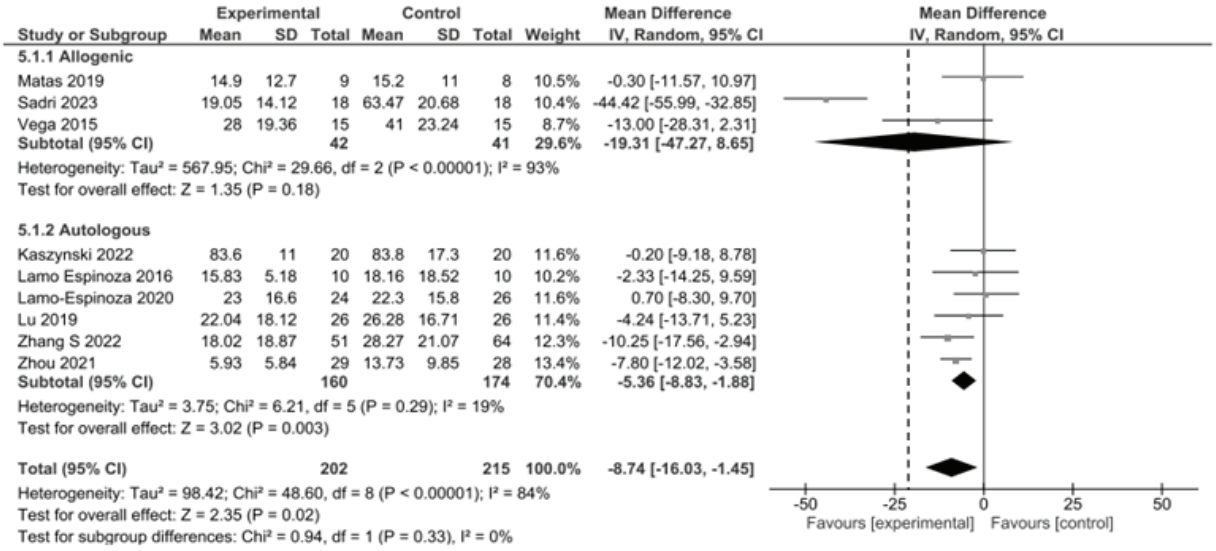
1.4. VAS-post score at 12 months: Autologous subgroup



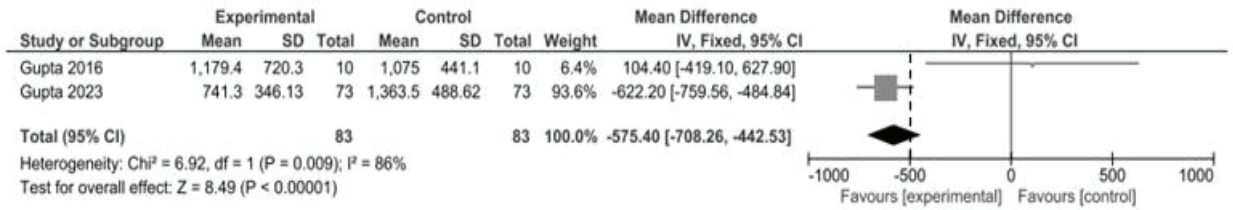
2. WOMAC at 12 months: Nine trials with 417 participants reported post score of WOMAC at the end of 12 months. The mean difference was -8.74 (95% CI -16.03 to -1.45) between the stem cell and the usual care arm. The difference was statistically significant but less than the MCID of 20, hence unimportant clinically. Two trials with 166 participants reported WOMAC on a scale of 0-2400 at the end of 12 months. They reported a mean difference of -575.40 (95% CI: -708.26 to -442.53) between the stem cell arm as compared to the usual care arm. The difference was statistically significant and clinically important. Two trials with 42 participants reported the change

in WOMAC score at the end of 12 months. The mean difference was -11.96 (95% CI -22.65 to -1.28) between the stem cell and the usual care arm. The difference was statistically significant but less than the MCID of 20, hence unimportant clinically.

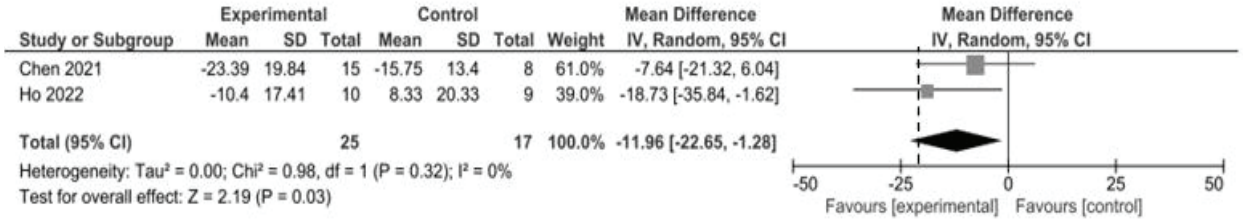
2.1. Forest plot showing the effect of stem cell therapy on WOMAC-post score as compared to usual care: 12 months



2.2. WOMAC-post score at 12 months (Scale: 0-2400)

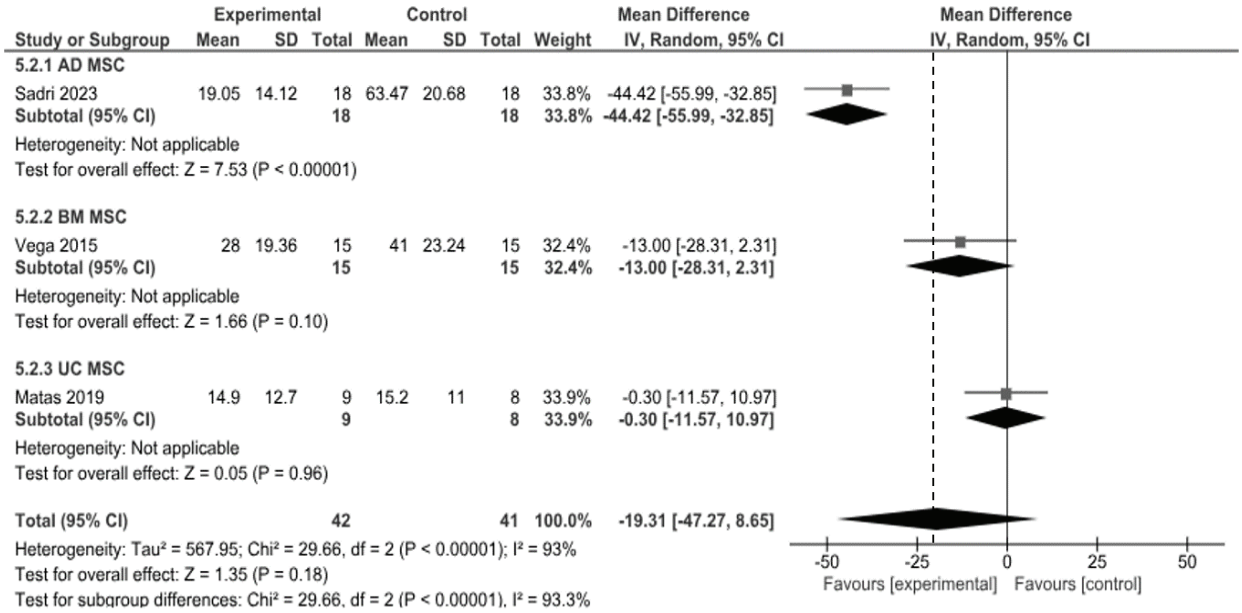


2.3. Forest plot showing the effect of stem cell therapy on change in WOMAC from baseline as compared to usual care: 12 months

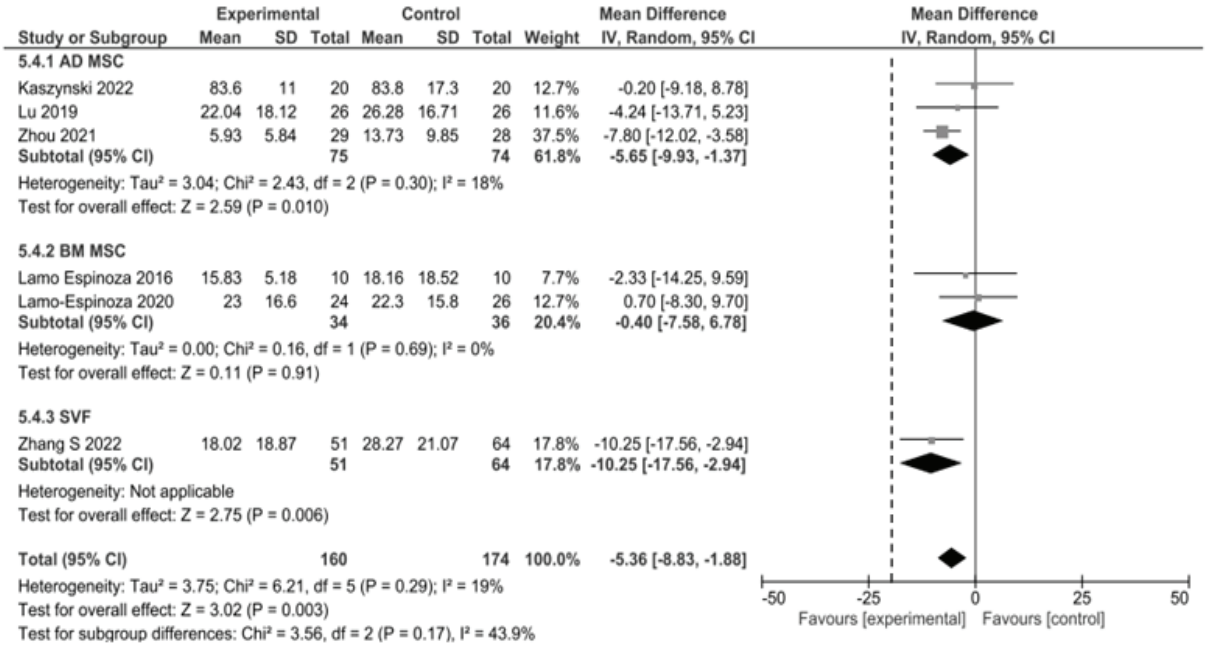


Subgroup analysis

2.4. WOMAC-post score at 12 months: Allogenic subgroup

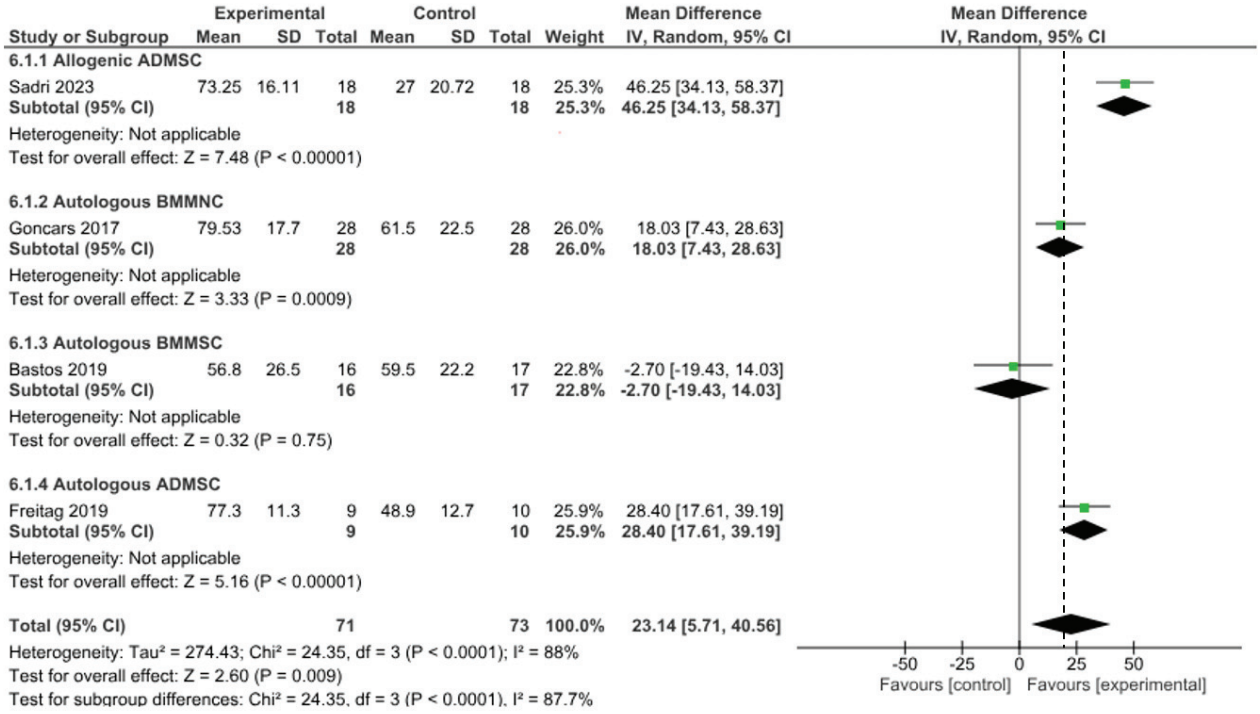


2.5. WOMAC-post score at 12 months: Autologous subgroup

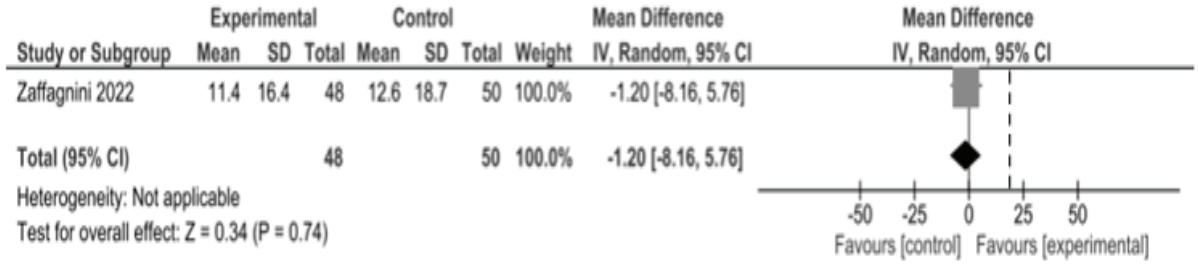


3. KOOS pain: Four trials with 144 participants reported post score of KOOS pain at the end of 12 months. The mean difference was 23.14 (95% CI: 5.71 to 40.56) between the stem cell and the usual care arm. The difference was statistically significant and crosses the MCID of 20, hence important clinically. One trial with 98 participants reported the change in KOOS pain score at the end of 12 months. The mean difference was -1.20 (95% CI: -8.16 to 5.76) between the stem cell and the usual care arm. The difference was statistically non-significant.

3.1. Forest plot showing the effect of stem cell therapy on KOOS pain-post score as compared to usual care: 12 months

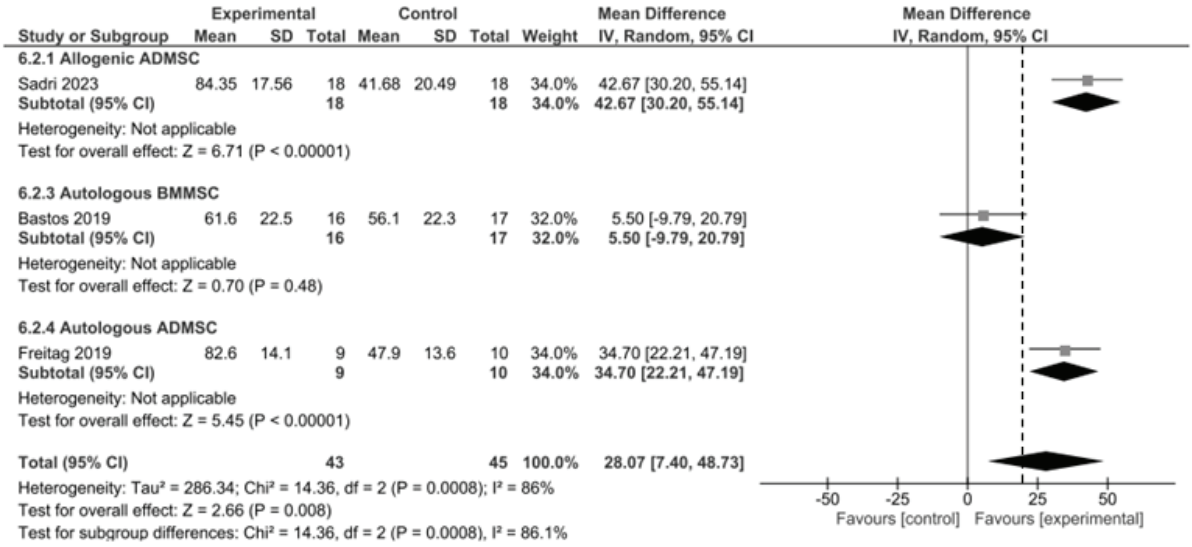


3.2. Forest plot showing the effect of stem cell therapy on KOOS pain-change score as compared to usual care: 12 months

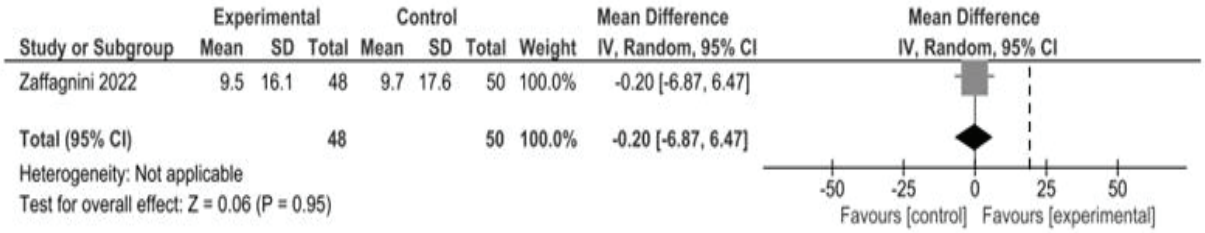


4. KOOS Symptom: Three trials with 88 participants reported post score of KOOS symptom at the end of 12 months. The mean difference was 28.07 (95% CI: 7.40 to 48.73) between the stem cell and the usual care arm. The difference is statistically significant and more than the MCID of 20, hence important clinically. One trial with 98 participants reported the change in KOOS symptom score at the end of 12 months. The mean difference was -0.20 (95% CI: -6.87 to 6.47) between the stem cell and the usual care arm. The difference was statistically non-significant.

4.1. Forest plot showing the effect of stem cell therapy on KOOS symptom-post score as compared to usual care: 12 months

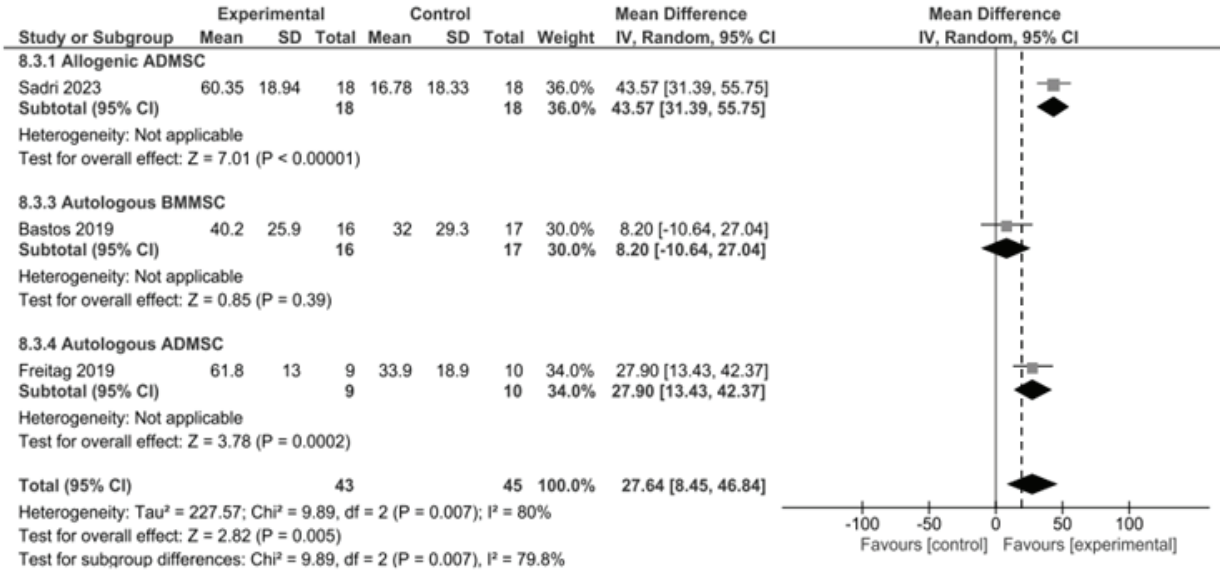


4.2. Forest plot showing the effect of stem cell therapy on KOOS symptom-change score as compared to usual care: 12 months

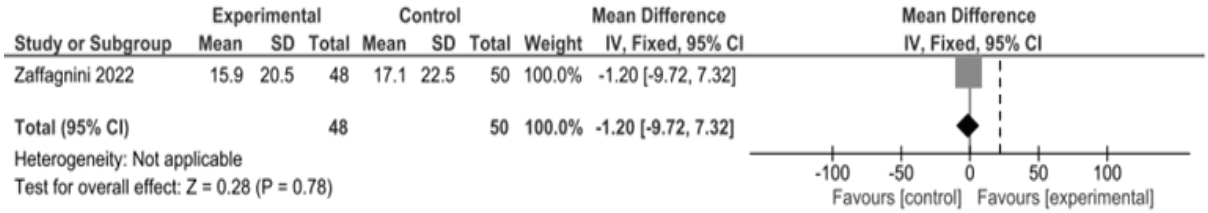


5. KOOS QoL: Three trials with 88 participants reported post score of KOOS QoL at the end of 12 months. The mean difference was 27.64 (95% CI: 8.45 to 46.84) between the stem cell and the usual care arm. The difference was statistically significant and crosses the MCID of 20, hence important clinically. One trial with 98 participants reported the change in KOOS QoL score at the end of 12 months. The mean difference was -1.20 (95% CI: -9.72 to 7.32) between the stem cell and the usual care arm. The difference was statistically non-significant.

5.1. Forest plot showing the effect of stem cell therapy on KOOS QoL-post score as compared to usual care: 12 months

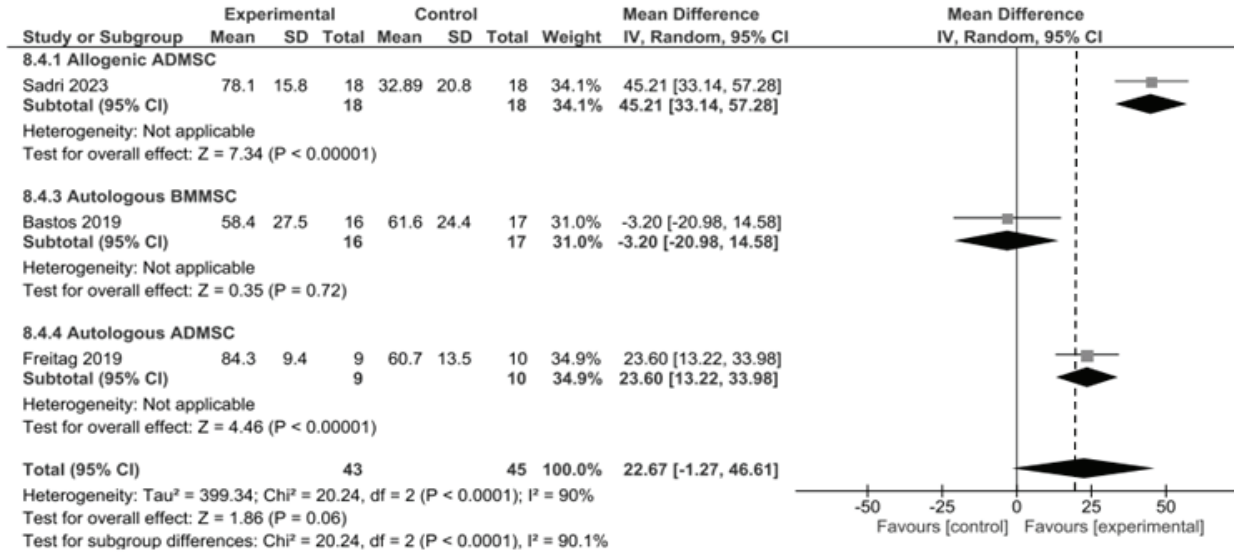


5.2. Forest plot showing the effect of stem cell therapy on KOOS QoL-change score as compared to usual care: 12 months

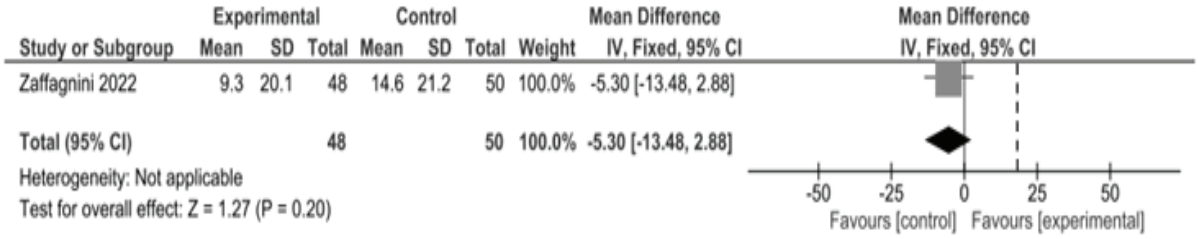


6. KOOS ADL: Three trials with 88 participants reported post score of KOOS ADL at the end of 12 months. The mean difference was 22.67 (95% CI: -1.27 to 46.61) between the stem cell and the usual care arm. The difference was statistically not significant. One trial with 98 participants reported the change in KOOS ADL score at the end of 12 months. The mean difference was -5.30 (95% CI: -13.48 to 2.88) between the stem cell and the usual care arm. The difference was statistically non-significant.

6.1. Forest plot showing the effect of stem cell therapy on KOOS ADL-post score as compared to usual care: 12 months



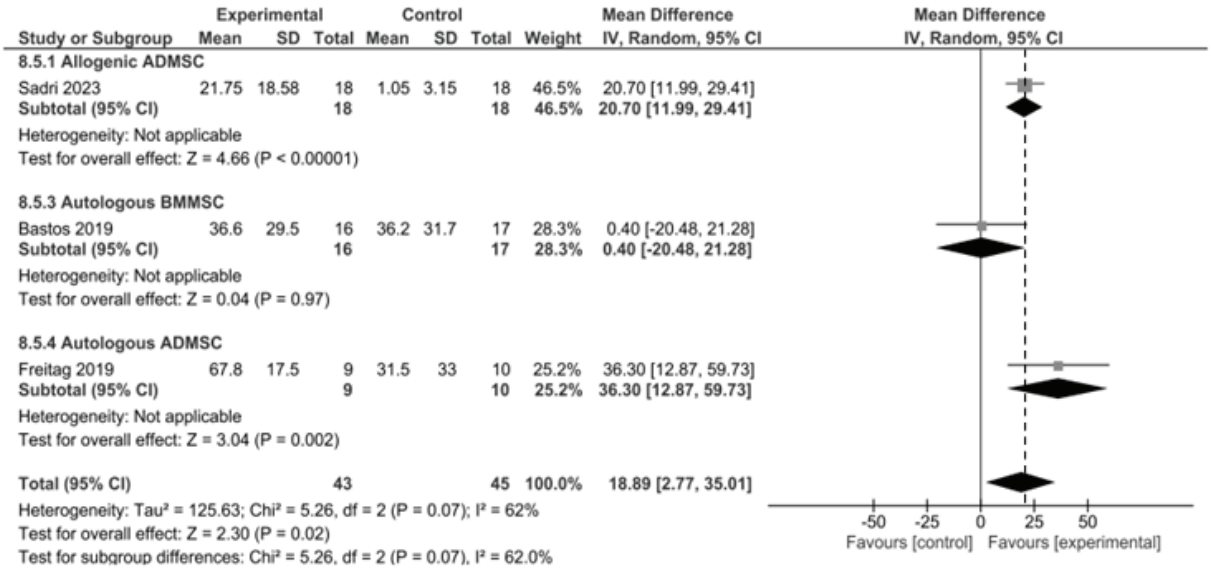
6.2. Forest plot showing the effect of stem cell therapy on KOOS ADL-change score as compared to usual care: 12 months



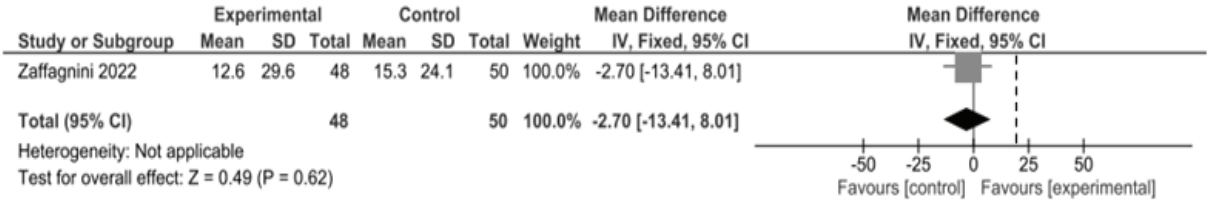
7. KOOS SPR: Three trials with 88 participants reported post score of KOOS SPR at the end of 12 months. The mean difference was 18.89 (95% CI: 2.77 to 35.01) between the stem cell and the usual care arm. The difference was statistically significant but less than the MCID of 20, hence unimportant clinically. One trial with 98 participants reported the change in KOOS SPR score at the

end of 12 months. The mean difference was -2.70 (95% CI: -13.41 to 8.01) between the stem cell and the usual care arm. The difference was statistically non-significant.

7.1 Forest plot showing the effect of stem cell therapy on KOOS SPR-post score as compared to usual care: 12 months



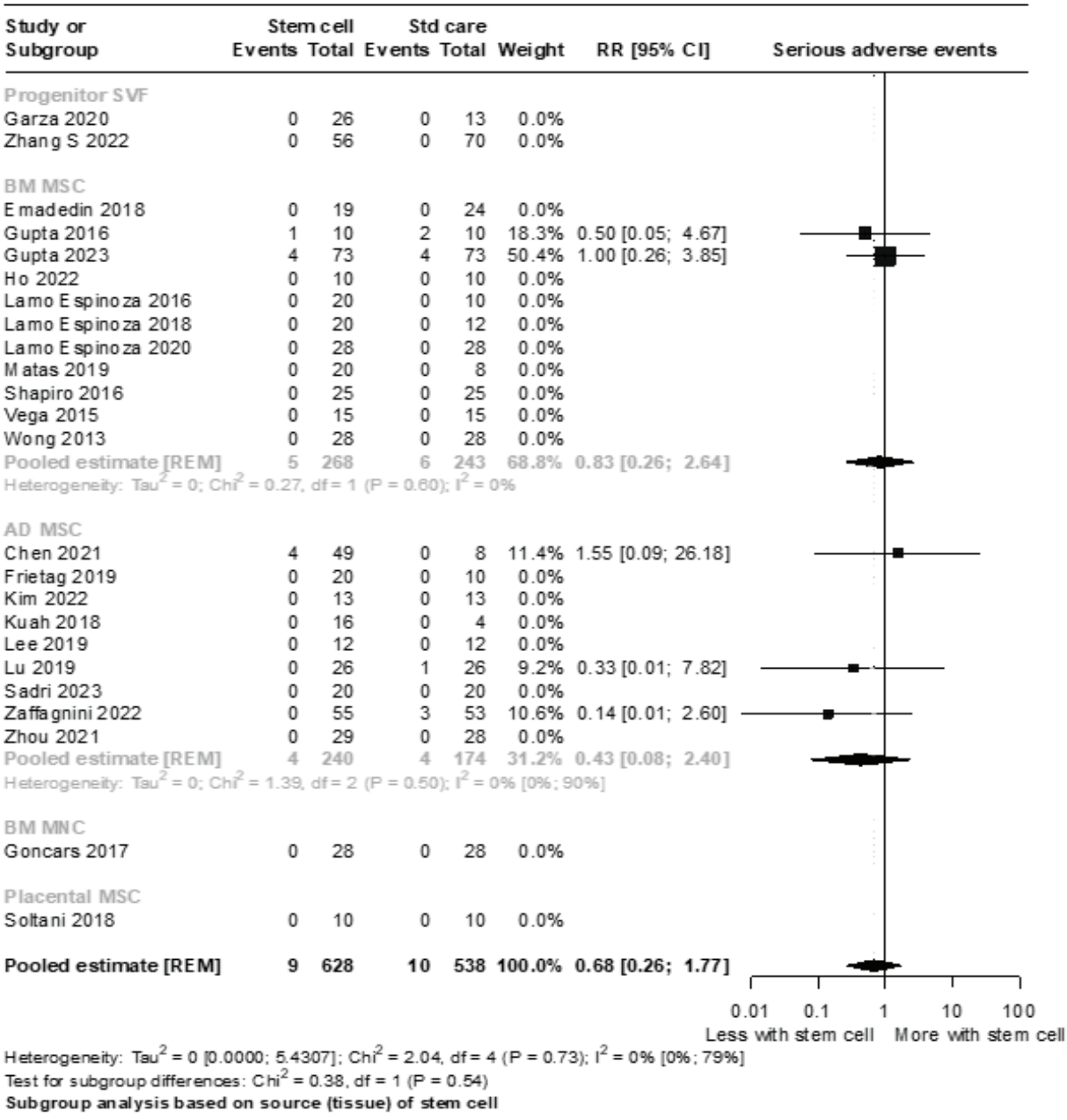
7.2. Forest plot showing the effect of stem cell therapy on KOOS SPR-change score as compared to usual care: 12 months



Undesirable effects:

8. Serious Adverse Events: Twenty-four studies with 1166 participants reported SAEs but did not find any statistically significant difference of SAEs in the stem cell group as compared to the usual care group. Pooled analysis revealed a risk ratio of 0.68 (95% CI: 0.26 to 1.77). Details of adverse events are added in supplement.

8.1. Forest plot showing the serious adverse events in the stem cell arm compared to the usual care arm.



SUMMARY OF FINDINGS:

Stem cell therapy compared to usual care for osteoarthritis

Patient or population: Osteoarthritis
Setting: Tertiary care
Intervention: Stem cell therapy
Comparison: Usual care

Outcomes	Anticipated absolute effects*(95% CI)		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with usual care	Risk with Stem cell therapy				
VAS 12 months- Post score	-	MD **1.76 lower** (2.59 lower to 0.93 lower)	-	474 (9 RCTs)	⊕⊕◯◯ Low[a,b]	
VAS 12 months- Change score	-	MD **0.39 lower** (1.7 lower to 0.92 higher)	-	142 (3 RCTs)	⊕⊕◯◯ Low[a,c]	
WOMAC 12 months- Post score	-	MD **8.74 lower** (16.03 lower to 1.45 lower)	-	417 (9 RCTs)	⊕⊕◯◯ Low[a,b]	
WOMAC 12 months- Change score	-	MD **11.96 lower** (22.65 lower to 1.28 lower)	-	42 (2 RCTs)	⊕◯◯◯ Very low[a,d,e]	
KOOS Pain 12 months- Post score	-	MD **23.14 higher** (5.71 higher to 40.56 higher)	-	144 (4 RCTs)	⊕⊕◯◯ Low[a,e]	
KOOS Symptom 12 months- Post score	-	MD **28.07 higher** (7.4 higher to 48.73 higher)	-	88 (3 RCTs)	⊕⊕◯◯ Low[a,e]	
KOOS QoL 12 months- Post score	-	MD **27.64 higher** (8.45 higher to 46.84 higher)	-	88 (3 RCTs)	⊕⊕◯◯ Low[a,e]	

SUMMARY OF FINDINGS:

Stem cell therapy compared to usual care for osteoarthritis

Patient or population: Osteoarthritis
Setting: Tertiary care
Intervention: Stem cell therapy
Comparison: Usual care

Outcomes	Anticipated absolute effects*(95% CI)		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with usual care	Risk with Stem cell therapy				
KOOS ADL 12 months- Post score	-	MD **22.67 higher** (1.27 lower to 46.61 higher)	-	88 (3 RCTs)	⊕◯◯◯ Very low[a,f]	
KOOS SPR 12 months- Post score	-	MD **18.89 higher** (2.77 higher to 35.01 higher)	-	88 (3 RCTs)	⊕⊕◯◯ Low[a,e]	

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **MD:** mean difference

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations
a. Downgraded by one level for inconsistency, as results are inconsistent across studies
b. Downgraded by one level for imprecision, as OIS not met
c. Downgraded by one level for imprecision as the effect estimate crosses the null effect line; OIS not met
d. >2/3rd studies by weight are at high risk of bias
e. Downgraded by one level for imprecision as wide CI; OIS not met
f. Downgraded by two levels for imprecision as very wide CI crossing the null effect line; OIS not met

EVIDENCE PROFILE:

Certainty assessment							Summary of findings				
							Study event rates (%)			Anticipated absolute effects	
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	With usual care	With Stem cell therapy	Relative effect (95% CI)	Risk with usual care	Risk difference with Stem cell therapy
VAS 12 months- Post score											
474 (9 RCTs)	Not serious	Serious[a]	Not serious	Serious[b]	None	⨁⨁◯◯ Low[a,b]	-	-	-	-	MD **1.76 lower** (2.59 lower to 0.93 lower)
VAS 12 months- Change score											
142 (3 RCTs)	Not serious	Serious[a]	Not serious	Serious[c]	None	⨁⨁◯◯ Low[a,c]	-	-	-	-	MD **0.39 lower** (1.7 lower to 0.92 higher)
WOMAC 12 months- Post score											
417 (9 RCTs)	Not serious	Serious[a]	Not serious	Serious[b]	None	⨁⨁◯◯ Low[a,b]	-	-	-	-	MD **8.74 lower** (16.03 lower to 1.45 lower)
WOMAC 12 months- Change score											
42 (2 RCTs)	Very serious[d]	Serious[a]	Not serious	Serious[e]	None	⨁◯◯◯ Very low[a,d,e]	-	-	-	-	MD **11.96 lower** (22.65 lower to 1.28 lower)
KOOS Pain 12 months- Post score											
144 (4 RCTs)	Not serious	Serious[a]	Not serious	Serious[e]	None	⨁⨁◯◯ Low[a,e]	-	-	-	-	MD **23.14 higher** (5.71 higher to 40.56 higher)
KOOS Symptom 12 months- Post score											

EVIDENCE PROFILE:

Certainty assessment							Summary of findings				
88 (3 RCTs)	Not serious	Serious[a]	Not serious	Serious[e]	None	⊕⊕◯◯ Low[a,e]	-	-	-	-	MD **28.07 higher** (7.4 higher to 48.73 higher)

KOOS QoL 12 months- Post score

88 (3 RCTs)	Not serious	Serious[a]	Not serious	Serious[e]	None	⊕⊕◯◯ Low[a,e]	-	-	-	-	MD **27.64 higher** (8.45 higher to 46.84 higher)

KOOS ADL 12 months- Post score

88 (3 RCTs)	Not serious	Serious[a]	Not serious	Very serious[f]	None	⊕◯◯◯ Very low[a,f]	-	-	-	-	MD **22.67 higher** (1.27 lower to 46.61 higher)

KOOS SPR 12 months- Post score

88 (3 RCTs)	Not serious	Serious[a]	Not serious	Serious[e]	None	⊕⊕◯◯ Low[a,e]	-	-	-	-	MD **18.89 higher** (2.77 higher to 35.01 higher)

CI: confidence interval; **MD:** mean difference

Explanations

a. Downgraded by one level for inconsistency, as results are inconsistent across studies

b. Downgraded by one level for imprecision, as OIS not met

c. Downgraded by one level for imprecision as the effect estimate crosses the null effect line; OIS not met

d. >2/3rd studies by weight are at high risk of bias

e. Downgraded by one level for imprecision as wide CI; OIS not met

f. Downgraded by two levels for imprecision as very wide CI crossing the null effect line; OIS not met

D. SUMMARY OF JUDGEMENTS:

The summary of the final judgments made by the GDG after careful consideration of the summary of evidence is tabulated below:

Desirable Effects	Trivial*
Undesirable Effects	Varies**
Certainty of evidence	Very Low
Values	Probably no important uncertainty or variability
Balance of effects	Does not favor either the intervention or the comparison
Resources required	Large costs***
Certainty of evidence of required resources	Moderate
Cost effectiveness	Probably favors the comparison
Equity	Probably reduced
Acceptability	Probably yes
Feasibility	Probably yes
Recommendations: Stem cell therapy is **not recommended** in routine practice for the treatment of osteoarthritis. It may be used only in the context of rigorously conducted randomized controlled trials.	

***** This judgment was made as there is very low certainty evidence of trivial reduction in pain and trivial improvement in function.
** This judgment was made as undesirable effects are variable and heterogenous.
*** The committee opined that stem cell treatment is associated with large costs.

E. CAVEATS IN EXISTING EVIDENCE:

The GDG opined that the existing evidence had the following caveats:

- Lack of sufficient number of RCTs with low risk of bias.
- Heterogeneity across trials in patient population, type of stem cell therapy uses ranging from mononuclear cells to mesenchymal stem cells and stromal vascular fraction, cell dosage, route of administration and time of administration.
- Use of both active and passive comparators in the trials.
- Use of adjunctive biological components (e.g., PRP) and co-interventions which might have impacted the outcomes.
- Limited long-term follow-up.
- Lack of cost effectiveness data.

REFERENCES:

1. Singh A, Das S, Chopra A, Danda D, Paul BJ, March L, Mathew AJ, Shenoy P, Gotay C, Palmer AJ, Antony B. Burden of osteoarthritis in India and its states, 1990-2019: findings from the Global Burden of disease study 2019. Osteoarthritis Cartilage. 2022 Aug; 30(8):1070-1078. doi: 10.1016/j.joca.2022.05.004.
2. Lamo-Espinosa JM, Blanco JF, Sánchez M, Moreno V, Granero-Moltó F, Sánchez-Guijo F, et al. Phase II multicenter randomized controlled clinical trial on the efficacy of intraarticular injection of autologous bone marrow mesenchymal stem cells with platelet rich plasma for the treatment of knee osteoarthritis. J Transl Med. 2020 Dec; 18(1):356.
3. Goncars V, Jakobsons E, Blums K, Briede I, Patetko L, Erglis K, et al. The comparison of knee osteoarthritis treatment with single-dose bone marrow-derived mononuclear cells vs. hyaluronic acid injections. Medicina (Mex). 2017; 53(2):101–8.
4. Lee WS, Kim HJ, Kim KI, Kim GB, Jin W. Intra-Articular Injection of Autologous Adipose Tissue-Derived Mesenchymal Stem Cells for the Treatment of Knee Osteoarthritis: A Phase IIb, Randomized, Placebo-Controlled Clinical Trial. Stem Cells Transl Med. 2019 Jun 1; 8(6):504–11
5. Khalifeh Soltani S, Forogh B, Ahmadbeigi N, Hadizadeh Kharazi H, Fallahzadeh K, Kashani L, et al. Safety and efficacy of allogenic placental mesenchymal stem cells for treating knee osteoarthritis: a pilot study. Cytotherapy. 2019 Jan; 21(1):54–63.
6. Chen CF, Hu CC, Wu CT, Wu HTH, Chang CS, Hung YP, et al. Treatment of knee osteoarthritis with intra-articular injection of allogeneic adipose-derived stem cells (ADSCs) ELIXCYTE®: a phase I/II, randomized, active-control, single-blind, multiple-center clinical trial. Stem Cell Res Ther. 2021 Dec; 12(1):562.
7. Wong KL, Lee KBL, Tai BC, Law P, Lee EH, Hui JHP. Injectable Cultured Bone Marrow–Derived Mesenchymal Stem Cells in Varus Knees with Cartilage Defects Undergoing High Tibial Osteotomy: A Prospective, Randomized Controlled Clinical Trial With 2 Years' Follow-up. Arthrosc J ArthroscRelat Surg. 2013 Dec; 29(12):2020–8.
8. Wakitani S, Imoto K, Yamamoto T, Saito M, Murata N, Yoneda M. Human autologous culture expanded bone marrow mesenchymal cell transplantation for repair of cartilage defects in osteoarthritic knees. Osteoarthritis Cartilage. 2002 Mar; 10(3):199–206.
9. Zhou Y, Li H, Xiang D, Shao J, Fu Q, Han Y, et al. The clinical efficacy of arthroscopic therapy with knee infrapatellar fat pad cell concentrates in treating knee cartilage lesion: a prospective, randomized, and controlled study. J Orthop Surg. 2021 Jan 28; 16(1):87.
10. Hernigou P, Auregan JC, Dubory A, Flouzat-Lachaniette CH, Chevallier N, Rouard H. Subchondral stem cell therapy versus contralateral total knee arthroplasty for osteoarthritis following secondary osteonecrosis of the knee. Int Orthop. 2018 Nov; 42(11):2563–71.
11. Wang Y, Jin W, Liu H, Cui Y, Mao Q, Fei Z, et al. Curative effect of human umbilical cord mesenchymal stem cells by intra articular injection for degenerative knee osteoarthritis. Zhongguo Xiu Fu Chong Jian Wai Ke Za Zhi 2016 Dec 8; 30(12):1472–7 Chinese. doi: 10.7507/1002-1892.20160305. PMID: 29786336.

12. Ho KK, Lee WY, Griffith JF, Ong MT, Li G. Randomized control trial of mesenchymal stem cells versus hyaluronic acid in patients with knee osteoarthritis – A Hong Kong pilot study. J Orthop Transl. 2022 Nov; 37:69–77 doi: 10.1016/j.jot.2022.07.012. PMID: 36262962; PMCID: PMC9550852.
13. Garay-Mendoza D, Villarreal-Martínez L, Garza-Bedolla A, Pérez-Garza DM, AcostaOlivo C, Vilchez-Cavazos F, et al. The effect of intra-articular injection of autologous bone marrow stem cells on pain and knee function in patients with osteoarthritis. Int J Rheum Dis. 2018 Jan; 21(1):140–7.
14. Freitag J, Bates D, Wickham J, Shah K, Huguenin L, Tenen A, et al. Adipose-derived mesenchymal stem cell therapy in the treatment of knee osteoarthritis: a randomized controlled trial. Regen Med. 2019 Mar; 14(3):213–30.
15. Baria M, Pedroza A, Kaeding C, Durgam S, Duerr R, Flanigan D, et al. Platelet-Rich Plasma Versus Microfragmented Adipose Tissue for Knee Osteoarthritis: A Randomized Controlled Trial. Orthop J Sports Med. 2022 Sep 1; 10(9):232596712211206.
16. Kaszyński J, Bąkowski P, Kiedrowski B, Stołowski Ł, Wasilewska-Burczyk A, Grzywacz K, et al. Intra-Articular Injections of Autologous Adipose Tissue or Platelet-Rich Plasma 191 Comparably Improve Clinical and Functional Outcomes in Patients with Knee Osteoarthritis. Biomedicines. 2022 Mar 16; 10(3):684.
17. Vega A, Martín-Ferrero MA, Del Canto F, Alberca M, García V, Munar A, et al. Treatment of Knee Osteoarthritis with Allogeneic Bone Marrow Mesenchymal Stem Cells: A Randomized Controlled Trial. Transplantation. 2015 Aug; 99(8):1681–90.
18. Kim JH, Kim KI, Yoon WK, Song SJ, Jin W. Intra-articular Injection of Mesenchymal Stem Cells After High Tibial Osteotomy in Osteoarthritic Knee: Two-Year Follow-up of Randomized Control Trial. Stem Cells Transl Med. 2022 Jun 22; 11(6):572–85.
19. Sadri B, Hassanzadeh M, Bagherifard A, Mohammadi J, Alikhani M, MoeinabadiBidgoli K, et al. Cartilage regeneration and inflammation modulation in knee osteoarthritis following injection of allogeneic adipose-derived mesenchymal stromal cells: a phase II, triple-blinded, placebo controlled, randomized trial. Stem Cell Res Ther. 2023 Jun 14; 14(1):162.
20. Matas J, Orrego M, Amenabar D, Infante C, Tapia-Limonchi R, Cadiz MI, et al. Umbilical Cord-Derived Mesenchymal Stromal Cells (MSCs) for Knee Osteoarthritis: Repeated MSC Dosing Is Superior to a Single MSC Dose and to Hyaluronic Acid in a Controlled Randomized Phase I/II Trial. Stem Cells Transl Med. 2019 Mar 1; 8(3):215–24.
21. Lu L, Dai C, Zhang Z, Du H, Li S, Ye P, et al. Treatment of knee osteoarthritis with intra-articular injection of autologous adipose-derived mesenchymal progenitor cells: a prospective, randomized, double-blind, active-controlled, phase IIb clinical trial. Stem Cell Res Ther. 2019 Dec; 10(1):143.
22. Emadedin M, Labibzadeh N, Liastani MG, Karimi A, Jaroughi N, Bolurieh T, et al. Intra-articular implantation of autologous bone marrow–derived mesenchymal stromal cells to treat knee osteoarthritis: a randomized, triple-blind, placebo-controlled phase 1/2 clinical trial. Cytotherapy. 2018 Oct; 20(10):1238–46.
23. Zhang S, Xu H, He B, Fan M, Xiao M, Zhang J, et al. Mid-term prognosis of the stromal vascular fraction for knee osteoarthritis: a minimum 5-year follow-up study. Stem Cell Res Ther. 2022 Mar 12; 13(1):105.

24. Zhang Y, Bi Q, Luo J, Tong Y, Yu T, Zhang Q. The Effect of Autologous Adipose-Derived Stromal Vascular Fractions on Cartilage Regeneration Was Quantitatively Evaluated Based on the 3D-FS-SPGR Sequence: A Clinical Trial Study. Du J, editor. BioMed Res Int. 2022 Jan 25; 2022:1–17.
25. Bastos R, Mathias M, Andrade R, Amaral RJFC, Schott V, Balduino A, et al. Intraarticular injection of culture-expanded mesenchymal stem cells with or without addition of platelet-rich plasma is effective in decreasing pain and symptoms in knee osteoarthritis: a controlled, double-blind clinical trial. Knee Surg Sports Traumatol Arthrosc. 2020 Jun; 28(6):1989–99.
26. Zaffagnini S, Andriolo L, Boffa A, Poggi A, Cenacchi A, Busacca M, et al. Microfragmented Adipose Tissue Versus Platelet-Rich Plasma for the Treatment of Knee 192 Osteoarthritis: A Prospective Randomized Controlled Trial at 2-Year Follow-up. Am J Sports Med. 2022 Sep; 50(11):2881–92.
27. Gupta PK, Chullikana A, Rengasamy M, Shetty N, Pandey V, Agarwal V, et al. Efficacy and safety of adult human bone marrow-derived, cultured, pooled, allogeneic mesenchymal stromal cells (Stempeucel®): preclinical and clinical trial in osteoarthritis of the knee joint. Arthritis Res Ther. 2016 Dec; 18(1):301.
28. Gupta PK, Maheshwari S, Cherian JJ, Goni V, Sharma AK, Tripathy SK, et al. Efficacy and Safety of Stempeucel in Osteoarthritis of the Knee: A Phase 3 Randomized, DoubleBlind, Multicenter, Placebo-Controlled Study. Am J Sports Med. 2023 Jul; 51(9):2254–66.
29. Shapiro SA, Kazmerchak SE, Heckman MG, Zubair AC, O'Connor MI. A Prospective, Single-Blind, Placebo-Controlled Trial of Bone Marrow Aspirate Concentrate for Knee Osteoarthritis. Am J Sports Med. 2017 Jan; 45(1):82–90.
30. Lamo-Espinosa JM, Mora G, Blanco JF, Granero-Moltó F, Nuñez-Córdoba JM, Sánchez-Echenique C, et al. Intra-articular injection of two different doses of autologous bone marrow mesenchymal stem cells versus hyaluronic acid in the treatment of knee osteoarthritis: multicenter randomized controlled clinical trial (phase I/II). J Transl Med. 2016 Dec; 14(1):246.
31. Kuah D, Sivell S, Longworth T, James K, Guermazi A, Cicuttini F, et al. Safety, tolerability and efficacy of intra-articular Progenza in knee osteoarthritis: a randomized double-blind placebo-controlled single ascending dose study. J Transl Med. 2018 Dec; 16(1):49.
32. Dulic O, Rasovic P, Lalic I, Kecojevic V, Gavrilovic G, Abazovic D, et al. Bone Marrow Aspirate Concentrate versus Platelet Rich Plasma or Hyaluronic Acid for the Treatment of Knee Osteoarthritis. Medicina (Mex). 2021 Nov 2; 57(11):1193.
33. Lamo-Espinosa JM, Mora G, Blanco JF, Granero-Moltó F, Núñez-Córdoba JM, LópezElío S, et al. Intra-articular injection of two different doses of autologous bone marrow mesenchymal stem cells versus hyaluronic acid in the treatment of knee osteoarthritis: long-term follow up of a multicenter randomized controlled clinical trial (phase I/II). J Transl Med. 2018 Dec; 16(1):213.
34. Hong Z, Chen J, Zhang S, Zhao C, Bi M, Chen X, et al. Intra-articular injection of autologous adipose-derived stromal vascular fractions for knee osteoarthritis: a double blind randomized self-controlled trial. Int Orthop. 2019 May; 43(5):1123–34.

35. Carvalho Schweich-Adami L, Silva RAD, Menezes JNDS, Baranoski A, Kassuya CAL, Bernardi L, et al. The intra-articular injection of adipose-derived stem cells decreases pain and reduces inflammation in knee osteoarthritis, with or without the addition of platelet rich plasma also improves functionality. J Tissue Eng Regen Med. 2022 Oct; 16(10):900–12.
36. Varma HS, Dadarya B, Vidyarthi A. The new avenues in the management of osteo-arthritis of knee--stem cells. J Indian Med Assoc. 2010 Sep; 108(9):583–5.
37. Sadat-Ali M, AlOmran AS, AlMousa SA, AlSayed HN, AlTabash KW, Azam MQ, et al. Autologous Bone Marrow-Derived Chondrocytes for Patients with Knee Osteoarthritis: A Randomized Controlled Trial. Schwingel PA, editor. Adv Orthop. 2021 Nov 20; 2021:1–7.
38. Hernigou P, Delambre J, Quiennec S, Poignard A. Human bone marrow mesenchymal stem cell injection in subchondral lesions of knee osteoarthritis: a prospective randomized study versus contralateral arthroplasty at a mean fifteen-year follow-up. Int Orthop. 2021 Feb; 45(2):365–73.
39. Garza JR, Campbell RE, Tjoumakaris FP, Freedman KB, Miller LS, Santa Maria D, et al. Clinical Efficacy of Intra-articular Mesenchymal Stromal Cells for the Treatment of Knee Osteoarthritis: A Double-Blinded Prospective Randomized Controlled Clinical Trial. Am J Sports Med. 2020 Mar; 48(3):588–98.
40. Vangsness CT, Farr J, Boyd J, Dellaero DT, Mills CR, LeRoux-Williams M. Adult Human Mesenchymal Stem Cells Delivered via Intra-Articular Injection to the Knee Following Partial Medial Meniscectomy: A Randomized, Double-Blind, Controlled Study. J Bone Jt Surg. 2014 Jan 15; 96(2):90–8.

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2. AVASCULAR NECROSIS OF HIP

A. BACKGROUND:

Avascular necrosis (AVN) also known as osteonecrosis, is a debilitating condition marked by the death of cellular components of bone because of disruption in sub-chondral blood supply. It predominantly affects the weight bearing joints, the most common being hip. The most common etiological factors include treatment with corticosteroids, fractures and dislocation, and alcohol abuse.[1] Early diagnosis and management can preserve the joint and delay the need for replacement. Without treatment the disease is progressive and ultimately leads to joint destruction.

B. RECOMMENDATIONS:

Stem cell therapy is **not recommended** in routine clinical practice for the treatment of avascular necrosis of hip.
Strength: Conditional[#]
Certainty of Evidence: Very Low

[#]It may be used only in the context of rigorously conducted randomized controlled trials.

Rationale/Justification:
This recommendation has been made as there is very low certainty evidence of trivial reduction in pain and no improvement in function. There is little or no difference in undesirable effects between stem cell therapy and usual care. In addition, the follow up period is limited to comment on the long-term safety of stem cell therapy. Results should be interpreted with caution, in view of various study limitations like high risk of bias, small number of participants and/or events.

C. SUMMARY OF EVIDENCE:

Key Question: In patients with avascular necrosis of hip, what is the efficacy and safety of stem cell therapy as compared to usual care?

Included Studies: A total of 4471 records were screened from the four databases. Automated checks and manual de-duplication were performed by EndNote and 86 duplicate articles were removed. Based on the titles and abstracts, 4385 studies underwent preliminary screening, of which 345 were found relevant for full-text review. Out of 345 records, 340 records that did not meet the inclusion criteria were excluded and the remaining five RCTs were included for qualitative and quantitative analysis. One RCT was identified through reviewing the references of the papers during the screening procedure. Finally, 6 RCTs met the 'reliable body of evidence' criteria specified by the GDG and were included in the present study for qualitative evaluation.[2-7]

Six included studies were published between 2012 to 2023. The most common disease stage observed among the patients enrolled in the included studies was stage I & II. Four (67%) studies included patients in stage I & II, and two (33%) studies enrolled patients in stage I, II & III using Association Research Circulation Osseous (ARCO) system. Bone marrow-derived stem cells of multipotent differential potential were employed as an intervention in five trials. One study utilized

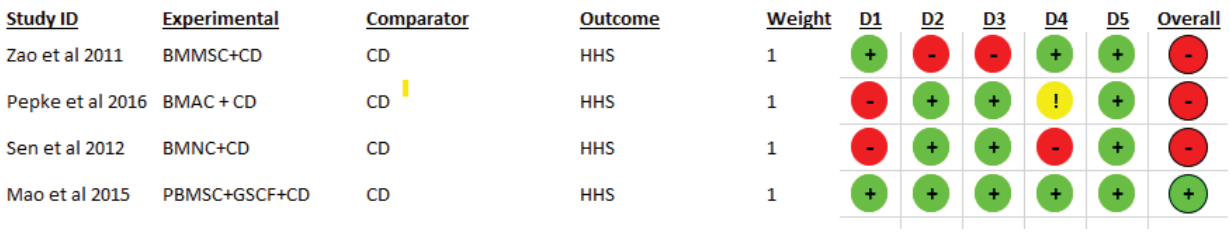
peripheral blood stem cells (PBSCs). In bone marrow-derived stem cells category two utilized bone marrow mesenchymal stem cells (BMMSCs), two used bone marrow aspirate concentrate (BMAC) and one used bone marrow mononuclear cells (BMMNCs).

Critical outcomes reviewed and their MCID:

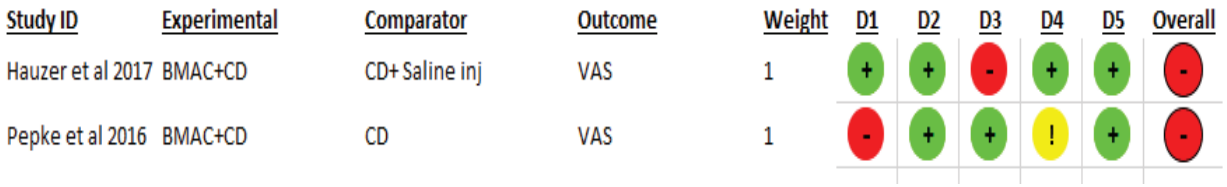
S. No.	Outcome reviewed	What does it measure?	MCID (if decided by the GDG)
1.	Harris Hip Score (HHS) Range: 0-100 Higher score is better	Standardized measure used to assess the severity of hip pain and functional limitations in individuals with hip conditions.	Absolute change of HHS by 20 points
2.	Visual Analog Scale (VAS) Range: 0-10 Higher score is worse	Validated measure for measuring intensity of pain	Absolute change of VAS score by 2 points
3.	Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)- Overall Range: 0-100 Higher score is worse	Self-administered questionnaire that is used to assess pain, stiffness, and function in patients with OA of the hip or knee.	Absolute change of WOMAC by 20 points
4.	Conversion to Total Hip Replacement (THR)	Number of patients who eventually required THR	-
5.	SAEs	Serious Adverse events	-

Risk of Bias assessment:

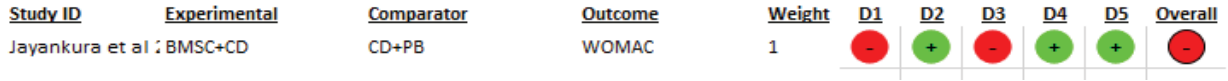
RoB2 assessment for Harris Hip Score:



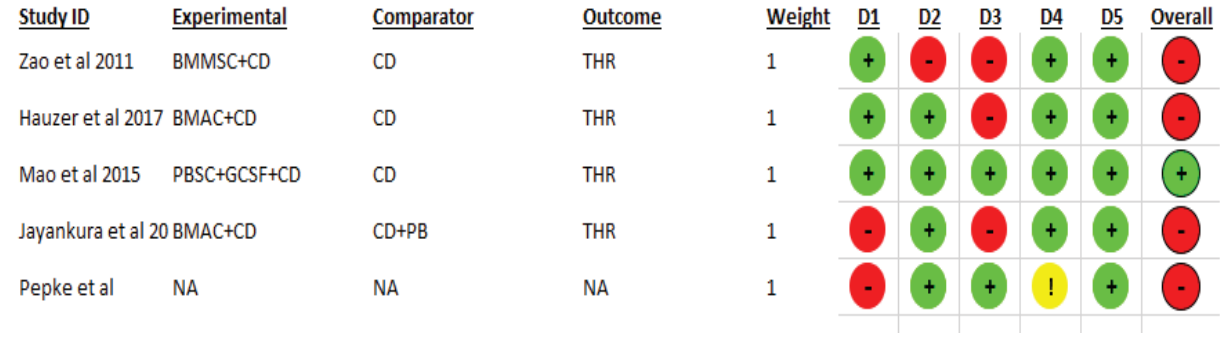
RoB2 assessment for VAS:



RoB2 assessment for WOMAC:



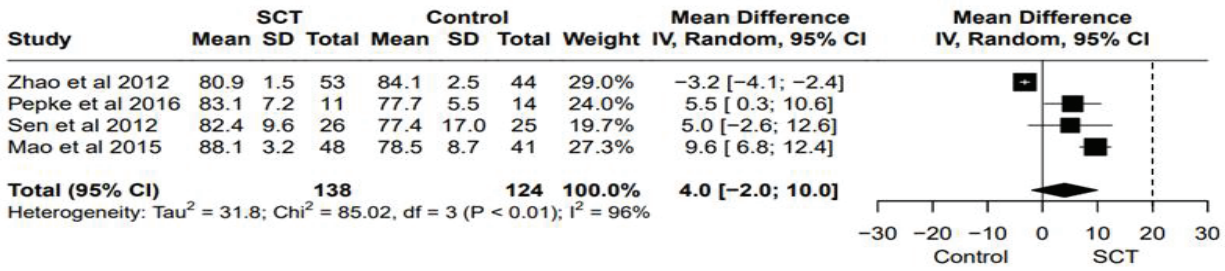
RoB2 assessment for THR:



Desirable Effects (Dotted line represents MCID)**:**

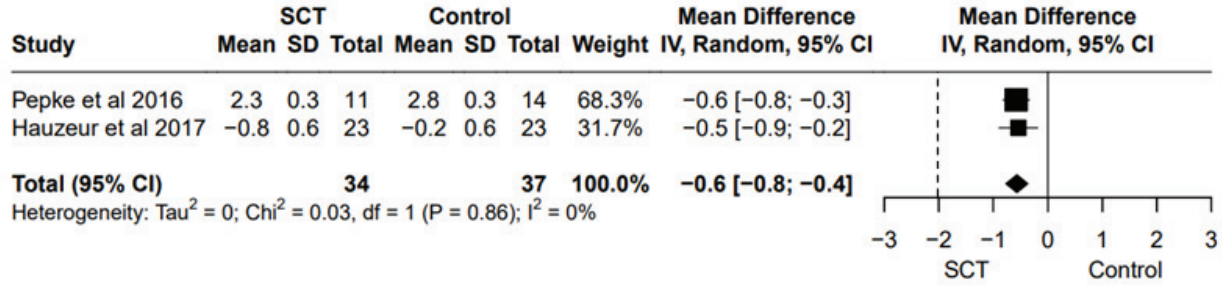
1. Harris Hip Score: Evidence from four trials, with a total of 262 participants reporting the Harris Hip score showed a mean difference of 4.0 (95% CI: -2.0 to 10.0) in the stem cell transplantation arm in comparison to usual care at the end of follow up which ranged from 24 to 36 months. The difference was statistically non-significant.

1.1 Forest plot showing the effect of Stem cell therapy on Harris Hip score as compared to usual care



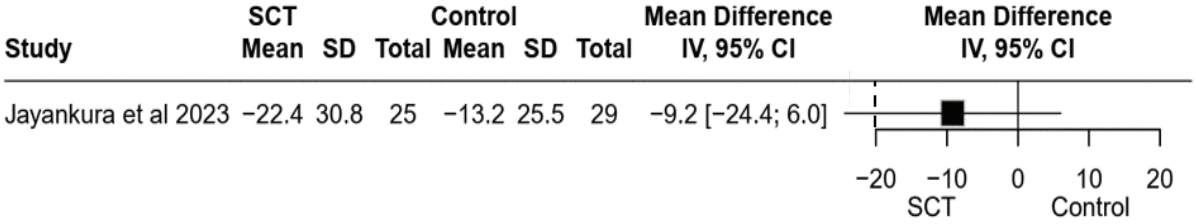
2. VAS: Evidence from two trials, with a total of 71 participants, reporting the VAS showed a mean difference of -0.6 (95% CI: -0.8 to -0.4) in the stem cell transplantation arm as compared to usual care at the end of 24 months. There seems to be a decrease in pain as the difference was statistically significant. However, it was less than half of MCID of 2. Therefore, the reduction in pain is unimportant clinically.

2.1. Forest plot showing the effect of stem cell therapy on VAS as compared to usual care: 24 months

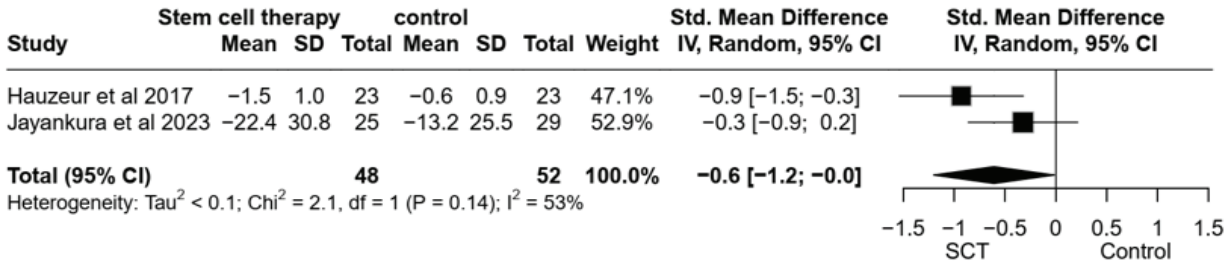


3. WOMAC: Evidence from one trial with a total of 54 participants reporting the WOMAC score showed a mean difference of -9.2 (95% CI: -24.4 to 6.0) in the stem cell group in comparison to usual care, which was statistically non-significant. Evidence from two trials with a total of 100 participants reporting the WOMAC score using standardized mean difference showed a difference of -0.6 (95% CI: -1.2 to -0.0) in the stem cell group in comparison to usual care at the end of follow-up which ranged from 12- 24 months. The result was statistically non-significant.

3.1 Forest plot showing the effect of stem cell therapy on WOMAC score (using MD) as compared to usual care:

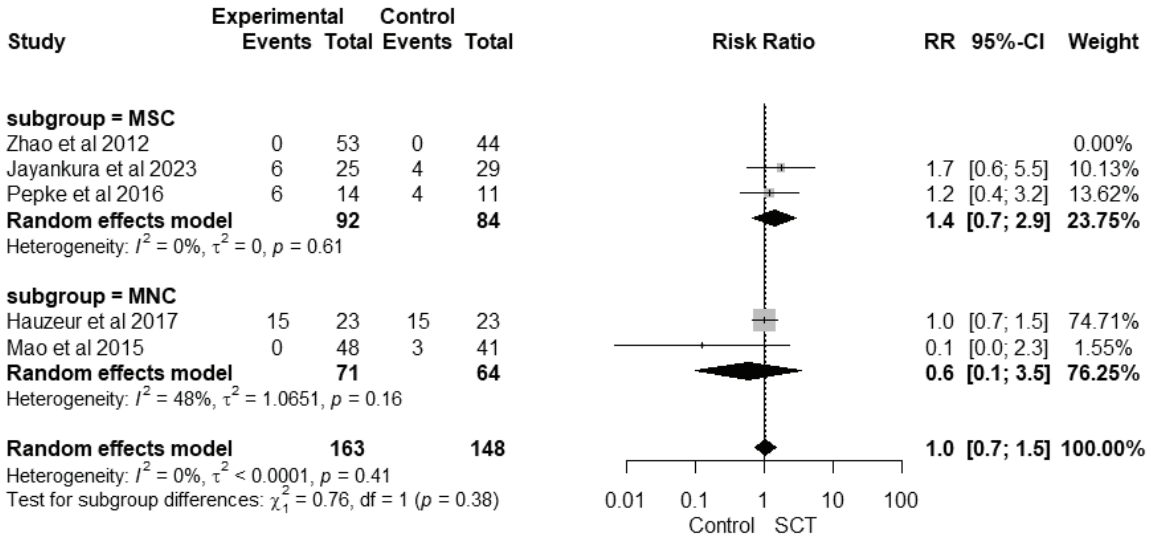


3.2. Forest plot showing the effect of stem cell therapy on WOMAC score (using SMD) as compared to usual care:



4. Total Hip Replacement: Evidence from five trials with 311 participants showed no statistically significant difference in the number of participants requiring total hip replacement after stem cell therapy as compared to usual care at the end of 24 months (RR 1.0 (95% CI: 0.7 to 1.5)).

4.1. Forest plot showing the effect of stem cell therapy on THR as compared to usual care: 24 months



Undesirable effects:

None of the trials reported any serious adverse events. The evidence is insufficient to draw firm conclusions due to limited long term follow up of trials.

SUMMARY OF FINDINGS:

Stem Cell Therapy compared to usual care for Avascular Necrosis of Hip

Patient or population: Avascular Necrosis of Hip
Setting: Hospital/Tertiary care
Intervention: Stem Cell Therapy
Comparison: Usual Care

Outcomes	Anticipated absolute effects*(95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Placebo/ Standard care	Risk with Stem Cell Therapy				
Harris Hip score (Quantitative analysis) (HHS) Assessed with: Radiography	-	MD **4 higher** (2 lower to 10 higher)	-	262 (4 RCTs)	⊕◯◯◯ Very low[a,b,c]	
Visual Analogue Scale (Quantitative analysis) (VAS) Assessed with: Questionnaire	-	MD **0.6 lower** (0.8 lower to 0.4 lower)	-	71 (2 RCTs)	⊕◯◯◯ Very low[a,d]	
Western Ontario and McMaster Universities Osteoarthritis Index (Quantitative analysis) (WOMAC) Assessed with: Questionnaire	-	MD **9.2 lower** (24.4 lower to 6 higher)	-	54 (1 RCT)	⊕◯◯◯ Very low[a,b,e]	
THR (Quantitative analysis) (HHS) Assessed with: Questionnaire	270 per 1,000	**270 per 1,000** (189 to 405)	**RR 1.0** (0.7 to 1.5)	311 (5 RCTs)	⊕◯◯◯ Very low[a,b]	

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations
a. Downgraded by two levels as more than 2/3rd of the studies (by wt.) were at high risk of bias.
b. Downgraded by one level for imprecision as wide CI crossing the line of null effect.
c. Downgraded by one level for inconsistency as results are inconsistent across studies.
d. Downgraded by one level for imprecision as results are precise for no benefit but OIS not met.
e. Downgraded by one level for inconsistency as it is inevaluable for a single study.

EVIDENCE PROFILE:

Stem Cell Therapy compared to Usual Care for Avascular Necrosis of Hip

Certainty assessment							Summary of findings				
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With Placebo/ Standard care	With Stem Cell Therapy		Risk with Placebo/ Standard care	Risk difference with Stem Cell Therapy
HHS (Quantitative analysis) (assessed with: Radiography)											
262 (4 RCTs)	Very serious[a]	Serious[c]	Not serious	Serious[b]	Inevaluable	⨁◯◯◯ Very low	-	-	-	-	MD **4 higher** (2 lower to 10 higher)
Visual Analogue Scale (Quantitative analysis) (assessed with: Questionnaire)											
71 (2 RCTs)	Very serious[a]	Not Serious	Not serious	Serious[d]	Inevaluable	⨁◯◯◯ Very low	-	-	-	-	MD **0.6 lower** (0.8 lower to 0.4 lower)
Western Ontario and McMaster Universities Osteoarthritis Index (Quantitative analysis) (assessed with: Questionnaire)											
54 (1 RCT)	Very serious[a]	Inevaluable[e]	Not serious	Serious[b]	Inevaluable	⨁◯◯◯ Very low	-	-	-	-	MD **9.2 lower** (24.4 lower to 6 higher)
THR (Quantitative analysis) (assessed with: Questionnaire)											
311 (5 RCTs)	Very serious[a]	Not serious	Not serious	Serious[b]	Inevaluable	⨁◯◯◯ Very low	40/148 (27.0%)	30/163 (18.4%)	**RR 1.0 (0.7 to 1.5)**	40/148 (27.0%)	**0 fewer per 1,000** (from 81 fewer to 135 more)

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations

a. Downgraded by two levels as more than 2/3rd of the studies (by wt.) were at high risk of bias.

b. Downgraded by one level for imprecision as wide CI crossing the line of null effect.

c. Downgraded by one level for inconsistency as results are inconsistent across studies.

d. Downgraded by one level for imprecision as results are precise for no benefit but OIS not met.

e. Downgraded by one level for inconsistency as it is inevaluable for a single study.

D. SUMMARY OF JUDGMENTS:

The summary of the final judgments made by the GDG after careful consideration of the summary of evidence is tabulated below:

Desirable Effects	Trivial*
Undesirable Effects	Trivial**
Certainty of evidence	Very Low
Values	Probably no important uncertainty or variability
Balance of effects	Does not favor either the intervention or the comparison
Resources required	Large costs***
Certainty of evidence of required resources	Moderate
Cost effectiveness	Probably favors the comparison
Equity	Probably reduced
Acceptability	Probably yes
Feasibility	Probably yes
Recommendations: Stem cell therapy is **not recommended** in routine practice for the treatment of avascular necrosis of hip. It may be used only in the context of rigorously conducted randomized controlled trials.	

*This judgment was made as there is very low certainty evidence of trivial reduction in pain and no improvement in function.

** This judgment was made as there is little or no difference in undesirable effects between stem cell therapy and usual care.

*** The committee opined that stem cell treatment is associated with large costs.

E. CAVEATS IN EXISTING EVIDENCE:

The GDG opined that the existing evidence had the following caveats:

1. Lack of sufficient number of RCTs with low risk of bias.
2. Small number of participants and/or events in the included trials
3. Varying units of randomization i.e., hip, patient
4. Heterogeneity across trials in patient population, type of stem cell therapy, cell dosage, route of administration and time of administration.
5. Use of both active and passive comparators in the trials.
6. Use of different scales and subscales for assessing the critical outcomes.
7. Lack of cost effectiveness data.

REFERENCES:

1. Konarski W, Poboży T, Śliwczyński A, Kotela I, Krakowiak J, Hordowicz M, Kotela A. Avascular Necrosis of Femoral Head—Overview and Current State of the Art.International Journal of Environmental Research and Public Health. 2022; 19(12):7348. https://doi.org/10.3390/ijerph19127348.
2. Zhao D, Cui D, Wang B, Tian F, Guo L, Yang L, et al. Treatment of early stage osteonecrosis of the femoral head with autologous implantation of bone marrow-derived and cultured mesenchymal stem cells. Bone. 2012;50(1):325-30.
3. Sen RK, Tripathy SK, Aggarwal S, Marwaha N, Sharma RR, Khandelwal N. Early results of core decompression and autologous bone marrow mononuclear cells instillation in femoral head osteonecrosis: a randomized control study.27.J Arthroplasty:2012; 679-86.
4. Hauzeur JP, De Maertelaer V, Baudoux E, Malaise M, Beguin Y, Gangji V. Inefficacy of autologous bone marrow concentrate in stage three osteonecrosis: a randomized controlled double-blind trial. Int Orthop. 2018 Jul;42(7):1429-1435. doi: 10.1007/s00264-017-3650-8. Epub 2017 Oct 7; PMID: 28988340.
5. Mao Q, Wang W, Xu T, Zhang S, Xiao L, Chen D, et al. Combination treatment of biomechanical support and targeted intra-arterial infusion of peripheral blood stem cells mobilized by granulocyte-colony stimulating factor for the osteonecrosis of the femoral head: a randomized controlled clinical trial. J Bone Miner Res. 2015;30(4):647-56.
6. Jayankura M, Thomas T, Seefried L, Dubrana F, Gunther KP, Rondia J, et al. Does Adjunction of Autologous Osteoblastic Cells Improve the Results of Core Decompression in Early-stage Femoral Head Osteonecrosis? A Double-blind, Randomized Trial. Clin OrthopRelat Res. 2023;481(8):1527-40.
7. Pepke W, Kasten P, Beckmann NA, Janicki P, Egermann M. Core Decompression and Autologous Bone Marrow Concentrate for Treatment of Femoral Head Osteonecrosis: A Randomized Prospective Study. Orthop Rev (Pavia). 2016 Mar 21;8(1):6162. doi: 10.4081/or.2016.6162. PMID: 27114808; PMCID: PMC4821226.

3. CARTILAGE DEFECTS

A. BACKGROUND:

Articular cartilage lesions are one of the most challenging clinical problems because of the poor healing capacity of the cartilage due to avascularity and lack of innervations. Defects in articular cartilage causes pain, swelling, and functional impairment affecting the quality of life, ultimately leading to degenerative arthritis. There are various treatment modalities ranging from preventive management, physical therapy, pharmacological & non-pharmacological. Several surgical and non-surgical treatments for full-thickness cartilage and osteochondral articular lesions currently exist including microfracture, osteochondral autograft transfer, osteochondral allograft transplantation, and autologous chondrocyte implantation (ACI). However, choosing one treatment over the other remains debatable.[1]

B. RECOMMENDATIONS:

Stem cell therapy is **not recommended** in routine clinical practice for the treatment of cartilage defects.
Strength: Conditional[#]
Certainty of Evidence: Very Low

[#]*It may be used only in the context of rigorously conducted randomized controlled trials.*

Rationale/Justification
This recommendation has been made as there is very low certainty evidence of trivial reduction in pain and no improvement in function. There is little or no difference in undesirable effects between stem cell therapy and usual care. In addition, the follow up period is limited to comment on the long-term safety of stem cell therapy. Results should be interpreted with caution, in view of various study limitations such as small number of participants and/or events, risk of bias and different sources of stem cell used.

C. SUMMARY OF EVIDENCE

Key Question: In patients with cartilage defects, what is the efficacy and safety of stem cell therapy as compared to usual care?

Included Studies: The combined searches of the 4 databases yielded 8027 results. Additionally, 14 studies were identified through reference searching of 2 published systematic reviews. After deduplication, 5364 studies were screened based on titles and abstracts and then the52 full-text articles were screened according to the eligibility criteria. Out of 52, only 14 articles met the inclusion criteria. Finally, 12 studies met the 'reliable body of evidence' criteria specified by the GDG were enrolled in the meta-analysis.[2-15]

Seven studies evaluated focal cartilage defects, 3 studies evaluated cartilage defects in osteoarthritis and 2 studies evaluated cartilage defects as well as focal cartilage defects in OA. The stem cells used included ADMSC, BMMSC, UCMSC, SDSC and SVF. In 8 studies, stem cell therapies were injected into the knee joint, whereas in the other 6, direct implantation was performed at the defect site. For details, refer to the supplement.

Below mentioned studies were excluded from the meta-analysis as they did not meet the criteria for "reliable body of evidence":

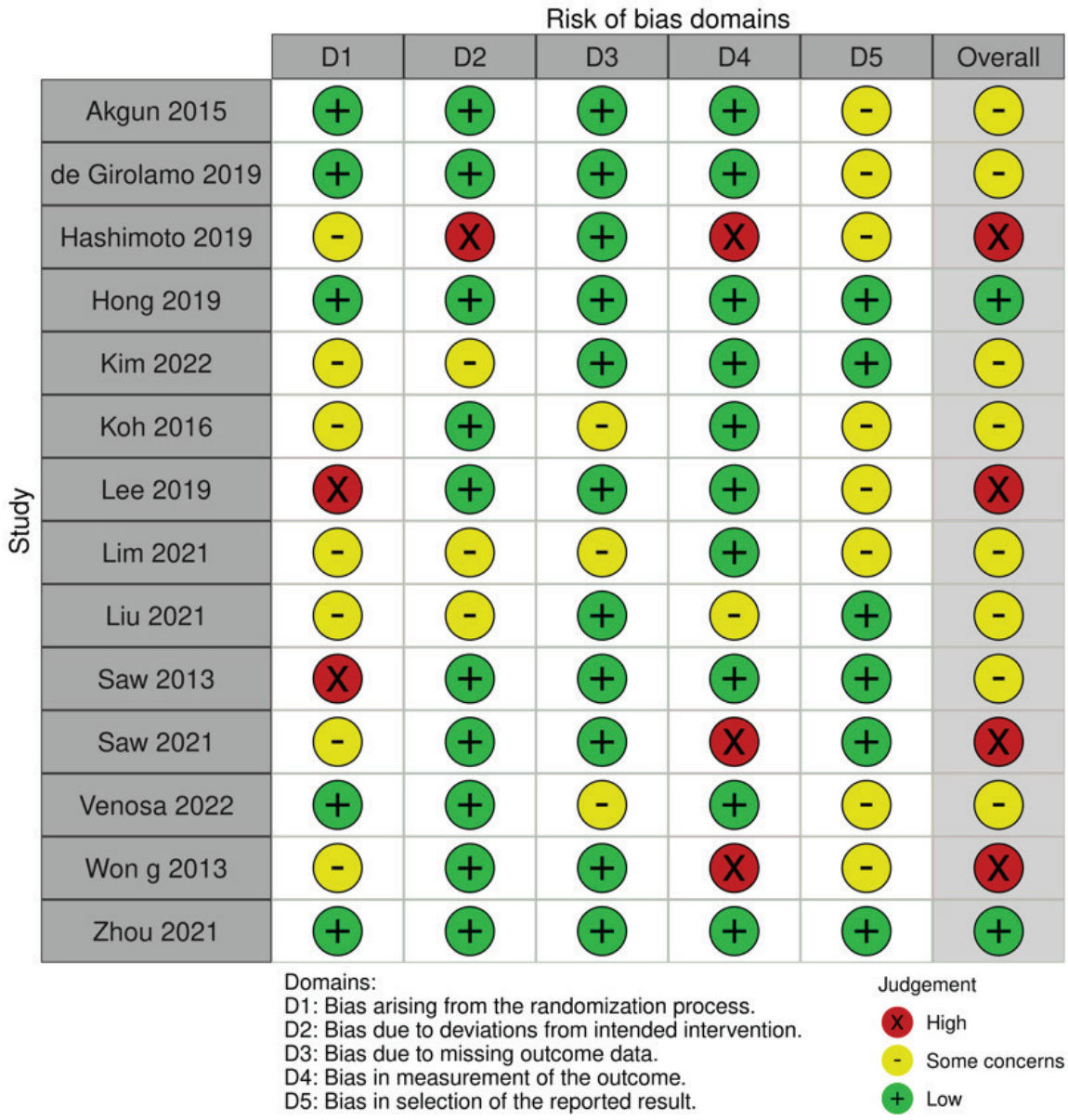
S. No.	Author	Reason for exclusion
1.	Hong et al. 2019[14]	Absence of stem cell characterization
2.	Venossa et al. 2022[15]	Absence of stem cell characterization

Critical outcomes reviewed and their MCID:

S. No.	Outcome reviewed	What does it measure?	MCID decided by the GDG
1.	Visual Analog Scale (VAS) Range: 0-10 Higher score is worse	Validated measure for measuring intensity of pain.	Absolute change of VAS score by 2 points
2.	Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)- Overall Range: 0-100 Higher score is worse	Self-administered questionnaire that is used to assess pain, stiffness, and function in patients with OA of the hip or knee.	Absolute change of WOMAC by 20 points
3.	Knee Injury and Osteoarthritis Outcome Score (KOOS) • Pain • Symptom • Activities of Daily living • Quality of Life • Sports and Recreation Range: 0-100 for each of the subscales Higher score is better	Self-reported outcome measure assessing the patient's opinion about the health, symptoms, and functionality of their knee.	Absolute change of KOOS by 20 points
4.	International Knee Documentation Committee Score (IKDC) Range: 0-100 Higher score is better	Subjective assessment of knee function	Absolute change of IKDC score by 20 points
5.	SAEs	Serious Adverse Events	

Risk of Bias Assessment:

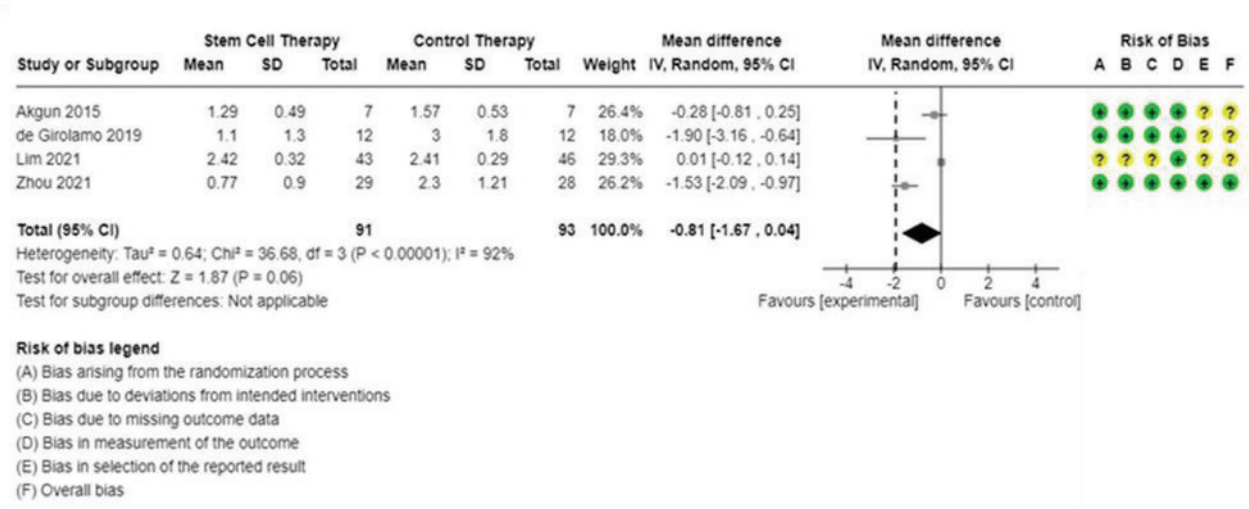
RoB2 assessment for subjective outcomes: VAS, WOMAC and KOOS



Desirable Effects (Dotted line represents MCID)**:**

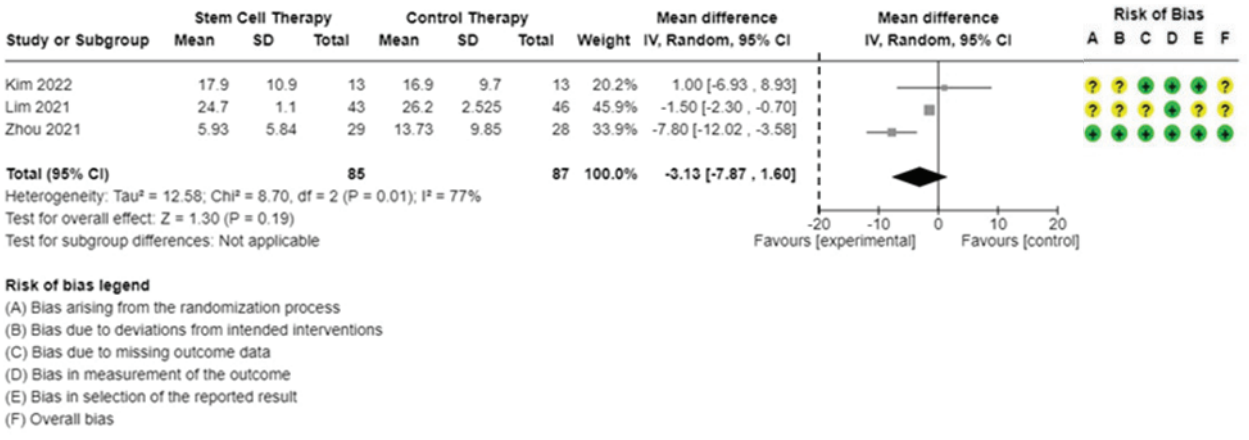
1. VAS: Evidence from four trials, with a total of 184 participants, reporting the VAS showed a mean difference of -0.81 (95% CI: -1.67 to 0.04) of pain in the stem cell transplantation arm as compared to usual care at the end of 12 months. The difference was statistically non-significant.

1.1 Forest plot showing the effect of stem cell therapy on VAS as compared to usual care: 12 months



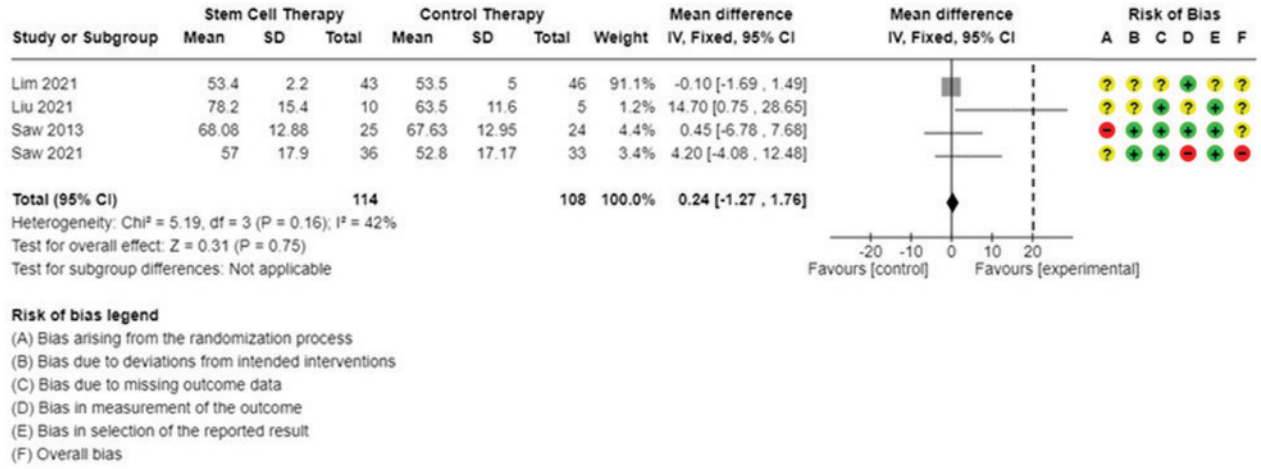
2. WOMAC: Evidence from three trials, with a total of 172 participants reporting the WOMAC score showed a mean difference of -3.13 (95% CI: -7.87 to 1.60) in the stem cell transplantation arm in comparison to usual care at the end of 12 months. The difference was statistically non-significant.

2.1 Forest plot showing the effect of stem cell therapy on WOMAC score as compared to usual care: 12 months



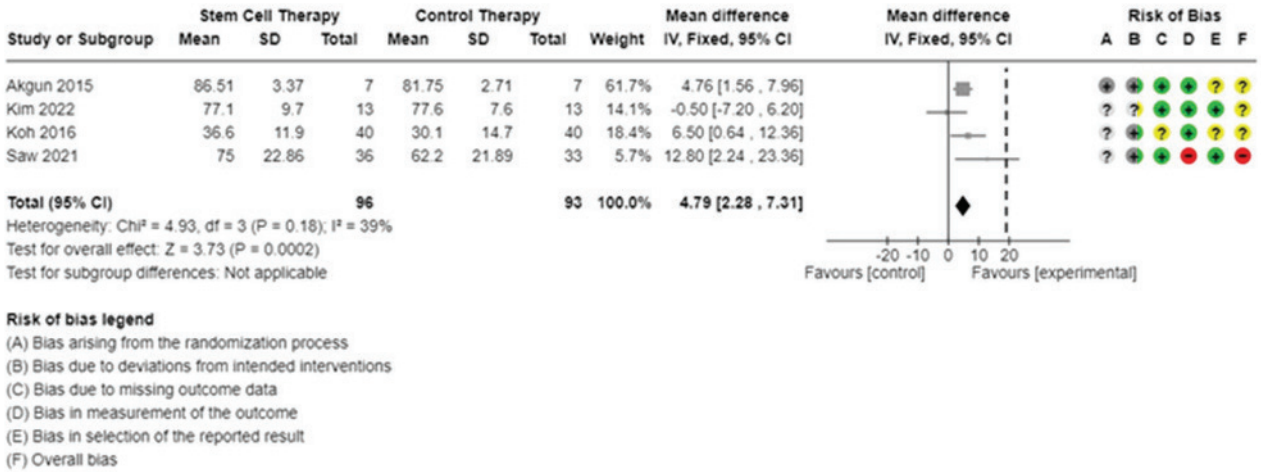
3. IKDC: Evidence from four trials, with a total of 222 participants reporting the IKDC score showed a mean difference of 0.24 (95% CI: -1.27 to 1.76) in the stem cell transplantation arm in comparison to usual care at the end of 12 months, suggesting no statistically significant difference in the two groups.

3.1 Forest plot showing the effect of stem cell therapy on IKDC score as compared to usual care: 12 months



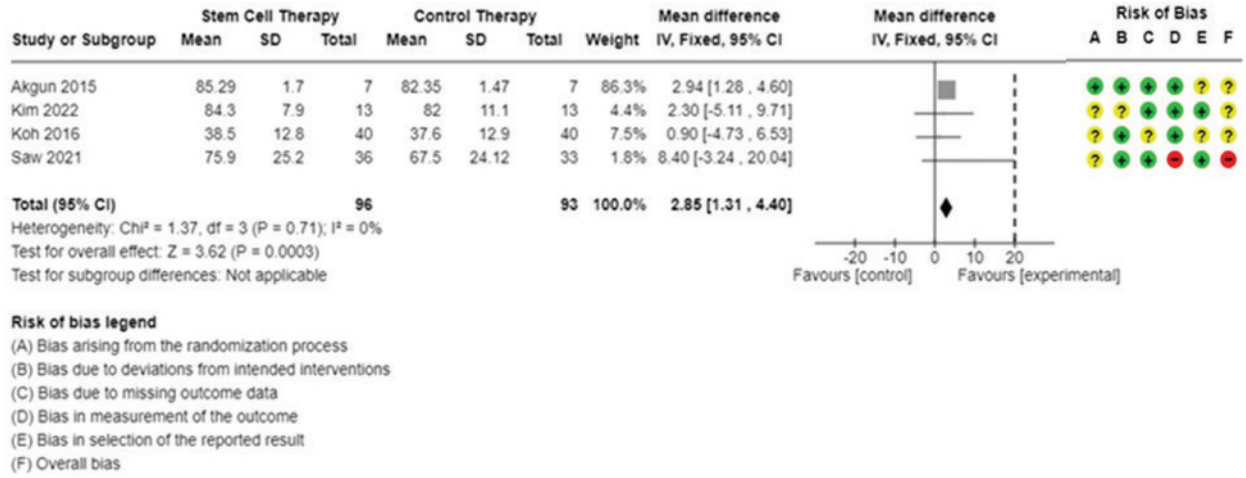
4. KOOS Pain: Evidence from four trials, with a total of 189 participants, reporting the KOOS Pain showed a mean difference of 4.79 (95% CI: 2.28 to 7.31) of pain in the stem cell transplantation arm compared to those on usual care at the end of 12 months. There seems to be a statistically significant decrease in pain, which is less than the MCID of 20 and therefore, unimportant clinically.

4.1 Forest plot showing the effect of stem cell therapy on KOOS-Pain as compared to usual care: 12 months



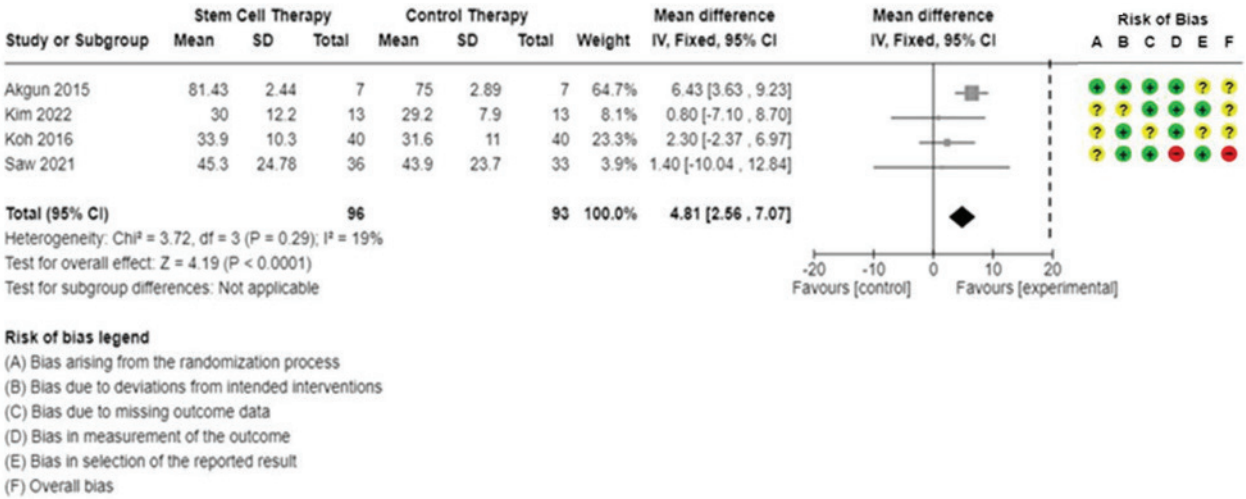
5. KOOS ADL: Evidence from four trials, with a total of 189 participants, reporting the KOOS ADL showed a mean difference of 2.85 (95% CI: 1.31 to 4.40) in the stem cell transplantation arm compared to those on usual care at the end of 12 months. There seems to be a statistically significant improvement in activities of daily living, which is less than a quarter of the MCID of 20. Therefore, the improvement is unimportant clinically.

5.1 Forest plot showing the effect of stem cell therapy on KOOS-ADL as compared to usual care: 12 months



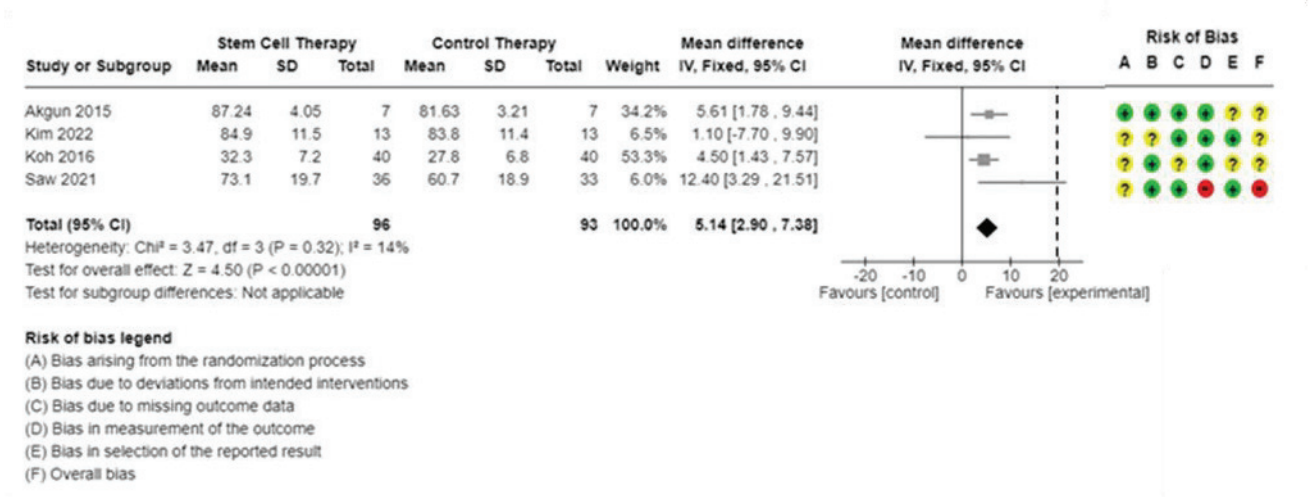
6. KOOS SPR: Evidence from four trials, with a total of 189 participants, reporting the KOOS SPR showed a mean difference of 4.81 (95% CI: 2.56 to 7.07) in the stem cell transplantation arm compared to those on usual care at the end of 12 months. There seems to be a statistically significant improvement, which is less than a quarter of the MCID of 20. Therefore, the improvement is unimportant clinically.

6.1 Forest plot showing the effect of stem cell therapy on KOOS-SPR as compared to usual care: 12 months



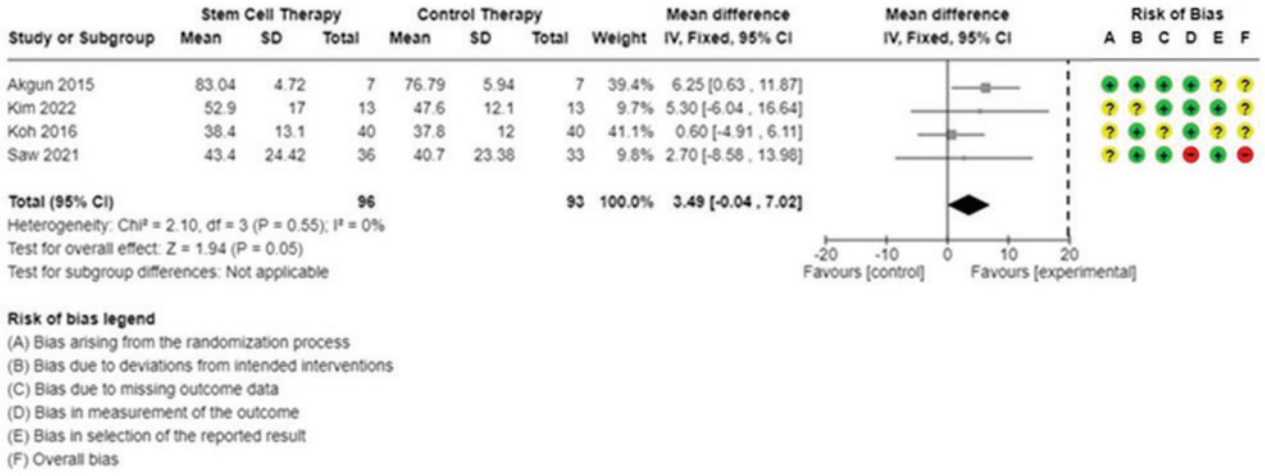
7. KOOS Symptom: Evidence from four trials, with a total of 189 participants, reporting the KOOS Symptom showed a mean difference of 5.14 (95% CI: 2.90 to 7.38) in the stem cell transplantation arm compared to those on usual care at the end of 12 months. There seems to be a statistically significant improvement, which is a quarter of the MCID of 20. Therefore, the improvement is unimportant clinically.

7.1 Forest plot showing the effect of stem cell therapy on KOOS symptom as compared to usual care: 12 months



8. KOOS QoL: Evidence from four trials, with a total of 189 participants, reporting the KOOS QoL showed a mean difference of 3.49 (95% CI: -0.04 to 7.02) in the stem cell transplantation arm compared to those on usual care at the end of 12 months. The difference was statistically non-significant.

8.1 Forest plot showing the effect of stem cell therapy on KOOS QoL as compared to usual care: 12 months



Undesirable effects:

Only one trial reported serious adverse events.[8] Three serious AEs (SAEs) occurred in 3 participants in the stem cell group, whereas two SAEs occurred in one participant in the usual care within the initial 48 weeks. These included implant site pain, pneumonia and renal cancer in the stem cell group and pneumonia and Hepatitis-B in the usual care group. In the 60-month follow-up, 8 SAEs occurred in 7 participants in the stem cell group and 7 SAEs in 5 participants in the usual care group.

SUMMARY OF FINDINGS:

Stem Cell Therapy compared to usual care for cartilage defects

Patient or population: Cartilage Defects
Setting: Tertiary care/hospital
Intervention: Stem Cell Therapy
Comparison: Usual Care

Outcomes	Anticipated absolute effects*(95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Control Therapy	**Risk with Stem Cell Therapy**				
KOOS - Activities of Daily Living at 12 months	-	MD **2.85 higher** (1.31 higher to 4.4 higher)	-	189 (4 RCTs)	⊕◯◯◯ Very low[a,b]	
KOOS Pain at 12 months	-	MD **4.79 higher** (2.28 higher to 7.31 higher)	-	189 (4 RCTs)	⊕◯◯◯ Very low[a,b]	
KOOS QoL at 12 months	-	MD **3.49 higher** (0.04 lower to 7.02 higher)	-	189 (4 RCTs)	⊕◯◯◯ Very low[a,c]	
KOOS Sports & Recreation at 12 months	-	MD **4.81 higher** (2.56 higher to 7.07 higher)	-	189 (4 RCTs)	⊕◯◯◯ Very low[a,b]	
KOOS Symptom at 12 months	-	MD **5.14 higher** (2.9 higher to 7.38 higher)	-	189 (4 RCTs)	⊕◯◯◯ Very low[a,b]	
VAS Score at 12 months	-	MD **0.81 lower** (1.67 lower to 0.04 higher)	-	184 (4 RCTs)	⊕◯◯◯ Very low[a,c,d]	
WOMAC Score at 12 months	-	MD **3.13 lower** (7.87 lower to 1.6 higher)	-	172 (3 RCTs)	⊕◯◯◯ Very low[a,c,d]	
IKDC Score at 12 months	-	MD **0.24 higher** (1.27 lower to 1.76 higher)	-	222 (4 RCTs)	⊕◯◯◯ Very low[a,b]	

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **MD:** mean difference; **OR:** odds ratio

SUMMARY OF FINDINGS:

Stem Cell Therapy compared to usual care for cartilage defects

Patient or population: Cartilage Defects
Setting: Tertiary care/hospital
Intervention: Stem Cell Therapy
Comparison: Usual Care

Outcomes	Anticipated absolute effects*(95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Control Therapy	**Risk with Stem Cell Therapy**				

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations

a. Downgraded two levels for risk of bias as more than 2/3rd of studies (by wt.) were at high risk of bias.
b. Downgraded by one level for imprecision as results are precise for no benefit but OIS not met.
c. Downgraded by one level for imprecision as wide CI crossing the line of null effect.
d. Downgraded by one level for inconsistency as results are inconsistent across studies.

EVIDENCE PROFILE:
Stem Cell Therapy compared to usual care for cartilage defects

Certainty assessment							Summary of findings				
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With Control Therapy	With Stem Cell Therapy		Risk with Control Therapy	Risk difference with Stem Cell Therapy
KOOS - Activities of Daily Living at 12 months											
189 (4 RCTs)	Very serious[a]	Not serious	Not serious	Serious[b]	Inevaluable	⊕◯◯◯ Very low	-	-	-	-	MD **2.85 higher** (1.31 higher to 4.4 higher)
KOOS Pain at 12 months											
189 (4 RCTs)	Very serious[a]	Not serious	Not serious	Serious[b]	Inevaluable	⊕◯◯◯ Very low	-	-	-	-	MD **4.79 higher** (2.28 higher to 7.31 higher)
KOOS QoL at 12 months											
189 (4 RCTs)	Very serious[a]	Not serious	Not serious	Serious[c]	Inevaluable	⊕◯◯◯ Very low	-	-	-	-	MD **3.49 higher** (0.04 lower to 7.02 higher)
KOOS SPR at 12 months											
189 (4 RCTs)	Very serious[a]	Not serious	Not serious	Serious[b]	Inevaluable	⊕◯◯◯ Very low	-	-	-	-	MD **4.81 higher** (2.56 higher to 7.07 higher)
KOOS Symptom at 12 months											
189 (4 RCTs)	very serious[a]	not serious	Not serious	Serious[b]	Inevaluable	⊕◯◯◯ Very low	-	-	-	-	MD **5.14 higher** (2.9 higher to 7.38 higher)

EVIDENCE PROFILE:
Stem Cell Therapy compared to usual care for cartilage defects

Certainty assessment							Summary of findings				
VAS Score at 12 months											
184 (4 RCTs)	very serious[a]	Serious[d]	Not serious	Serious[c]	Inevaluable	⊕◯◯◯ Very low	-	-	-	-	MD 0.**81 lower** (1.67 lower to 0.04 higher)
WOMAC Score at 12 months											
172 (3 RCTs)	very serious[a]	Serious[d]	Not serious	Serious[c]	Inevaluable	⊕◯◯◯ Very low	-	-	-	-	MD **3.13 lower** (7.87 lower to 1.6 higher)
IKDC Score at 12 months											
222 (4 RCTs)	very serious[a]	not serious	Not serious	Serious[b]	Inevaluable	⊕◯◯◯ Very low	-	-	-	-	MD **0.24 higher** (1.27 lower to 1.76 higher)

CI: confidence interval; **MD:** mean difference

Explanations

a. Downgraded two levels for risk of bias as more than 2/3rd of studies (by wt.) were at high risk of bias.
b. Downgraded by one level for imprecision as results are precise for no benefit but OIS not met.
c. Downgraded by one level for imprecision as wide CI crossing the line of null effect.
d. Downgraded by one level for inconsistency as results are inconsistent across studies.

D. SUMMARY OF JUDGEMENTS:

The summary of the final judgments made by the GDG after careful consideration of the summary of evidence is tabulated below:

Desirable Effects	Trivial*
Undesirable Effects	Trivial**
Certainty of evidence	Very low
Values	Probably no important uncertainty or variability
Balance of effects	Does not favor either the intervention or the comparison
Resources required	Large costs***
Certainty of evidence of required resources	Moderate
Cost effectiveness	Probably favors the comparison
Equity	Probably reduced
Acceptability	Probably yes
Feasibility	Probably yes
Recommendations: Stem cell therapy is **not recommended** in routine practice for the treatment of cartilage defects. It may be used only in the context of rigorously conducted randomized controlled trials.	

***This judgment was made as there is very low certainty evidence of trivial reduction in pain and no improvement in function.

**This judgment was made as there is little or no difference in undesirable effects between stem cell therapy and usual care.

***The committee opined that stem cell treatment is associated with large costs.

E. CAVEATS IN EXISTING EVIDENCE:

The GDG opined that the existing evidence had the following caveats:

- Lack of sufficient number of RCTs with low risk of bias.
- Small number of participants and/or events in the included trials.
- Heterogeneity across trials in patient population, type of stem cell therapy used and their source, cell dosage and route of administration.
- Use of both active and passive comparators in the trials.
- Use of adjunctive biological components (e.g., PRP) and co-interventions which might have impacted the outcomes.
- Limited safety data.
- Lack of cost effectiveness data.

REFERENCES:

1. Brittberg M. Clinical articular cartilage repair—an up to date review. Annals of Joint. 2018 Nov 19;3.
2. Kim J, Kim K, Yoon W, Song S, Jin W. Intra-articular Injection of Mesenchymal Stem Cells after High Tibial Osteotomy in Osteoarthritic Knee: Two-Year Follow-up of Randomized Control Trial. Stem cells translational medicine. 2022 Jun 22;11(6):572–85.
3. Koh YG, Kwon OR, Kim YS, Choi YJ, Tak DH. Adipose-derived mesenchymal stem cells with microfracture versus microfracture alone: 2-year follow-up of a prospective randomized trial. Arthroscopy J Arthroscopic Relat Surg. 2016;32(1):97 109.
4. Lee W, Kim H, Kim K, Kim G, Jin W. Intra-Articular Injection of Autologous Adipose Tissue-Derived Mesenchymal Stem Cells for the Treatment of Knee Osteoarthritis: A Phase IIb, Randomized, Placebo-Controlled Clinical Trial. Stem Cells Translational Medicine. 2019 Jun;8(6):504–11.
5. Akgun I, Unlu MC, Erdal OA, Ogut T, Erturk M, Ovali E, et al. Matrix-induced autologous mesenchymal stem cell implantation versus matrix-induced autologous chondrocyte implantation in the treatment of chondral defects of the knee: a 2-year randomized study. Arch Orthop Trauma Surg. 2015;135(2):251–63.
6. Wong K, Lee K, Tai B, Law P, Lee E, Hui J. Injectable Cultured Bone Marrow Derived Mesenchymal Stem Cells in Varus Knees With Cartilage Defects Undergoing High Tibial Osteotomy: A Prospective, Randomized Controlled Clinical Trial With 2 Years' Follow-up. Arthroscopy-The Journal of arthroscopic and related surgery. 2013 Dec;29(12):2020–8.
7. Hashimoto Y, Nishida Y, Takahashi S, Nakamura H, Mera H, Kashiwa K, et al. Transplantation of autologous bone marrow-derived mesenchymal stem cells under arthroscopic surgery with microfracture versus microfracture alone for articular cartilage lesions in the knee: A multicenter prospective randomized control clinical trial. Regenerative Therapy. 2019 Dec 1;11:106–13.
8. Lim HC, Park YB, Ha CW, Cole BJ, Lee BK, Jeong HJ, et al. Allogeneic Umbilical Cord Blood–Derived Mesenchymal Stem Cell Implantation Versus Microfracture for Large, Full-Thickness Cartilage Defects in Older Patients: A Multicenter Randomized Clinical Trial and Extended 5-Year Clinical Follow-up. Orthop J Sports Med [Internet]. 2021;9(1). Available from:https://www.embase.com/search/results?subaction=viewrecord&id=L2010162706&from =export.
9. Saw KY, Anz AW, Ng RCS, Jee CSY, Low SF, Dorvault C, et al. Arthroscopic Subchondral Drilling Followed by Injection of Peripheral Blood Stem Cells and Back to Table of Contents 47 Stem Cell Therapy for Cartilage Defects Hyaluronic Acid Showed Improved Outcome Compared to Hyaluronic Acid and Physiotherapy for Massive Knee Chondral Defects: A Randomized Controlled Trial. Arthroscopy J Arthroscopic Relat Surg. 2021;37(8):2502–17.
10. Liu Y, Yen C, Liu T, Chang C, Shih T, Wang J, et al. Safety and Efficacy of Kartigen(R) in Treating Cartilage Defects: A Randomized, Controlled, Phase I Trial. POLYMERS. 2021 Sep;13(18).
11. de Girolamo L, Schönhuber H, Viganò M, Bait C, Quaglia A, Thiebat G, et al. Autologous Matrix-Induced Chondrogenesis (AMIC) and AMIC Enhanced by Autologous Concentrated

Bone Marrow Aspirate (BMAC) Allow for Stable Clinical and Functional Improvements at up to 9 Years Follow-Up: Results from a Randomized Controlled Study. J ClinMed. 2019 Mar; 21;8(3).

12. Saw K, Anz A, Jee C, Merican S, Ng R, Roohi S, et al. Articular Cartilage Regeneration With Autologous Peripheral Blood Stem Cells Versus Hyaluronic Acid: A Randomized Controlled Trial. Arthroscopy-The Journal of Arthroscopic-The Journal of Arthroscopic and related surgery. 2013 Apr;29(4):684–94.
13. Zhou Y, Li H, Xiang D, Shao J, Fu Q, Han Y, et al. The clinical efficacy of arthroscopic therapy with knee infrapatellar fat pad cell concentrates in treating knee cartilage lesion: a prospective, randomized, and controlled study. J Orthop Surg Res. 2021 Jan; 28;16(1).
14. Hong Z, Chen J, Zhang S, Zhao C, Bi M, Chen X, et al. Intra-articular injection of autologous adipose-derived stromal vascular fractions for knee osteoarthritis: a doubleblind randomized self-controlled trial. Int Orthop. 2019 May;43(5):1123–34.
15. Venosa M, Calafiore F, Mazzoleni M, Romanini E, Cerciello S, Calvisi V. Platelet Rich Plasma and Adipose-Derived Mesenchymal Stem Cells in Association with Arthroscopic Microfracture of Knee Articular Cartilage Defects: A Pilot Randomized Controlled Trial. Adv Orthop [Internet]. 2022;2022((Venosa M., michelevenosa@hotmail.com; Calafiore F., francescocalafiore93@libero.it; Mazzoleni M., manuelmazzoleni4@gmail.com; Calvisi V., vittorio.calvisi@univaq.it) Department of Life, Health and Environmental Sciences, University of l'Aquila, Via VetoioCoppito 2, L'Aquila, Italy). Available from: https://www.embase.com/search/results?subaction=viewrecord&id=L2018111413&from=export

4. TENDINOPATHY

A. BACKGROUND:

Tendinopathy is a common disorder in athletes and the general population. It is characterized by pain and swelling in addition to functional limitations. The most common overuse tendinopathies involve the rotator cuff tendon, medial and lateral elbow epicondyles, patellar tendon, gluteal tendons and the Achilles tendon.[1] In addition to physical therapy, several therapeutic options like pharmacological (Corticosteroids, non-steroidal anti-inflammatory drugs, etc.) and surgical interventions have been used over time,however, their effectiveness remains ambiguous.Thus, there remains an unmet need to search for new options for management of tendinopathy.

B. RECOMMENDATIONS:

Stem cell therapy is **not recommended** in routine clinical practice for the treatment of tendinopathy.
Strength: Conditional[#]
Certainty of Evidence: Very Low

[#]*It may be used only in the context of rigorously conducted randomized controlled trials.*

Rationale/Justification
This recommendation has been made as there is very low certainty evidence of trivial reduction in pain and no improvement in function. There is little or no difference in undesirable effects between stem cell therapy and usual care. In addition, the follow up period is limited to comment on the long-term safety of stem cell therapy. Results should be interpreted with caution, in view of various study limitations like small number of participants and/or events, risk of bias and different sources of stem cell used.

C. SUMMARY OF EVIDENCE:

Key Question: In patients with tendinopathy, what is the efficacy and safety of stem cell therapy as compared to usual care?

Included studies: The electronic search of the four databases revealed 723 records. Out of which, 337 duplicate records and 209 non-clinical studies were removed. The title and abstract of 177 studies were screened for eligibility. After screening, 13 reports were sought for retrieval; out of which nine reports were included in this systematic review. Out of these nine studies, three studies met the 'reliable body of evidence' criteria specified by the GDG and thus were included in this meta-analysis.[2-10]

Two studies compared the effect of stem cell therapy in patients with tendinopathy of weight-bearing joints whereas one compared the effect on non-weight-bearing joints. The trials used AD-MSC, BM-MSC and BMAC as the stem cell intervention. For details, refer to the supplement.

Below mentioned studies were excluded from the meta-analysis as they did not meet the criteria for "reliable body of evidence":

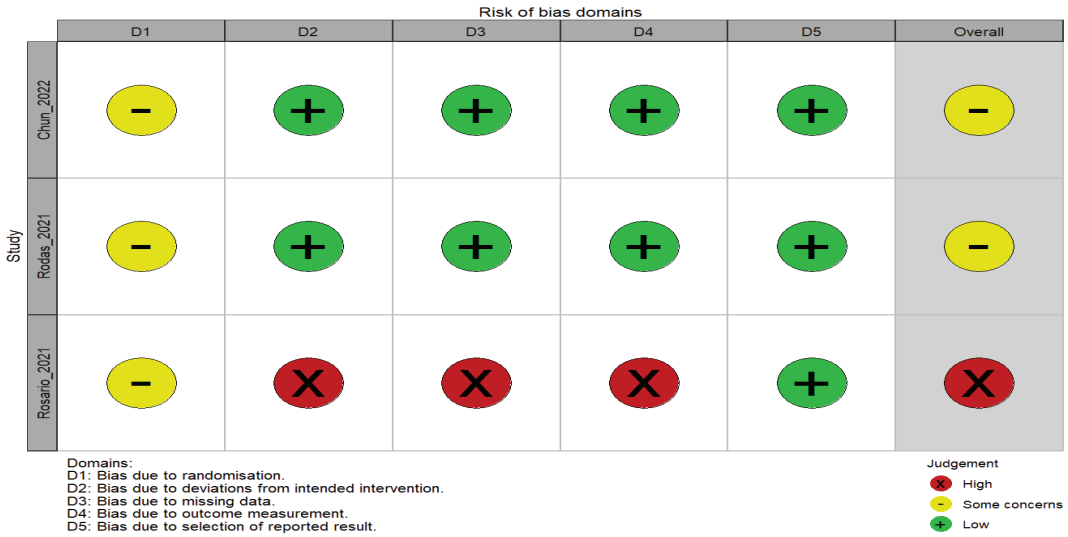
1.	Albano et al. 2017[2]	Absence of stem cell characterization
2.	Usuelli et al. 2017[5] (same trial as Albano 2017)	Absence of stem cell characterization
3.	Centeno et al. 2020[6]	Absence of stem cell characterization
4.	Hurd et al. 2020[8]	Absence of stem cell characterization
5.	Randelli et al. 2022[10]	Absence of stem cell characterization

Critical outcomes reviewed and their MCID:

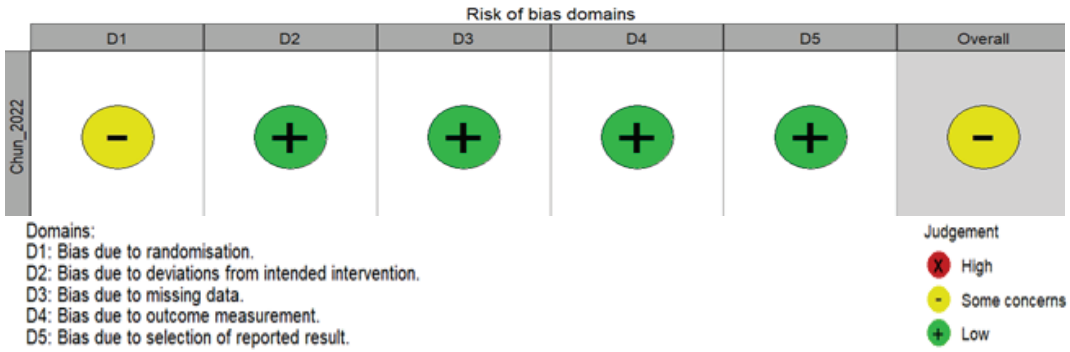
S. No	Outcome reviewed	What does it measure?	MCID decided by the GDG
1.	Visual Analog Scale (VAS) Range: 0-10 Higher score is worse	Validated measure for measuring intensity of pain	Absolute change of VAS score by 2 points
2.	American Shoulder and Elbow Surgeons (ASES) score Range: 0-100 Higher score is better	Patient reported outcome measure to assess shoulder condition.	Absolute change of ASES score by 20 points
3.	SAEs	Serious adverse events	

Risk of Bias assessment:

VAS outcome:



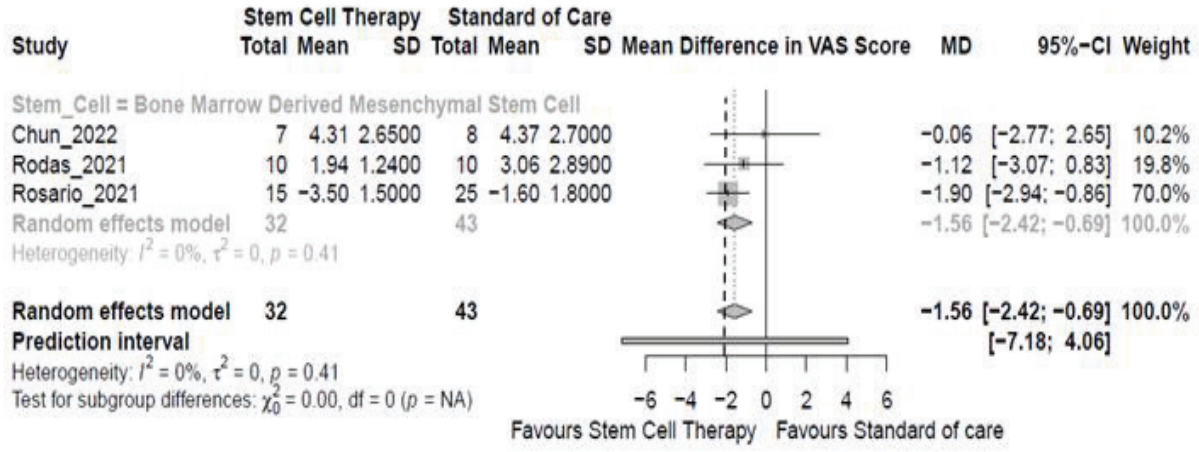
ASES Outcome:



Desirable Effects (Dotted line represents MCID)**:**

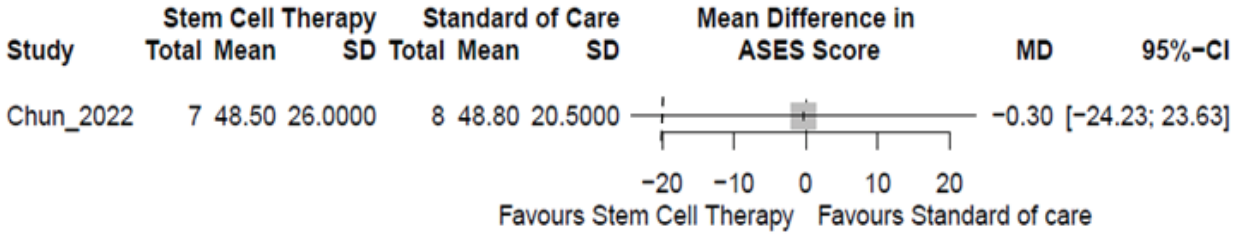
1. VAS: Evidence from three trials, with a total of 75 participants, reporting the VAS showed a mean difference of -1.56 (95% CI: -2.42 to -0.69) in the stem cell therapy arm as compared to those on usual care at the end of 6 months. There seems to be a statistically significant decrease in pain, which does not cross the MCID of 2. Therefore, the reduction in pain is unimportant clinically.

1.1 Forest plot showing reduction in pain between stem cell therapy versus usual care by using VAS: 6 months



2. ASES: Evidence from one trial, with a total of 15 participants reporting the ASES score showed a mean difference of -0.30 (95% CI: -24.23 to 23.63) in the stem cell therapy arm in comparison to usual care at the end of 3 months. The difference was statistically non-significant.

2.1 Forest plot of included studies assessing American Shoulder and Elbow Surgeons (ASES) Scale between stem cell therapy versus usual care: 3 months



Undesirable effects:

None of the trials reported serious adverse events. The evidence is insufficient to draw firm conclusions due to limited long term follow up of trials.

SUMMARY OF FINDINGS:

Stem cell compared to standard of care for Tendinopathy

Patient or population: Tendinopathy
Setting: Tertiary care
Intervention: Stem cell
Comparison: usual care

Outcomes	Anticipated absolute effects*(95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with standard of care	**Risk with Stem cell**				
ASES Scale from: 0 to 100 follow-up: mean 6 months	-	MD 0.30 lower (24.23 lower to 23.63 higher)	-	15 (1 RCT)	⊕◯◯◯ Very low[a,b,c]	
VAS Scale from 0 to 10 follow-up: mean 6 months	-	MD 1.56lower (2.42 lower to 0.69lower)	-	75 (3 RCTs)	⊕◯◯◯ Very low[a,c]	

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **MD:** mean difference; **RR:** Risk ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations
a. Downgraded by two levels for risk of bias as more than 2/3rd of the studies (by wt.) were at high risk of bias
b. Downgraded by one level for inconsistency as it is inevaluable for single study
c. Downgraded by one level for imprecision as OIS not met

EVIDENCE PROFILE

Stem cell compared to standard of care for Tendinopathy

Certainty assessment							Summary of findings				
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With standard of care	With Stem cell		Risk with standard of care	Risk difference with Stem cell
ASES (follow-up: mean 6 months; Scale from: 0 to 100)											
15 (1 RCT)	very serious[a]	Inevaluable[b]	not serious	serious[c]	none	⊕◯◯◯ Very low[a,b,c]	-	-	-	-	MD **0.30 lower** (24.23 lower to 23.63 higher)
VAS (follow-up: mean 6 months)											
75 (3 RCTs)	very serious[a]	not serious	not serious	Serious[c]	none	⊕◯◯◯ Very low[a,c]	-	-	-	-	MD **1.56 lower** (2.42 lower to 0.69 lower)

CI: confidence interval; **MD:** mean difference; **OR:** odds ratio

Explanations

a. Downgraded by two levels for risk of bias as more than 2/3rd of the studies (by wt.) were at high risk of bias.
b. Downgraded by one level for inconsistency as it is inevaluable for single study.
c. Downgraded by one level for imprecision as OIS not met.

D. SUMMARY OF JUDGEMENTS:

The summary of the final judgments made by the GDG after careful consideration of the summary of evidence is tabulated below:

Desirable Effects	Trivial*
Undesirable Effects	Trivial**
Certainty of evidence	Very low
Values	Probably no important uncertainty or variability
Balance of effects	Does not favor either the intervention or the comparison
Resources required	Large costs***
Certainty of evidence of required resources	Moderate
Cost effectiveness	Probably favors the comparison
Equity	Probably reduced
Acceptability	Probably yes
Feasibility	Probably yes
Recommendations: Stem cell therapy is **not recommended** in routine practice for the treatment of tendinopathy. It may be used only in the context of rigorously conducted randomized controlled trials.	

*This judgment was made as there is very low certainty evidence of trivial reduction in pain and no improvement in function.

**This judgment was made as there is little or no difference in undesirable effects between stem cell therapy and usual care.

***The committee opined that stem cell treatment is associated with large costs.

E. CAVEATS IN EXISTING EVIDENCE:

The GDG opined that the existing evidence had the following caveats:

1. Lack of sufficient number of RCTs with low risk of bias.
2. Small number of participants and events in the included trials.
3. Heterogeneity across trials in patient population, type of stem cell therapy used and cell dosage.
4. Use of both active and passive comparators in the trials.
5. Lack of long term follow up of participants thus providing insufficient evidence on the safety of this experimental therapy.
6. Lack of cost effectiveness data.

REFERENCES:

1. Millar, NL, Silbernagel, KG, Thorborg, K et al. Tendinopathy. Nat Rev Dis Primers. 2021 Feb 3;7(1)https://doi.org/10.1038/s41572-020-00234-1.
2. Albano D, Messina C, Usuelli FG, et al. Magnetic resonance and ultrasound in achilles tendinopathy: Predictive role and response assessment to platelet-rich plasma and adipose-derived stromal vascular fraction injection. Eur J Radiol 2017; 95: 130-5.
3. Rodas G, Soler-Rich R, Rius-Tarruella J, et al. Effect of Autologous Expanded Bone Marrow Mesenchymal Stem Cells or Leukocyte-Poor Platelet-Rich Plasma in Chronic Patellar Tendinopathy (With Gap >3 mm): Preliminary Outcomes After 6 Months of a Double-Blind, Randomized, Prospective Study. Am J Sports Med 2021; 49(6): 1492-504.
4. Rosario DAV, Faleiro TB, Franco B, Daltro GC, Marchetto R. Comparison between Concentrated Bone Marrow Aspirate and Corticoid in Gluteal Tendinopathy. Acta Ortop Bras 2021; 29(1): 26-9.
5. Usuelli FG, Grassi M, Maccario C, et al. Intratendinous adipose-derived stromal vascular fraction (SVF) injection provides a safe, efficacious treatment for Achilles tendinopathy: results of a randomized controlled clinical trial at a 6-month follow-up. Knee Surg SportsTraumatol Arthrosc 2018; 26(7): 2000-10.
6. Centeno C, Fausel Z, Stemper I, Azuike U, Dodson E. A Randomized Controlled Trial of the Treatment of Rotator Cuff Tears with Bone Marrow Concentrate and Platelet Products Compared to Exercise Therapy: A Midterm Analysis. Stem Cells Int 2020; 2020: 5962354.
7. Chun SW, Kim W, Lee SY, et al. A randomized controlled trial of stem cell injection for tendon tear. Sci Rep 2022; 12(1): 818.
8. Hurd JL, Facile TR, Weiss J, et al. Safety and efficacy of treating symptomatic, partial-thickness rotator cuff tears with fresh, uncultured, unmodified, autologous adipose-derived regenerative cells (UA-ADRCs) isolated at the point of care: a prospective, randomized, controlled first-in-human pilot study. J Orthop Surg Res 2020; 15(1): 122.
9. Lamas JR, Garcia-Fernandez C, Tornero-Esteban P, et al. Adverse effects of xenogenic scaffolding in the context of a randomized double-blind placebo-controlled study for repairing full-thickness rotator cuff tears. Trials 2019; 20(1): 387.
10. Randelli PS, Cucchi D, Fossati C, et al. Arthroscopic Rotator Cuff Repair Augmentation With Autologous Microfragmented Lipoaspirate Tissue Is Safe and Effectively Improves Short-term Clinical and Functional Results: A Prospective Randomized Controlled Trial With 24-Month Follow-up. Am J Sports Med 2022; 50(5): 1344-57.

5. NON-UNION OF BONE

A. BACKGROUND:

FDA defines non-union of bone fracture as a fracture that persists for a minimum of 9 months without signs of healing for three months. They are often associated with prolonged treatment and multiple surgeries. With an estimated global prevalence of nine million annually, this condition results in patients living with pain, a reduced quality of life and associated psychological, social and financial repercussions.[1]

B. RECOMMENDATIONS:

Stem cell therapy is **not recommended** in routine clinical practice for the treatment of non-union of bone fracture.
Strength: Conditional[#]
Certainty of Evidence: Very Low

[#]It may be used only in the context of rigorously conducted randomized controlled trials.

Rationale/Justification

The evidence is inadequate in quantity and quality to determine the safety and efficacy of stem cell therapy in patients with non-union of bone fracture. In addition, the follow up period is limited to comment on the side effect profile and long-term safety is not known. Results need to be interpreted with caution due to small number of participants and/or events, limited duration of follow up in the single study that evaluated the clinical and functional outcomes of Collagen/PGA Scaffolds and Cell-Based Therapy in scaphoid bone non unions.

C. SUMMARY OF EVIDENCE

Key Question: In patients with Non-union of bone fracture, what is the efficacy and safety of stem cell therapy as compared to usual care?

Included studies: Of the total records, 659 studies were retrieved from Embase, 92 studies were retrieved from PubMed, 42 studies from Web of Science and 71 studies were retrieved from Cochrane database. Full text was evaluated for 27 articles for possible inclusion. But, among these 21 records were excluded and 6 RCTs were included. Only 1 trial met the 'reliable body of evidence' criteria as specified by the GDG and was used for synthesizing evidence.[2-7]

The single trial by Toosi et al included patients of nonunion of scaphoid fractures and used collagen/polyglycolic acid (CPGA) scaffolds with bone marrow mesenchymal stem cell (BM-MSC) therapy in the intervention arm and autologous bone tissue graft in the comparator arm.

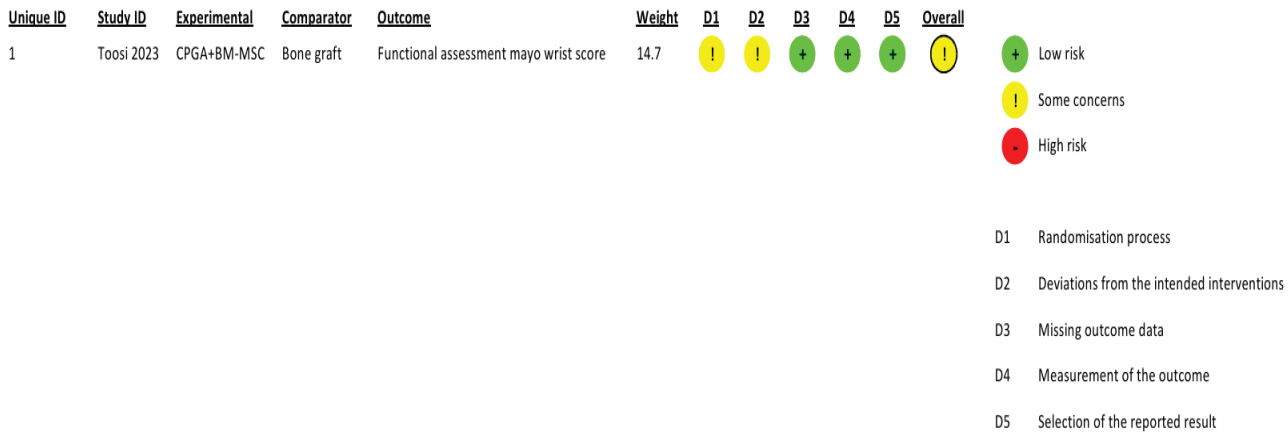
Below mentioned studies were excluded from the meta-analysis as they did not meet the criteria for "reliable body of evidence":

S. No.	Author	Reason for exclusion
1.	Zhang et al. 2018[2]	Absence of stem cell characterization
2	Bajada et al. 2008[3]	Incomplete data reported in conference abstract
3.	Yuan et al. 2006[4]	Absence of stem cell characterization
4.	Zhai et al. 2016[5]	Critical outcomes not reported
5.	Hernigou et al. 2018[6]	Included only infected cases of non-union, findings would be non-generalizable

Critical outcomes reviewed and their MCID:

S. No	Outcome reviewed	What does it measure?	MCID decided by the GDG
1.	Quick Disabilities of Arm, Shoulder & Hand (QDASH) score Range: 0-100 Higher score is worse	Questionnaire to measure physical function and symptoms in people with any or multiple musculoskeletal disorders of the upper limb	Absolute change of QDASH score by 20 points
2.	Mayo wrist score (MWS) Range: 0-100 Higher score is better	Score to evaluate the functioning of the wrist.	Absolute change of Mayo wrist score by 20 points
3.	SAEs	Serious Adverse Events	

Risk of Bias Assessment:

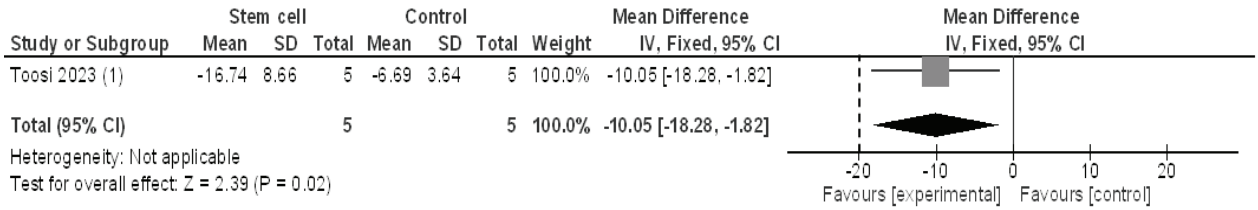


Desirable Effects (Dotted line represents MCID)**:**

There is insufficient evidence to draw firm conclusions regarding the desirable effects of stem cell therapy in patients with non-union of bone fracture.

1. QDASH: Evidence from one RCT of 10 participants of scaphoid non-union reporting the QDASH (Quick disability of the arm, shoulder and hand) score at the end of 3 months showed a mean difference of -10.05 (95% CI: -18.28 to -1.82) between the stem cell therapy arm as compared to the usual care. The difference was statistically significant but about half of the MCID of 20, hence unimportant clinically.

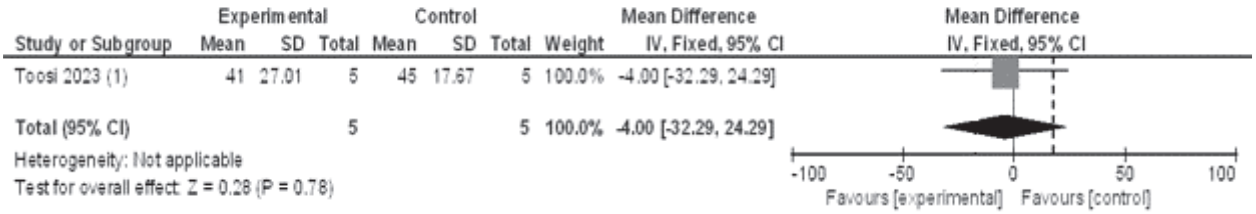
1.1. Forest plot showing the effect of stem cell therapy on QDASH score as compared to usual care: 3 months:



Footnotes
(1) Decrease in QDASH from baseline

2. Mayo wrist score: Evidence from one RCT of 10 participants evaluated wrist functions (among participants with scaphoid fracture) following treatment with stem cell derived products and showed a mean difference of -4.00 (95% CI: -32.29 to 24.29). However, no statistically significant difference was seen between the two groups.

2.1. Forest plot showing the effect of stem cell therapy on reduction in pain and disability as compared to usual care: 3 months



Footnotes
(1) Change in Mayo wrist score

Undesirable effects:
No severe adverse events were reported. The evidence is insufficient to draw firm conclusions due to limited long term follow up of the trial.

SUMMARY OF FINDINGS:

Any Stem cell and product derived from stem cells compared to Usual Care in treatment of nonunion of bone for Non union of Bone fracture

Patient or population: Non union of Bone
Setting: Tertiary care
Intervention: Any Stem cell and product derived from stem cells
Comparison: Usual Care

Outcomes	Anticipated absolute effects*(95% CI)		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Usual Care	**Risk with Any Stem cell and product derived from stem cells**				
QDASH at 3 months	-	MD **10.05 lower** (18.28 lower to 1.82 lower)	-	10 (1 RCT)	⊕◯◯◯ Very low[a,b,c]	
Mayo wrist score at 3 months	-	MD **4 lower** (32.29 lower to 24.29 higher)	-	10 (1 RCT)	⊕◯◯◯ Very low[a,b,d]	

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations
a. Downgraded by two levels for risk of bias as single study with unclear risk of bias
b. Downgraded by one level for inconsistency as it was inevaluable for single study
c. Downgraded by one level for imprecision as OIS not met
d. Downgraded by two levels for imprecision as very wide CI

GRADE EVIDENCE PROFILE

Any Stem cell and product derived from stem cells compared to Usual Care in treatment of non-union of bone

Certainty assessment							Summary of findings				
							Study event rates (%)			Anticipated absolute effects	
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	With Usual Care/ Conventional Carein treatment of non-union of bone	With Any Stem cell and product derived from stem cells	Relative effect (95% CI)	Risk with Usual Care/ Conventional Carein treatment of nonunion of bone	Risk difference with any stem cell and product derived from stem cells
QDASH at 3 months											
10 (1 RCT)	Very serious[a]	Inevaluable[b]	Not serious	Serious[c]	Inevaluable	⊕◯◯◯ Very low[a,b,c]	-	-	-	-	MD **10.05 lower** (18.28 lower to 1.82 lower)
Mayo wrist score at 3 months											
10 (1 RCT)	Very serious[a]	Inevaluable[b]	Not serious	Very serious[d]	Inevaluable	⊕◯◯◯ Very low[a,b,d]	-	-	-	-	MD **4 lower** (32.29 lower to 24.29 higher)

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations

a. Downgraded by two levels for risk of bias as single study with unclear risk of bias.
b. Downgraded by one level for inconsistency as it was inevaluable for single study.
c. Downgraded by one level for imprecision as OIS not met.
d. Downgraded by two levels for imprecision as very wide CI.

D. SUMMARY OF JUDGEMENTS:

The summary of the final judgments made by the GDG after careful consideration of the summary of evidence is tabulated below:

Desirable Effects	Don't know*
Undesirable Effects	Don't know*
Certainty of evidence	Very low
Values	Probably no important uncertainty or variability
Balance of effects	Does not favor either the intervention or the comparison
Resources required	Large costs**
Certainty of evidence of required resources	Moderate
Cost effectiveness	Probably favors the comparison
Equity	Probably reduced
Acceptability	Probably yes
Feasibility	Probably yes
Recommendations: Stem cell therapy is **not recommended** in routine practice for the treatment of non-union of bone. It may be used only in the context of rigorously conducted randomized controlled trials.	

***** The evidence was inadequate in quantity and quality to determine the safety and efficacy of stem cell therapy in patients with non-union of bone fracture.
**The committee opined that stem cell treatment is associated with large costs.

E. CAVEATS IN EXISTING EVIDENCE:

The GDG opined that the existing evidence had the following caveats:

1. Lack of sufficient number of RCTs with low risk of bias.
2. Small number of participants and events in the included trial.
3. Lack of long term follow up of participants thus providing insufficient evidence on the safety of this experimental therapy.
4. Lack of cost effectiveness data.

REFERENCES:

1. Stewart SK. Fracture Non-Union: A Review of Clinical Challenges and Future Research Needs. Malays Orthop J. 2019 Jul;13(2):1-10. doi: 10.5704/MOJ.1907.001. PMID: 31467644; PMCID: PMC6702984.
2. Zhang H, Xue F, Jun Xiao H. Ilizarov method in combination with autologous mesenchymal stem cells from iliac crest shows improved outcome in tibial non-union. Saudi J Biol Sci. 2018 May;25(4):819–25.
3. Bajada S, Harrison P, Kuiper JH, Balbouzis T, Ashton BA, Pullicino VC, et al. The first prospective randomised controlled trial of bone marrow stromal stem cell implantation for the treatement of refractory fracture non-union: conclusions from the pilot study. Orthop Proc. 2008 Aug 1;90-B(SUPP_III):571–571.
4. Yuan J, Zhou Z, Liu Y, Zhu Z. Study of Marrow Stem Cell Transplant for Treatment of Bone Nonunion and Bone Defection. Chin J Rehabil THEORY Pract. 2006;12(8):706–7.
5. Zhai L, Ma XL, Jiang C, Zhang B, Liu ST, Xing GY. Human autologous mesenchymal stem cells with extracorporeal shock wave therapy for nonunion of long bones. Indian J Orthop. 2016 Sep;50(5):543–50.
6. Hernigou P, Dubory A, Homma Y, FlouzatLachaniette CH, Chevallier N, Rouard H. Single-stage treatment of infected tibial non-unions and osteomyelitis with bone marrow granulocytes precursors protecting bone graft. Int Orthop. 2018 Oct;42(10):2443–50.
7. Toosi S, Naderi-Meshkin H, Moradi A, Daliri M, Moghimi V, Majd HM, et al. Scaphoid Bone Nonunions: Clinical and Functional Outcomes of Collagen/PGA Scaffolds and Cell-Based Therapy. ACS Biomater Sci Eng. 2023 Apr 10;9(4):1928–39.

6. MENISCAL TEAR/MENISCOPATHY

A. BACKGROUND:

The meniscus plays a vital role in maintaining the stability of the knee joint along with optimizing the tibio-femoral load transfer and distribution. This also helps in preserving the health of the articular cartilage. Meniscal tears are very common injuries of the knee with an estimated incidence of 61/100,000 population per year.[1] Management of meniscal tears is dependent upon multiple factors such as age of the patient, the etiology & complexity of the tear and the severity of symptoms.

B. RECOMMENDATIONS:

Stem cell therapy is **not recommended** in routine clinical practice for the treatment of meniscopathy/meniscal tear.
Strength: Conditional[#]
Certainty of Evidence: Very Low

[#]It may be used only in the context of rigorously conducted randomized controlled trials.

Rationale/Justification:
This recommendation has been made as there is very low certainty evidence of trivial reduction in pain and no improvement in function. The undesirable effects are variable and heterogenous. In addition, the follow up period is limited to comment on long-term safety of stem cell therapy. Results should be interpreted with caution in view of various study limitations like risk of bias and small number of participants and events in the single trial.

C. SUMMARY OF EVIDENCE:

Key Question: In patients with Meniscal Tear/Meniscopathy, what is the efficacy and safety of stem cell therapy as compared to usual care?

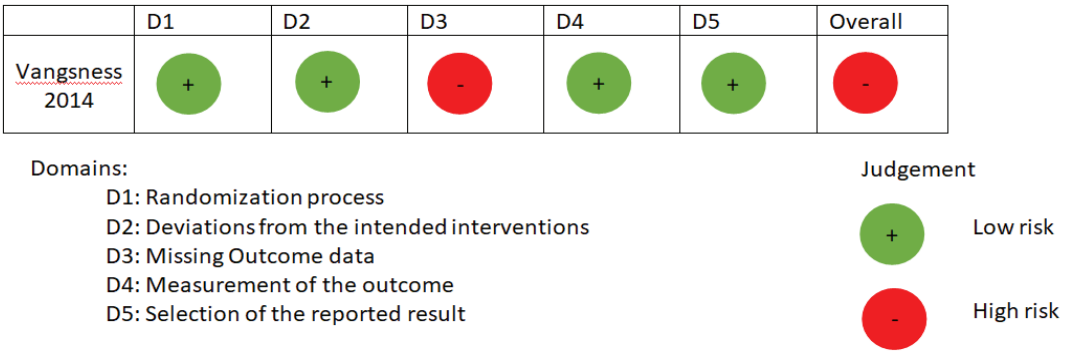
Included Studies: A systematic search of electronic databases and manual screening of relevant literature yielded a total of 38650 citations. After an initial screening based on titles and abstracts and removing duplicates, 50 studies were identified as potentially eligible for full-text review. Following a detailed assessment against the inclusion and exclusion criteria, only one study could be included in the final analysis.[2]

The single included study investigated the safety and effectiveness of intra-articular injections of human mesenchymal stem cells for tissue restoration and prevention of degenerative changes in the knee. The study included 55 patients who underwent partial medial meniscectomy, and they were randomized into three groups: one receiving a low dose of 50 million allogeneic mesenchymal stem cells (Group A), another receiving a higher dose of 150 million cells (Group B), and a control group receiving a sodium hyaluronate vehicle.

Critical outcomes reviewed and their MCID:

S. No	Outcome reviewed	What does it measure?	MCID decided by the GDG
1.	Visual Analog Scale (VAS) Range: 0-100 Higher score is worse	Validated measure for measuring intensity of pain	Absolute change of VAS score by 20points
2.	Lysholm Knee Scale Score (LKSS) Range:0-100 Higher score is better	Patient-reported outcome measure used to evaluate the functional status of the knee joint.	Absolute change of LKSS by 20 points
3.	SAEs	Serious Adverse Events	

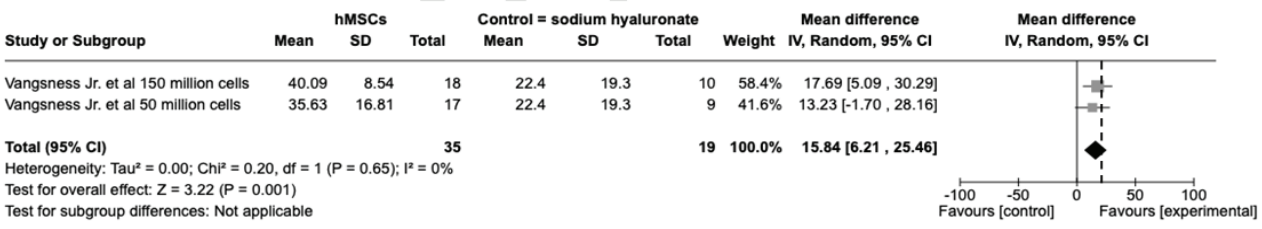
Risk of Bias assessment:



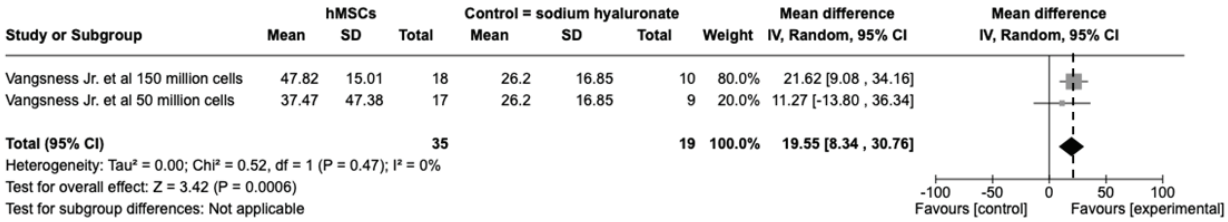
Desirable Effects (Dotted line represents MCID)**:**

1. VAS: Evidence from one trial, with a total of 54participants, reporting the VAS showed a mean difference in pain reduction of 15.84 (95% CI: 6.21 to 25.46) in the stem cell transplantation arm as compared to those on usual care at the end of six months and a mean reduction of 19.55 (95% CI: 8.34 to 30.76) at the end of 12 months. There seems to be a decrease in pain, which does not cross the MCID of 20. Therefore, the reduction in pain, though statistically significant, is unimportant clinically at both time points.

1.1 Forest plot showing the effect of stem cell therapy on reduction in pain as compared to usual care: 6 months

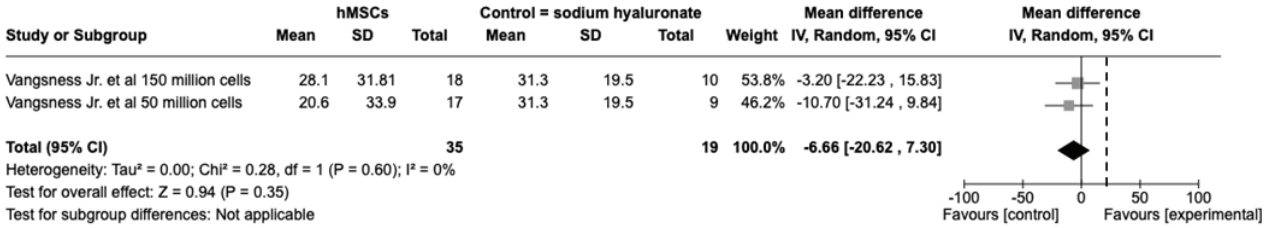


1.2 Forest plot showing the effect of stem cell therapy on reduction in pain as compared to usual care: 12 months

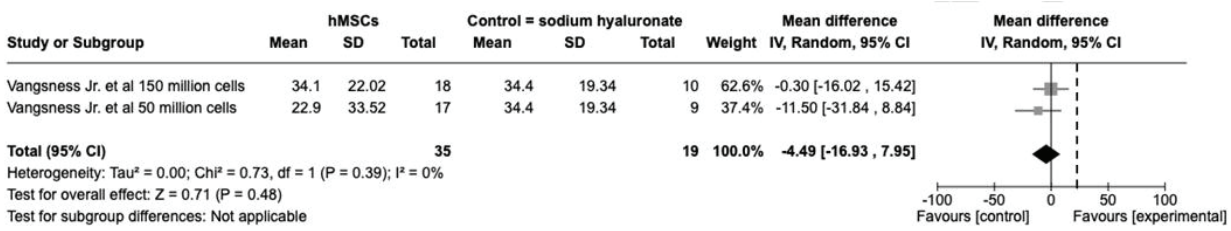


2. Lysholm Knee Scale Score: Evidence from one trial, with a total of 54 participants reporting the Lysholm Knee Scale score showed a mean difference of -6.66 (95% CI -20.62 to 7.30) in the stem cell transplantation arm in comparison to usual care at the end of six months and -4.49 (95% CI -16.93 to 7.95) at the end of 12 months. The differences were statistically non-significant.

2.1 Forest plot showing the effect of stem cell therapy on functional improvement as compared to usual care: 6 months



2.2 Forest plot showing the effect of stem cell therapy on functional improvement as compared to usual care: 12 months



Undesirable effects:

The single trial reported nine serious adverse events in eight participants which were deemed by the blinded investigators as unlikely to have been related to the investigational agent. The SAEs in the stem cell therapy arm included acute myocardial infarction, ileus, femur fracture, fibula fracture, osteoarthritis, meniscus lesion. The SAEs in usual care arm included small intestinal obstruction and hand fracture. The evidence is insufficient to draw firm conclusions due to limited long term follow up of the trial.

SUMMARY OF FINDINGS:

Any Stem cell and product derived from stem cells compared to Usual Care in treatment of Meniscopathy/Meniscal Tear

Patient or population: Meniscopathy/Meniscal Tear
Setting: Tertiary care
Intervention: Stem cell therapy
Comparison: Usual care

Outcomes	Anticipated absolute effects*(95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	**Risk with Outcomes**				
Visual Analogue Scale (post scores) - At 6 months	-	MD 15.84 higher (6.21 higher to 25.46 higher)	-	54 (1 RCT)	⊕◯◯◯ Very Low[a,b,c]	
Visual Analogue Scale (post scores) - At 12 months	-	MD 19.55higher (8.34 higher to 30.76 higher)	-	54 (1RCT)	⊕◯◯◯ Very Low[a,b,c]	
Lysholm knee scale score- 6 months	-	MD 6.66 lower (20.62 lower to 7.30 higher)	-	54 (1 RCT)	⊕◯◯◯ Very Low[a,b,d]	
Lysholm knee scale score- 12 months	-	MD 4.49 lower (16.93 lower to 7.95 higher)	-	54 (1 RCT)	⊕◯◯◯ Very Low[a,b,d]	

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **MD:** mean difference; **RR:** risk ratio; **SMD:** standardized mean difference

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations
a. Downgraded by two levels for single study with high risk of bias
b. Single study was downgraded one level for inconsistency as it was inevaluable.
c. Downgraded one level for imprecision as 95 % CI crossed the minimum threshold value defined by MCID and OIS not met
d. Downgraded one level for imprecision as 95% CI crossed the line of null effect

GRADE EVIDENCE PROFILE

Any stem cell and product derived from stem cells compared to usual care in treatment of meniscal tear/ meniscopathy

Certainty assessment							Summary of findings				
							Study event rates (%)			Anticipated absolute effects	
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	With Usual Care/ Conventional Carein treatment of nonunion of bone	With Any Stem cell and product derived from stem cells	Relative effect (95% CI)	Risk with Usual Care/ Conventional Carein treatment of nonunion of bone	Risk difference with Any Stem cell and product derived from stem cells
Reduction in pain: Visual analog scale: 6 months											
54 (1 RCT)	Very Serious[a]	Inevaluable[b]	Not serious	Serious[c]	Inevaluable	⊕◯◯◯ Very Low	-	-	-	-	MD 15.84 higher (6.21 higher to 25.46 higher)
Reduction in pain: Visual analog scale: 12 months											
54 (1 RCT)	Very Serious[a]	Inevaluable[b]	Not serious	Serious[c]	Inevaluable	⊕◯◯◯ Very Low	-	-	-	-	MD 19.55 higher (8.34 higher to 30.76 higher)
Functional Assessment: Lysholm knee scale score: 6 months											
54 (1 RCT)	Very Serious[a]	Inevaluable[b]	Not serious	Serious[d]	Inevaluable	⊕◯◯◯ Very Low	-	-	-	-	MD 6.66 lower (20.62 lower to 7.30 higher)
Functional Assessment: Lysholm knee scale score: 12 months											
54 (1 RCT)	Serious[a]	Inevaluable[b]	Not serious	Serious[d]	Inevaluable	⊕◯◯◯ Very Low	-	-	-	-	MD 4.49 lower (16.93 lower to 7.95 higher)

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations:

a. Downgraded by two levels for single study with high risk of bias.

b. Single study was downgraded one level for inconsistency as it was inevaluable.

c. Downgraded one level for imprecision as 95 % CI crossed the minimum threshold value defined by MCID and OIS not met

d. Downgraded one level for imprecision as 95% CI crossed the line of null effect.

D. SUMMARY OF JUDGEMENTS:

The summary of the final judgments made by the GDG after careful consideration of the summary of evidence is tabulated below:

Desirable Effects	Trivial*
Undesirable Effects	Varies**
Certainty of evidence	Very low
Values	Probably no important uncertainty or variability
Balance of effects	Does not favor either the intervention or the comparison
Resources required	Large costs***
Certainty of evidence of required resources	Moderate
Cost effectiveness	Probably favors the comparison
Equity	Probably reduced
Acceptability	Probably yes
Feasibility	Probably yes
Recommendations: Stem cell therapy is **not recommended** in routine practice for the treatment of meniscal tear/meniscopathy. It may be used only in the context of rigorously conducted randomized controlled trials.	

***** This judgment was made as there is very low certainty evidence of trivial reduction in pain and no improvement in function.

** This judgment was made as the undesirable effects are variable and heterogenous.

*** The committee opined that stem cell treatment is associated with large costs.

E. CAVEATS IN EXISTING EVIDENCE:

The GDG opined that the existing evidence had the following caveats:

1. Lack of sufficient number of RCTs with low risk of bias.
2. Small number of participants and/or events in the included trial.
3. Limited long-term follow-up.
4. Lack of cost effectiveness data.

REFERENCES:

1. Patil SS, Shekhar A, Tapasvi SR. Meniscal Preservation is Important for the Knee Joint. Indian J Orthop. 2017 Sep-Oct;51(5):576-587. doi: 10.4103/orthoIJOrtho_247_17. PMID: 28966381; PMCID: PMC5609379.
2. Vangsness CT, Farr J, Boyd J, Dellaero DT, Mills CR, LeRoux-Williams M. Adult Human Mesenchymal Stem Cells Delivered via Intra-Articular Injection to the Knee Following Partial Medial Meniscectomy: A Randomized, Double-Blind, Controlled Study. J Bone Jt Surg. 2014 Jan 15; 96(2):90–8.

III. PRIORITY AREAS FOR FUTURE RESEARCH

Stem cell therapy is a rapidly growing field with significant potential, but continued research is needed to optimize stem cell types, delivery methods, and clinical outcomes. It is essential to adopt an evidence-based approach in the development of these regenerative therapies, ensuring that the best available evidence is used to evaluate their true effectiveness and safety. Currently, most available evidence is of very low certainty.

Based on the assessment of evidence (clinically important difference, statistical significance and certainty of evidence) for the safety and efficacy of stem cell therapy in the included orthopedic conditions, priority areas for future research were identified and are as follows:

- Osteoarthritis: Some outcomes almost reach clinically important effects, but the certainty of this evidence is very low. Therefore, new rigorously designed large studies with appropriate type of stem cell therapy are needed as a priority.

- Meniscopathy/Meniscal injury: One study shows clinically important effect in one outcome but the certainty of evidence is very low. Based on the limited evidence, research should be encouraged.

Further studies are required to demonstrate and establish the mechanism of action of stem cell therapy and optimize selection of stem cell type & route of administration through well designed preclinical studies and large multicenter RCTs with adequate long-term follow up. In addition, primary research to understand the values and preferences of Indian patients as well as studies on cost effectiveness of stem cell therapy is also encouraged.

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IV. ANNEXURES

Annexure 1: CONTRIBUTORS

STEERING GROUP:

Dr. Rajiv Bahl, Secretary Department of Health Research (DHR) and DG, Indian Council of Medical Research (ICMR)- Chairman
Dr. Atul Goel, Director, Directorate General of Health Services (DGHS), New Delhi -Co-chairman
Dr. Anil Kumar, Additional Director General, Dte GHS, New Delhi
Dr. VG Somani, Joints Drug Controller, The Central Drugs Standard Control Organization (CDSCO), New Delhi
Dr. Rubina Bose, Deputy Drugs Controller Central Drugs Standard Control Organization (CDSCO), New Delhi
Dr. Rajan Kapoor, Sr. Consultant, Army Hospital R&R, New Delhi
Dr. Kavita Gaur, Assistant Professor, Lady Hardinge Medical College (LHMC), New Delhi
Dr. Pramit Ghosh, Scientist-E & Officer on Special Duty, Office of DG, ICMR Hqrs, New Delhi
Dr. Varsha Dalal, Scientist-D, DHR-ICMR, New Delhi
Dr. Siddharth Kapahtia, Scientist-D, DHR-ICMR, New Delhi
Dr. Hemlata, Scientist-D, Discovery Division, ICMR Hqrs, New Delhi

GUIDELINE DEVELOPMENT GROUP:

Dr. Kameshwar Prasad, Fortis Flt Lt Rajan Dhall Hospital, Vasant Kunj, New Delhi - Methodologist
Dr. Jeeva Sankar Mari, AIIMS, New Delhi- Methodologist
Dr. Rakesh Lodha, AIIMS, New Delhi- Methodologist
Dr. Anil Gurtoo, Lady Hardinge Medical College (LHMC), New Delhi
Dr. Ranjan Das, All India Institute of Hygiene & Public Health, Kolkata
Dr. Shankar Prinja, Post Graduate Institute of Medical Education & Research, Chandigarh
Dr. Roli Mathur, Indian Council of Medical Research (ICMR) Headquarters, New Delhi
Dr. Vikram Gota, Advanced Centre for Treatment, Research and Education in Cancer (ACTREC), Mumbai
Dr. Rama Baru, Jawaharlal Nehru University, New Delhi
Dr. Priya Parmar, India Cancer Society, New Delhi
Ms. Manisha Bhattacharya, Mental Health Foundation, Kolkata

Subject Experts

Stem cells:

Dr. Anurag Aggarwal, Trivedi School of Biosciences, Ashoka University, Sonipat, Haryana
Dr. Alok Srivastava, Christian Medical College, Vellore
Dr. Sujata Mohanty, AIIMS, New Delhi
Dr. Maneesha Inamdar, Institute for Stem Cell Science and Regenerative Medicine, Bengaluru
Dr. Anupam Kumar, Institute of Liver and Biliary Sciences, New Delhi

Dr. Naresh K, Sree Chitra Tirunal Institute for Medical Sciences and Technology (SCTIMST), Kerala

Orthopedics:

Dr. Sumit Sural, Maulana Azad Medical College, New Delhi
Dr. Raj Bahadur, Regional Spinal Injury Centre, Punjab
Dr. Mihir Patel, King Edward Memorial (KEM) Hospital, Mumbai
Dr. Ravi Mittal, AIIMS, New Delhi
Dr. Anil Kumar Jain, Ex. University College of Medical Sciences, New Delhi
Dr. Mathew Varghese, St. Stephens Hospital, New Delhi

Systematic Review Teams:

Osteoarthritis:

Dr. Surjit Singh, Department of Pharmacology, AIIMS, Jodhpur, Rajasthan,
Dr. Shoban Babu Varthya, Department of Pharmacology, AIIMS, Jodhpur, Rajasthan, Muhammed
Dr. Aaqib Shamim, Department of Pharmacology, AIIMS, Jodhpur, Rajasthan
Dr. Aswini Saravanan, Department of Pharmacology, AIIMS, Jodhpur, Rajasthan
Dr. Krishna Tiwari, Department of Pharmacology, AIIMS, Jodhpur, Rajasthan
Dr. Isha Yadav, Department of Pharmacology, AIIMS, Jodhpur, Rajasthan
Dr. Rakesh Dodiya, Department of Pharmacology, AIIMS, Jodhpur, Rajasthan
Dr. Abhishek Anil, Department of Pharmacology, AIIMS, Jodhpur, Rajasthan
Dr. Divesh Jalan, Department of Dermatology, Venereology and Leprology, PGIMER, Chandigarh,
Dr. Ankita Chugh, Department of Dentistry, AIIMS, Jodhpur, Rajasthan
Dr. Vinay Kumar Chugh, Department of Dentistry, AIIMS, Jodhpur, Rajasthan
Dr. Pradeep Dwivedi, Department of Pharmacology, AIIMS, Jodhpur, Rajasthan

Avascular necrosis of hip:

Dr. Dipika Bansal, Clinical Research Unit, Department of Pharmacy Practice, National Institute of Pharmaceutical Education and Research, Mohali, Punjab
Dr. Siddharth Sharma, Department of Orthopedics, PGIMER, Chandigarh
Dr. Amit Kondal, Department of Pharmacy Practice, National Institute of Pharmaceutical Education and Research, Mohali, Punjab
Mr. Saroj Kundan Bharti, NIPER, Mohali
Ms. Mamidi Niveditha, NIPER, Mohali
Mr. Mohammed Safeer VS (PhD scholar), NIPER, Mohali
Ms. Sai Roopa Kasimisetty (M. Pharm), NIPER, Mohali

Cartilage Defects:

Dr. Siddhartha Sharma, Department of Orthopedics, PGIMER, Chandigarh
Dr. Ankit Dadra, Department of Orthopedics, PGIMER, Chandigarh

Dr. Prasoon Kumar, Department of Orthopedics, PGIMER, Chandigarh
Dr. Riddhi Gohil, Department of Orthopedics, PGIMER, Chandigarh
Dr. Ashima
Dr. Sandeep Patel, Department of Orthopedics, PGIMER, Chandigarh
Dr. Sameer Aggarwal, Department of Orthopedics, PGIMER, Chandigarh
Dr. Mandeep S. Dhillon, Department of Orthopedics, PGIMER, Chandigarh

Tendinopathy:

Dr. Anand Srinivasan, Department of Pharmacology, AIIMS, Bhubaneswar
Dr. Rituparna Maiti, Department of Pharmacology, AIIMS, Bhubaneswar
Dr. Sujit Kumar Tripathy, Department of Orthopedics, AIIMS, Bhubaneswar
Dr. Somnath Mukherjee, Department of Transfusion Medicine & blood centre, AIIMS, Bhubaneswar
Dr. Archana Mishra, Department of Pharmacology, AIIMS, Bhubaneswar

Non-union of bone:

Dr. Phulen Sarma, Department of Pharmacology, AIIMS Guwahati
Dr. Anusuya Bhattacharyya, Department of Ophthalmology, AIIMS Guwahati
Ms. Hardeep Kaur, PGIMER, Chandigarh
Dr. Kashif Ahmed, Department of Orthopedics, AIIMS Guwahati
Dr. Richard Kirubakaran, Lead Epidemiologist, 3 analytics, Tamil Nadu, India
Prof. (Dr.) Ashok Puranik, Dept. of Orthopaedics, and Executive Director, AIIMS Guwahati
Prof. Jatin Sarma, Dept. of Biotechnology, Bodoland University, Assam

Meniscopathy:

Dr. Tarun Goyal, Department of Orthopaedics, AIIMS Bathinda
Dr. Shashank Paliwal, Department of Anaesthesia, AIIMS Bathinda
Dr. Pankaj K Sharma, Department of Orthopaedics, AIIMS Bathinda
Dr. Lakshmana Das, Department of Orthopaedics, AIIMS Bathinda

EXTERNAL REVIEW:

Dr. Kiran Mukhopadhyay, N R S Medical College & Hospital, Kolkata
Dr. Rajagopalan Iyer, Mahatma Gandhi Medical College and Research Institute, Puducherry

ICMR-DHR SECRETARIAT:

Dr. Pramit Ghosh, Scientist-E & Officer on Special Duty, Office of DG, ICMR Hqrs
Dr. Varsha Dalal, Scientist-D, DHR-ICMR, New Delhi
Dr. Siddharth Kapahtia, Scientist-D, DHR-ICMR, New Delhi
Dr. Hemlata, Scientist-D, Division of Basic Medical Sciences, ICMR Hqrs, New Delhi
Dr. Dimpi Vohra, Project Research Scientist-II
Dr. Ritu Jain, Project Research Scientist-II
Ms. Ritu Panthri, Executive Assistant

Annexure 2: DECLARATION OF INTEREST (DoI)

Name	Declaration Interest (s)	Management of conflict(s) of interest
Dr. Sushama Nagarkar, Patient representative from Yash Charitable Trust	Declared that the outcome of the meeting or work may affect the interests of people with whom she has substantial personal/professional interests.	The steering group observed this as a potential conflict of interest and therefore decided against her inclusion in the GDG.
Dr. Kameshwar Prasad, Fortis Flt Lt Rajan Dhall Hospital, Vasant Kunj, New Delhi	None declared	Not applicable
Dr. Jeeva Sankar Mari, AIIMS (AIIMS), New Delhi	None declared	Not applicable
Dr. Rakesh Lodha, AIIMS, New Delhi	None declared	Not applicable
Dr. Anil Gurtoo, Lady Hardinge Medical College (LHMC), New Delhi	None declared	Not applicable
Dr. Ranjan Das, All India Institute of Hygiene & Public Health, Kolkata	None declared	Not applicable
Dr. Shankar Prinja, Post Graduate Institute of Medical Education & Research, Chandigarh	None declared	Not applicable
Dr. Roli Mathur, Indian Council of Medical Research (ICMR) Headquarters, New Delhi	None declared	Not applicable
Dr. Vikram Gota, Advanced Centre for Treatment, Research and Education in Cancer (ACTREC), Mumbai	None declared	Not applicable
Dr. Rama Baru, Jawaharlal Nehru University, New Delhi	None declared	Not applicable
Dr. Priya Parmar, India Cancer Society, New Delhi	None declared	Not applicable
Ms. Manisha Bhattacharya, Mental Health Foundation, Kolkata	None declared	Not applicable
Dr. Anurag Aggarwal, Trivedi School of Biosciences, Ashoka University, Sonipat, Haryana	None declared	Not applicable
Dr. Alok Srivastava, Christian Medical College, Vellore	None declared	Not applicable
Dr. Sujata Mohanty, AIIMS, New Delhi	She declared that she is a member of the Subject Expert Committees of CDSCO & NMC.	The Steering Group did not see it as a potential CoI.
Dr. Maneesha Inamdar, Institute for Stem Cell Science and Regenerative Medicine, Bengaluru	None declared	Not applicable

Dr. Anupam Kumar, Institute of Liver and Biliary Sciences, New Delhi	None declared	Not applicable
Dr. Naresh K, Sree Chitra Tirunal Institute for Medical Sciences and Technology (SCTIMST), Kerala	None declared	Not applicable
Dr. Sumit Sural, Maulana Azad Medical College, New Delhi	None declared	Not applicable
Dr. Raj Bahadur, Regional Spinal Injury Centre, Punjab	None declared	Not applicable
Dr. Mihir Patel, King Edward Memorial (KEM)Hospital, Mumbai	None declared	Not applicable
Dr. Ravi Mittal, AIIMS, New Delhi	None declared	Not applicable
Dr. Anil Kumar Jain, Ex. University College of Medical Sciences, New Delhi	None declared	Not applicable
Dr. Mathew Varghese, St. Stephens Hospital, New Delhi	None declared	Not applicable
Dr. Kiran Mukhopadhyay, N R S Medical College & Hospital, Kolkata	None declared	Not applicable
Dr. Rajagopalan Iyer, Mahatma Gandhi Medical College and Research Institute, Puducherry	None declared	Not applicable

CENTRE FOR EVIDENCE-BASED GUIDELINES

The Centre for Evidence based Guidelines was established in February 2023 at the Department of Health Research in collaboration with DGHS, NHSRC, various program divisions of DoHFW, and other stakeholders under the umbrella of Ministry of Health & Family Welfare (MoHFW). The main mandate is to develop evidence-based guidelines by systematically reviewing available evidence and applying the GRADE methodology to assess the certainty of evidence. In addition, the centre conducts capacity-building activities, including workshops on systematic reviews and the GRADE approach, as well as training sessions to enhance the competency of Guideline Development Group (GDG) and other stakeholders in guideline development methodologies. Through these initiatives, it ensures that healthcare decisions are informed by the best available evidence, ultimately improving patient care and health outcomes. In September 2024, the Centre established Technical Resource Centres (TRCs) across the country to assist in evidence synthesis by conducting systematic reviews and meta-analyses, thereby enabling consistent, high-quality guideline development.

Our Team

Smt. Anu Nagar, Joint Secretary, DHR
Sh. BB Senapati, Deputy Secretary, DHR
Dr. Tushar Karmakar, Deputy Secretary, DHR
Dr. Roopa Hariprasad, Scientist F
Dr. Chanchal Goyal, Scientist E
Dr. Vikas Dhikav, Scientist E
Dr. Varsha Dalal, Scientist D
Dr. Siddharth Kapahtia, Scientist D
Dr. Vikas Dhiman, Scientist C
Dr. Dimpi Vohra, Project Research Scientist-II
Dr. Ritu Jain, Project Research Scientist-II
Ms. Neeti Pandey, Project Research Scientist-II
Dr. Vikram Pal Gandhi, Project Research Scientist-II
Mr. Hitesh Tiwari, Project Research Scientist-II
Dr. Rajeeve L Pillai, Project Manager
Mr. S. P. Sinha, Finance Manager
Ms. Ritu Panthri, Executive Assistant
Ms. Madhu Bala, Executive Assistant
Mr. Haris Chandra Sahoo, MTS
Mr. Rohit Ratra, MTS