Evidence-based Guidelines for the use of Stem Cell Therapy

Orthopedic Conditions



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Department of Health Research Directorate General of Health Services

Ministry of Health & Family Welfare Government of India



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.

ICMR-DHR, DGHS and its scientists, members of the Steering Group, GDG and systematic review teams disclaim all liability for the accuracy or completeness of the guideline. The team further disclaims all liability for any damages whatsoever (direct or indirect) arising out of the use or inability to use the information and procedures mentioned in this guideline. New studies in the future may lead to a revision in the existing recommendations. All MoHFW guidelines are subject to regular review and may be updated or withdrawn.

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.

Rain Bree

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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

ADL:Activities of Daily LivingADMSCs:Adipose tissue-Derived Mesenchymal Stem CellsAEs:Adverse EventsARCO:Association Research Circulation OsseousASES:American Shoulder and Elbow SurgeonAVN:Avascular NecrosisBMA:Bone Marrow AspirationBMAC:Bone Marrow Mono Nuclear CellBMMSC:Bone Marrow Mono Nuclear CellCD:Core DecompressionCI:Confidence IntervalCPGA:Collagen/ Polyglycolic AcidDol:Declaration of InterestEtD:Evidence to DecisionFCD:Food and Drug AdministrationCDG:Guideline Development GroupGDT:Guideline Development ToolGRADE:Grading of Recommentations, Assessment, Development and EvaluationHA:Hyaluronic AcidHHS:Hurnis Hip ScorehMSCs:Iterrational Knee Documentation CommitteeKL:Kelgren-LawrenceKOOS:Knee Injury and Osteoarthritis Outcome ScoreLKSS:Uysins ScoreMA:MesandysinsGCD:OsteoarthritisON:OsteoarthritisONS:MesandysinsGDG:OsteoarthritisGDG:OsteoarthritisGRADE:International Knee CellsIKDC: <th></th> <th></th> <th></th>			
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RR:Relative RiskSAEs:Severe Adverse EventsSCT:Stem Cell TherapySD:Standard DeviationSDSC:Synovium Derived Stem Cell	RoB	:	Risk of Bias
SCT:Stem Cell TherapySD:Standard Deviation	RR	:	Relative Risk
SD : Standard Deviation	SAEs	:	Severe Adverse Events
	SCT	:	Stem Cell Therapy
SDSC : Synovium Derived Stem Cell	SD	:	Standard Deviation
	SDSC	:	Synovium Derived Stem Cell
SE : Standard Error	SE	:	Standard Error
SMD : Standardized Mean Difference	SMD	:	Standardized Mean Difference
SPR : Sports and Physical Recreation	SPR	:	Sports and Physical Recreation
SR : Systematic Review	SR	:	Systematic Review
SVF : Stromal Vascular Fraction	SVF	:	Stromal Vascular Fraction
THR : Total Hip Replacement	THR	:	Total Hip Replacement
UCMSCs : Umbilical Cord-Derived Mesenchymal Stem Cells	UCMSCs	:	Umbilical Cord-Derived Mesenchymal Stem Cells
VAS : Visual Analog Scale	VAS	:	Visual Analog Scale
WHO : World Health Organization	WHO	:	World Health Organization
WOMAC : Western Ontario and Macmaster Universities Arthritis Index	WOMAC	:	Western Ontario and Macmaster Universities Arthritis Index
YLD : Years Lived with Disability	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.

Evidence-based Guidelines for the use of Stem Cell Therapy: Orthopedic Conditions

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 <i>*It may be used only in the</i> <i>context of rigorously conducted</i> <i>randomized controlled trials.</i>	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 <i>#It may be used only in the</i> <i>context of rigorously conducted</i> <i>randomized controlled trials.</i>	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 <u>not</u> <u>recommended</u> in routine clinical practice for the treatment of cartilage defects. Strength: Conditional [#] Certainty of Evidence: Very Low <i>#It may be used only in the</i> <i>context of rigorously conducted</i> <i>randomized controlled trials.</i>	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 <u>not</u> <u>recommended</u> in routine clinical practice for the treatment of tendinopathy. Strength: Conditional [#] Certainty of Evidence: Very Low <i>#It may be used only in the</i> <i>context of rigorously conducted</i> <i>randomized controlled trials.</i>	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 <i>#It may be used only in the</i> <i>context of rigorously conducted</i> <i>randomized controlled trials.</i>	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 <u>not</u> <u>recommended</u> in routine clinical practice for the treatment of meniscopathy/ meniscal tear. Strength: Conditional [#] Certainty of Evidence: Very Low <i>#It may be used only in the</i> <i>context of rigorously conducted</i> <i>randomized controlled trials.</i>	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.

Evidence-based Guidelines for the use of Stem Cell Therapy: Orthopedic Conditions

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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 WHO¹

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 postrandomization
- 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.

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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.	WesternOntarioandMcMasterUniversitiesOsteoarthritisIndex(WOMAC)- OverallRange: 0-100Higher 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.	KneeInjuryandOsteoarthritisOutcomeScore (KOOS)••Pain•Symptom•Quality of Life•Activities of Dailyliving••SportsandRecreationRange: 0-100 for each of thesubscalesUisher again 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.	Higher score is better SAEs	Serious adverse events	-

Risk of bias assessment:

					as domains		
_		D1	D2	D3	D4	D5	Overall
	Baria et al 2022		+	+		+	
	Chen et al 2021	+	+	+		+	
	Emadedin et al 2018	+	+	+	+	+	+
	Freitag et al 2019		+			+	+
	Gupta et al 2016	+	+	+	+	+	+
	Gupta et al 2023	+	+	+	+	+	+
	Ho et al 2022	+	+	+		+	
	Hong et al 2018	+	+	+	+	+	+
	Kaszynski et al 2022	+	+	+	+	+	+
	Kim et al 2022	+	+	+	+	+	+
	Lee et al 2019	+	+	+	+	+	+
	Lu et al 2019	+	+	+	+	+	+
	Matas et al 2019	+	$\overline{+}$	+	$\overline{+}$	(+)	+
ĺ	Sadri et al 2023	+	$\overline{+}$	+	$\overline{+}$	+	+
	Soltani et al 2018		+	+	+	+	
	Wang et al 2016		+	+	X	+	X
	Zhang S et al 2022	+	+	+	+	+	+
	Zhang Y et al 2022	+	(+)	$\overline{+}$	+	+	+
	Goncars et al 2017	_	+	$\overline{+}$	×	+	X
	Lamo Espinosa et al 2020	+	+	$\overline{+}$	×	+	X
	Wong et al 2013	+	+	$\overline{+}$	X	$\overline{+}$	++
	Hernigou et al 2020	—	(+)	$\overline{+}$	+	$\overline{+}$	+
	Kuah et al 2018	+	—	$\overline{+}$	(+)	$\overline{+}$	(+)
	Sadat–Ali et al 2021	×	$\overline{+}$	$\overline{+}$		$\overline{+}$	
	Wakitani et al 2002		+	+		$\overline{+}$	X
F	Zhou et al 2021	+	$\overline{+}$	+	—	$\overline{+}$	+
F	Garay–Mendoza et al 2017		$\overline{+}$	+		$\overline{+}$	
┝	Vega et al 2015	+	(+)	(+)	—	H	
┝	Bastos et al 2020	- A		H		H	\mathbf{H}
┝	Garza et al 2020	- `		(+)		H	\mathbf{H}
┝	Varma et al 2010						
F	Zaffagnini et al 2022	+		$\overline{+}$		$\overline{+}$	
-	Schweich–Adami et al 2022	$\overline{+}$		+			
	Vangsness et al 2014	$\overline{+}$		$\overline{+}$		H	
	Dulic et al 2021						
	Hernigou et al 2018						
	Lamo Espinosa et al 2016						
F	Lamo Espinosa et al 2018						
	Shapiro et al 2016	Domains:					dgement

VAS, WOMAC, KOOS, and other scores Risk of bias domains

D3: Bias due to missing outcome data. D4: Bias in measurement of the outcome. D5: Bias in selection of the reported result.

 Some concerns + Low

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

	Expe	erimen	tal	C	Control			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
4.1.1 Allogenic									<u>.</u>
Gupta 2016	4.66	4.11	10	4.05	3.71	10	4.3%	0.61 [-2.82, 4.04]	
Gupta 2023	3.35	1.73	73	6.11	2.18	73	14.7%	-2.76 [-3.40, -2.12]	-
Matas 2019	1.33	0.84	9	2.21	0.98	8	13.6%	-0.88 [-1.75, -0.01]	-
Sadri 2023	3.25	1.58	18	7.47	1.54	18	12.9%	-4.22 [-5.24, -3.20]	i
Vega 2015	3.3	2.32	15	5.1	3.1	15	8.5%	-1.80 [-3.76, 0.16]	
Subtotal (95% CI)			125			124	54.0%	-2.14 [-3.53, -0.75]	◆
Heterogeneity: Tau ² =	1.90; Chi	2 = 28.	39, df =	4 (P <	0.000	1); l ² = 1	86%		i
Test for overall effect: 2	Z = 3.01	(P = 0.	003)						
4.1.2 Autologous									i I
Kaszynski 2022	2.8	2.2	20	3	2.2	20	11.2%	-0.20 [-1.56, 1.16]	
Lamo Espinoza 2016	2	2.96	10	4	1.48	10	8.1%	-2.00 [-4.05, 0.05]	
Lamo-Espinoza 2020	3.5	2.5	24	4.5	2.2	26	11.5%	-1.00 [-2.31, 0.31]	+++
Zhang S 2022	1.69	1.63	51	3.42	0.99	64	15.1%	-1.73 [-2.24, -1.22]	t
Subtotal (95% CI)			105			120	46.0%	-1.29 [-2.04, -0.54]	
Heterogeneity: Tau ² = 1	0.24; Chi	² = 5.0	6, df =	3(P = 0).17); F	= 41%			
Test for overall effect: 2	Z = 3.38	(P = 0.	0007)						
Total (95% CI)			230			244	100.0%	-1.76 [-2.59, -0.93]	•
Heterogeneity: Tau ² =	1.12; Chi	² = 42.	22, df =	8 (P <	0.0000	01); I ² =	81%		
Test for overall effect:				<u> </u>		<u> </u>			-10 -5 0 5 10 Favours [experimental] Favours [control]
Test for subgroup diffe		·	1. C. 2. C. 5	= 1 (P =	= 0.30)	, l ² = 8.	6%		Favours [experimental] Favours [control]

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

	Expe	Control				Mean Difference	Mean Difference		
Study or Subgroup	Mean SD Total			Mean SD Total		Weight	IV, Random, 95% Cl	IV, Random, 95% CI	
4.4.1 Allogenic									
Chen 2021	-3.34	2.78	15	-2.5	2.58	8	20.5%	-0.84 [-3.11, 1.43]	
Kuah 2018 Subtotal (95% CI)	-2.11	0.51	16 31	-0.93	1.1	4	39.0% 59.5%	-1.18 [-2.29, -0.07] -1.11 [-2.11, -0.12]	
Heterogeneity: Tau ² =	0.00; Cł	ni² = 0.		1 (P =	0.79);			-1.11[-2.11, -0.12]	•
Test for overall effect:	Z = 2.20	(P=0	0.03)						
4.4.2 Autologous									
Zaffagnini 2022 Subtotal (95% CI)	-1.3	2.4	49 49	-1.9	2.8	50 50	40.5% 40.5%	0.60 [-0.43, 1.63] 0.60 [-0.43, 1.63]	
Heterogeneity: Not ap Test for overall effect:		i (P = 0	0.25)						
Total (95% CI)			80			62	100.0%	-0.39 [-1.70, 0.92]	•
Heterogeneity: Tau ² = Test for overall effect:				2 (P =	0.06);	l ² = 64	%		-1050510
Test for subgroup diffe				f = 1 (P)	= 0.02	2), $ ^2 = {$	31.9%		Favours [experimental] Favours [control]

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)

	Experimental			Control				Mean Difference	M	ean Difference	
Study or Subgroup	Mean	Mean SD Total Mean SD Tota		Total	Weight	IV, Fixed, 95% C	t N	/, Fixed, 95% Cl	, 95% Cl		
Gupta 2016	1,179.4	720.3	10	1,075	441.1	10	6.4%	104.40 [-419.10, 627.90]			
Gupta 2023	741.3	346.13	73	1,363.5	488.62	73	93.6%	-622.20 [-759.56, -484.84]			
Total (95% CI)			83			83	100.0%	-575.40 [-708.26, -442.53]	-		
Heterogeneity: Chi ² =	6.92, df =	1 (P = 0.	009); l²	= 86%					-1000 -500	0 500	1000
Test for overall effect:	Z = 8.49 (P < 0.000	001)						Favours [experim		1000

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

	Exp	eriment	al	C	ontrol			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% Cl	I IV, Random, 95% CI
Chen 2021	-23.39	19.84	15	-15.75	13.4	8	61.0%	-7.64 [-21.32, 6.04]	
Ho 2022	-10.4	17.41	10	8.33	20.33	9	39.0%	-18.73 [-35.84, -1.62]	
Total (95% CI)			25			17	100.0%	-11.96 [-22.65, -1.28]	-
Heterogeneity: Tau ² =	0.00; Ch	i ² = 0.98	8, df = 1	(P = 0.3	32); l² =	0%			-50 -25 0 25 50
Test for overall effect:	Z = 2.19	(P = 0.0)3)						Favours [experimental] Favours [control]

Subgroup analysis

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



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

	Expe	eriment	tal	(Control			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% C	I IV, Random, 95% CI
5.4.1 AD MSC									1
Kaszynski 2022	83.6	11	20	83.8	17.3	20	12.7%	-0.20 [-9.18, 8.78]	
Lu 2019	22.04	18.12	26	26.28	16.71	26	11.6%	-4.24 [-13.71, 5.23]	·
Zhou 2021 Subtotal (95% CI)	5.93	5.84	29 75	13.73	9.85	28 74	37.5% 61.8%	-7.80 [-12.02, -3.58] -5.65 [-9.93, -1.37]	 ◆
Heterogeneity: Tau ² = 3	3.04: Chi	² = 2.43	. df = 2	2 (P = 0.	30): l ² =	18%			
Test for overall effect: Z					,				
5.4.2 BM MSC									
Lamo Espinoza 2016	15.83	5.18	10	18.16	18.52	10	7.7%	-2.33 [-14.25, 9.59]	·
Lamo-Espinoza 2020	23	16.6	24	22.3		26	12.7%	0.70 [-8.30, 9.70]	i
Subtotal (95% CI)			34			36	20.4%	-0.40 [-7.58, 6.78]	
Heterogeneity: Tau ² = 0).00; Chi	² = 0.16	, df = 1	(P = 0.	69); l ² =	:0%			
Test for overall effect: Z				,	,.				
5.4.3 SVF									
Zhang S 2022	18.02	18.87	51	28.27	21.07	64	17.8%	-10.25 [-17.56, -2.94]	
Subtotal (95% CI)			51			64		-10.25 [-17.56, -2.94]	→
Heterogeneity: Not app	licable								
Test for overall effect: 2		(P = 0.0	06)						
Total (95% CI)			160			174	100.0%	-5.36 [-8.83, -1.88]	•
Heterogeneity: Tau ² = 3	3.75 [.] Chi	² = 6.21		i (P = 0	29): l ² =				
Test for overall effect: 2				, (i – 0,	20/11 -	10/0			-50 -25 0 25 50 Favours [experimental] Favours [control]

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

	Exp	eriment	tal	C	ontrol			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
6.1.1 Allogenic ADMS	C								
Sadri 2023	73.25	16.11	18	27	20.72	18	25.3%	46.25 [34.13, 58.37]	
Subtotal (95% CI)			18			18	25.3%	46.25 [34.13, 58.37]	
Heterogeneity: Not app	licable						1.0		
Test for overall effect: 2	Z = 7.48	(P < 0.	00001)						
6.1.2 Autologous BMI	MNC								
Goncars 2017	79.53	17.7	28	61.5	22.5	28	26.0%	18.03 [7.43, 28.63]	
Subtotal (95% CI)			28			28	26.0%	18.03 [7.43, 28.63]	•
Heterogeneity: Not app	licable								
Fest for overall effect: 2	Z = 3.33	(P = 0.	0009)						
6.1.3 Autologous BMI	MSC								
Bastos 2019	56.8	26.5	16	59.5	22.2	17	22.8%		
Subtotal (95% CI)			16			17	22.8%	-2.70 [-19.43, 14.03]	•
Heterogeneity: Not app	licable								
Fest for overall effect: 2	Z = 0.32	(P = 0.	75)						
5.1.4 Autologous ADM	MSC								
Freitag 2019	77.3	11.3	9	48.9	12.7	10	25.9%	28.40 [17.61, 39.19]	
Subtotal (95% CI)			9			10	25.9%	28.40 [17.61, 39.19]	▲
Heterogeneity: Not app	licable								
est for overall effect: 2	Z = 5.16	(P < 0.	00001)						
fotal (95% CI)			71			73	100.0%	23.14 [5.71, 40.56]	-
Heterogeneity: Tau ² = 2	274.43;	Chi ² = 2	24.35, 0	if = 3 (P	< 0.000	01); I² =	88%		-50 -25 0 25 50
Test for overall effect: 2		•							Favours [control] Favours [experimental]
lest for subgroup differ	rences:	$Chi^2 = 2$	24.35, 0	f = 3 (P	< 0.000	01), l ² =	87.7%		· · · · · · · · · · · · · · · · · · ·

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

	Experimental Control						Mean Difference	Mean Difference		
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI	
Zaffagnini 2022	11.4	16.4	48	12.6	18.7	50	100.0%	-1.20 [-8.16, 5.76]		
Total (95% CI)			48			50	100.0%	-1.20 [-8.16, 5.76]	•	
Heterogeneity: Not ap Test for overall effect:		(P = 0).74)						-50 -25 0 25 50 Favours [control] Favours [experimental]	

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

Expe	rimen	tal	Control				Mean Difference	Mean Difference		
Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI		
9.5	16.1	48	9.7	17.6	50	100.0%	-0.20 [-6.87, 6.47]	₽ (
		48			50	100.0%	-0.20 [-6.87, 6.47]	•		
plicable	/D = 0	05)						-50 -25 0 25 50 Favours (control) Favours (experimental)		
	Mean 9.5 plicable	Mean SD 9.5 16.1 Dlicable	9.5 16.1 48	Mean SD Total Mean 9.5 16.1 48 9.7 48 plicable	Mean SD Total Mean SD 9.5 16.1 48 9.7 17.6 48 plicable	Mean SD Total Mean SD Total 9.5 16.1 48 9.7 17.6 50 48 50 plicable 50	Mean SD Total Mean SD Total Weight 9.5 16.1 48 9.7 17.6 50 100.0% 48 50 100.0% 50 100.0%	Mean SD Total Mean SD Total Weight IV, Random, 95% CI 9.5 16.1 48 9.7 17.6 50 100.0% -0.20 [-6.87, 6.47] 48 50 100.0% -0.20 [-6.87, 6.47]		

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

	eriment	tal	c	ontrol			Mean Difference	Mean Difference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
8.3.1 Allogenic ADMS	с								
Sadri 2023	60.35	18.94	18	16.78	18.33	18	36.0%	43.57 [31.39, 55.75]	
Subtotal (95% CI)			18			18	36.0%	43.57 [31.39, 55.75]	: ◆
Heterogeneity: Not app	licable								
Test for overall effect: 2	2 = 7.01	(P < 0.	00001)						
0.2.2 Autologous DM	100								
8.3.3 Autologous BMM									_ i
Bastos 2019	40.2	25.9	16 16	32	29.3	17	30.0%	8.20 [-10.64, 27.04]	
Subtotal (95% CI)			16			17	30.0%	8.20 [-10.64, 27.04]	
Heterogeneity: Not app									
Test for overall effect: 2	2 = 0.85	(P = 0.	39)						
8.3.4 Autologous ADM	ISC								
Freitag 2019	61.8	13	9	33.9	18.9	10	34.0%	27.90 [13.43, 42.37]	1 <u>+</u>
Subtotal (95% CI)			9			10	34.0%	27.90 [13.43, 42.37]	•
Heterogeneity: Not app	licable								
Test for overall effect: 2	2 = 3.78	(P = 0.	0002)						
Total (95% CI)			43			45	100.0%	27.64 [8.45, 46.84]	
Heterogeneity: Tau ² = 2	227.57;	Chi ² = 9).89, df	= 2 (P =	= 0.007); I ² = 8	0%	_	
Test for overall effect: 2									-100 -50 0 50 100
Test for subgroup differ	ences:	Chi ² = 9	.89, df	= 2 (P =	= 0.007)), l² = 79	9.8%		Favours [control] Favours [experimental]

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

	Expe	rimen	tal	С	ontrol			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% Cl
Zaffagnini 2022	15.9	20.5	48	17.1	22.5	50	100.0%	-1.20 [-9.72, 7.32]	
Total (95% CI)			48			50	100.0%	-1.20 [-9.72, 7.32]	•
Heterogeneity: Not ap Test for overall effect:		(P = 0).78)						-100 -50 0 50 100 Favours [control] Favours [experimental]

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 not significant.

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

	Experimental			C	ontrol			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
8.4.1 Allogenic ADMSC	;								
Sadri 2023	78.1	15.8	18 18	32.89	20.8	18 18	34.1%		
Subtotal (95% CI)			10			10	34.170	45.21 [33.14, 57.28]	
Heterogeneity: Not appli									
Test for overall effect: Z	= 7.34	(P < 0	.00001)					
8.4.3 Autologous BMM	SC								
Bastos 2019	58.4	27.5	16	61.6	24.4	17	31.0%	-3.20 [-20.98, 14.58]	
Subtotal (95% CI)			16			17	31.0%	-3.20 [-20.98, 14.58]	
Heterogeneity: Not appli	cable								
Test for overall effect: Z	= 0.35	(P = 0	.72)						
8.4.4 Autologous ADM	sc								
Freitag 2019	84.3	9.4	9	60.7	13.5	10	34.9%	23.60 [13.22, 33.98]	
Subtotal (95% CI)			9			10	34.9%	23.60 [13.22, 33.98]	
Heterogeneity: Not appli	cable								
Test for overall effect: Z		(P < 0	.00001)					
Total (95% CI)			43			45	100.0%	22.67 [-1.27, 46.61]	
Heterogeneity: Tau ² = 39	99.34; (Chi ² =	20.24,	df = 2 (i	P < 0.0	0001); F	² = 90%	_	
Test for overall effect: Z	= 1.86	(P = 0	.06)						-50 -25 0 25 50 Favours [control] Favours [experimental
Test for subgroup differe	ences: (Chi ² =	20.24,	df = 2 (F	P < 0.0	001), F	² = 90.1%		Pavours (control) Pavours (experimental)

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

	Expe	rimen	tal	С	ontrol			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Zaffagnini 2022	9.3	20.1	48	14.6	21.2	50	100.0%	-5.30 [-13.48, 2.88]	
Total (95% CI)			48			50	100.0%	-5.30 [-13.48, 2.88]	•
Heterogeneity: Not ap Test for overall effect:		(P = 0	.20)						-50 -25 0 25 50 Favours [control] Favours [experimental]

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.

tudy or ubgroup		n cell Total	Sto Events	care Total	Weight	RR [95%	CI]	Serious adverse events
rogenitor SVF								
arza 2020	0	26	0	13	0.0%			
hang S 2022	0	56	0	70	0.0%			:
MMSC								
madedin 2018	0	19	0	24	0.0%			
upta 2016	1	10	2	10	18.3%	0.50 [0.05;	4.67]	B .
upta 2023	4	73	4	73	50.4%	1.00 [0.26;	3.85]	
o 2022	0	10	0	10	0.0%			
amo Espinoza 2016	0	20	0	10	0.0%			
am o Espinoza 2018	0	20	0	12	0.0%			
amo Espinoza 2020	0	28	0	28	0.0%			
atas 2019	0	20	0	8	0.0%			
hapiro 2016	0	25	0	25	0.0%			
ega 2015	0	15	0	15	0.0%			
Vong 2013	0	28	0	28	0.0%			
ooled estimate [REM]	5	268	6	243	68.8%	0.83 [0.26;	2.641	
eterogeneity: Tau ² = 0; Ch	i ² = 0.27,	df= 1	(P = 0.60); ² = 1	0.96	- /	-	
D MSC								
hen 2021	4	49	0	8	11.4%	1.55 [0.09; 2	26.18]	
rietag 2019	0	20	0	10	0.0%			
im 2022	0	13	0	13	0.0%			
uah 2018	0	16	0	4	0.0%			
ee 2019	0	12	0	12	0.0%			
u 2019	0	26	1	26	9.2%	0.33 [0.01;	7.82]	_
adri 2023	0	20	0	20	0.0%		-	
affagnini 2022	0	55	3	53	10.6%	0.14 [0.01;	2.601	₽
hou 2021	0	29	0	28	0.0%	. ,	-	
ooled estimate [REM]	4	240	4	174	31.2%	0.43 [0.08;	2.401	
eterogeneity: Tau ² = 0; Ch	i ² = 1.39,	df= 2						
MMNC								
oncars 2017	0	28	0	28	0.0%			
lacental MSC								
oltani 2018	0	10	0	10	0.0%			
ooled estimate [REM]	9	628	10	538	100.0%	0.68 [0.26;	1.77]	· · · · · · · · · · · · · · · · · · ·
							(0.01 0.1 1 10 1

Test for subgroup differences: $Chi^2 = 0.38$, df = 1 (P = 0.54) Subgroup analysis based on source (tissue) of stem cell

SUMMARY OF FINDINGS:

Stem cell therapy compared to usual care for osteoarthritis

Patient or population: Osteoarthritis Setting: Tertiary care

	Anticipated abs	Anticipated absolute effects*(95% Cl)			Certainty of the	
Outcomes	Risk with usual care	Risk with Stem cell therapy	Relative effect (95% CI)	No of participants (studies)	evidence (GRADE)	Comments
VAS 12 months- Post score		MD 1.76 lower (2.59 lower to 0.93 lower)	,	474 (9 RCTs)	⊕⊕⊖⊖ Lowab	
VAS 12 months- Change score		MD 0.39 lower (1.7 lower to 0.92 higher)	1	142 (3 RCTs)	⊕⊕⊖⊖ Lowac	
WOMAC 12 months- Post score		MD 8.74 lower (16.03 lower to 1.45 lower)		417 (9 RCTs)	⊕⊕⊖⊖ Lowab	
WOMAC 12 months- Change score		MD 11.96 lower (22.65 lower to 1.28 lower)	ı	42 (2 RCTs)	⊕⊖⊖⊖ Very lowade	
KOOS Pain 12 months- Post score		MD 23.14 higher (5.71 higher to 40.56 higher)		144 (4 RCTs)	⊕⊕⊖⊖ Loware	
KOOS Symptom 12 months- Post score		MD 28.07 higher (7.4 higher to 48.73 higher)	ı	88 (3 RCTs)	⊕⊕⊖⊖ Lowa.e	
KOOS QoL 12 months- Post score	ı	MD 27.64 higher (8.45 higher to 46.84 higher)	1	88 (3 RCTs)	⊕⊕⊖⊖ Lowae	

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Setting: Tertiary care Intervention: Stem cell therapy Comparison: Usual care Anticipated absolute effects*(95% CI) Risk with usual Risk with Stem cell Outcomes care MD 22.67 higher KOOS ADL 12 months- Post - (1.27 lower to 46.61 higher) KOOS SPR 12 months- Post - MD 18.89 higher score MD 18.89 higher) MD 18.89 higher KOOS SPR 12 months- Post - (2.77 higher to 35.01 higher	Relative effect (95% CI)	No of participants (studies) 88 (3 RCTs)	Certainty of the evidence	
ADL 12 months- Post : SPR 12 months- Post	Relative effect (95% CI)	No of participants (studies) 88 3 RCTs)	Certainty of the evidence	
Risk with usualOutcomesCareADL 12 months- PostSPR 12 months- PostSPR 12 months- Post	Relative effect (95% CI)	No of participants (studies) 38 3 RCTs)	evidence	
ADL 12 months- Post		38 3 RCTS)	(GRADE)	Comments
SPR 12 months- Post		(⊕⊖⊖⊖ Very lowaf	
		88 (3 RCTs)	⊕⊕⊖⊖ Lowae	
*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	d on the assumed 1	isk in the compariso	n group and the relative e	ffect of the interventior
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.	he estimate of the e rue effect is likely t	ffect. be close to the esti	nate of the effect, but there	is a possibility that it is
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.	may be substantiall rue effect is likely t	y different from the obstantially di	estimate of the effect. ferent from the estimate o	f effect.

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EVIDENCE PROFILE:

	Anticipated absolute effects	Risk difference with Stem cell therapy						
findings	Anticipate	Risk with usual care						
Summary of findings	Dolotivo	effect (95% CI)						
v ,	it rates (%)	With Stem cell therapy						
	Study event rates (%)	With usual care						
	Overall	certainty of evidence						
	Publication bias							
ent	Imprecision							
ertainty assessm	SS							
Certainty asses								
		Risk of bias						
	Douticinouto	Follow-up						

VAS 12 months- Post score

MD 1.76 lower (2.59 lower to 0.93 lower)		MD 0.39 lower (1.7 lower to 0.92 higher)
MD (2.5 0.9		MD (1.) 0.9
'		ı
		·
		ı
'		ı
⊕⊕⊖⊖ Low ^{a,b}		⊕⊕⊖⊖ Low ^{a,c}
None		None
Serious ^b		Serious ^c
Not serious		Not serious
Serious ^a	core	Serious ^a
Not serious	· Change so	Not serious
474 (9 RCTs)	VAS 12 months- Change score	142 (3 RCTs)

WOMAC 12 months- Post score

MD 8.74 lower (16.03 lower to 1.45 lower)		MD 11.96	lower	(22.65 lower to	1.28 lower)
'		-			
1		-			
		-			
⊕⊕⊖⊖ Low ^{a,b}		000⊕	Very	low ^{a,d,e}	
None		None			
Serious ^b		Serious ^e			
Not serious		Not serious			
Serious ^a	ige score	Serious ^a			
Not serious	nths- Chan	Very	serious ^d		
417 (9 RCTs)	WOMAC 12 months- Change score	42	(2 RCTs)		

KOOS Pain 12 months- Post score

	MD 23.14	higher	(5.71 higher to	40.56 higher)	
					•
	$\bigcirc \bigcirc \oplus \oplus \bigcirc$	Low ^{a,e}			-
	None				
	Serious ^e				-
	Not serious				-
21 2001 G	Serious ^a				-
nu -siniini	Not	serious			•
WOOD LAIN 12 MINIMIS- LOSI SCOLE	144	(4 RCTs)			

K00S Symptom 12 months- Post score

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EVIDENCE PROFILE:

		Cert	Certainty assessment	ent					Summary of findings	indings	
88 (3 RCTs)	Not serious	Serious ^a	Not serious	Seriouse	None	⊕⊕⊖⊖ Lowae					MD 28.07 higher (7.4 higher to 48.73 higher)
K00S QoL 12 months- Post score	onths- Po:	st score									
88 (3 RCTs)	Not serious	Serious ^a	Not serious	Seriouse	None	⊕⊕⊖⊖ Low ^{a,e}	1	1	1	1	MD 27.64 higher (8.45 higher to 46.84 higher)
K00S ADL 12 months- Post score	onths-Po	st score									
88 (3 RCTs)	Not serious	Serious ^a	Not serious	Very serious ^f	None	⊕⊖⊖⊖ Very low ^{a,f}			1	1	MD 22.67 higher (1.27 lower to 46.61 higher)
KOOS SPR 12 months- Post score	onths- Po:	st score									
88 (3 RCTs)	Not serious	Serious ^a	Not serious	Serious ^e	None	⊕⊕⊖⊖ Lowa,e	1	I	-		MD 18.89 higher

CI: confidence interval; MD: mean difference

(2.77 higher to 35.01 higher)

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

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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	Moderate
resources	
Cost effectiveness	Probably favors the comparison
Equity	Probably reduced
Acceptability	Probably yes
Feasibility	Probably yes
Decommondations, Stom call the way	wie not recommended in reutine practice for the treatment

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.

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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)	Standardized measure used to assess	Absolute change of
	Range: 0-100	the severity of hip pain and functional	HHS by 20 points
	Higher score is better	limitations in individuals with hip	
		conditions.	
2		17.11.1	
2.	Visual Analog Scale	Validated measure for measuring	Absolute change of
	(VAS)	intensity of pain	VAS score by 2
	Range: 0-10		points
	Higher score is worse		
3.	Western Ontario and	Self-administered questionnaire that is	Absolute change of
	McMaster Universities	used to assess pain, stiffness, and	WOMAC by 20
	Osteoarthritis Index	function in patients with OA of the hip	points
	(WOMAC)- Overall	or knee.	
	Range: 0-100		
	Higher score is worse		
4.	Conversion to Total Hip	Number of patients who eventually	-
	Replacement (THR)	required THR	
5.	SAEs	Serious Adverse events	-

Risk of Bias assessment:

RoB2 assessment for Harris Hip Score:

Study ID	Experimental	<u>Comparator</u>	Outcome	Weight	<u>D1</u>	<u>D2</u>	<u>D3</u>	<u>D4</u>	<u>D5</u>	Overall
Zao et al 2011	BMMSC+CD	CD	HHS	1	+	•	•	+	+	•
Pepke et al 2016	BMAC + CD	ср	HHS	1	•	+	+	!	+	•
Sen et al 2012	BMNC+CD	CD	HHS	1	•	+	+	•	+	•
Mao et al 2015	PBMSC+GSCF+CD	CD	HHS	1	+	+	+	+	+	+

RoB2 assessment for VAS:

<u>Study ID</u> Hauzer et al 2017 Pepke et al 2016		<u>Comparator</u> CD+ Saline inj CD	<u>Outcome</u> VAS VAS	<u>Weight</u> 1 1	<u>D1</u> + -	<u>D2</u> +	D3 •	<u>D4</u> +	<u>D5</u> +	Overall
RoB2 assess	sment for WOM	AC:								
<u>Study ID</u> Jayankura et al	Experimental 2 BMSC+CD	<u>Comparator</u> CD+PB	<u>Outcome</u> WOMAC	<u>Weight</u> 1	<u>D1</u>	<u>D2</u> +	<u>D3</u>	<u>D4</u> +	<u>D5</u> +	Overall
RoB2 assess	sment for THR:									
Study ID	Experimental	Comparator	Outcome	<u>Weight</u>	<u>D1</u>	<u>D2</u>	<u>D3</u>	<u>D4</u>	<u>D5</u>	<u>Overall</u>
Zao et al 2011	BMMSC+CD	CD	THR	1	+	•	•	+	+	•
Hauzer et al 201	17 BMAC+CD	CD	THR	1	+	+	•	+	+	•
Mao et al 2015	PBSC+GCSF+CD	CD	THR	1	+	+	+	+	+	+
Jayankura et al	20 BMAC+CD	CD+PB	THR	1	•	+	•	+	÷	Ō
Pepke et al	NA	NA	NA	1	Ó	•	•	!	÷	ē

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

		SCT		(Contr	ol		Mean Difference		N	lean	Diffe	erence	e	
Study	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% (IV,	Rand	lom,	95%	CI	
Zhao et al 2012	80.9	1.5	53	84.1	2.5	44	29.0%	-3.2 [-4.1; -2.4]				•			
Pepke et al 2016	83.1	7.2	11	77.7	5.5	14	24.0%	5.5 [0.3; 10.6]					-		
Sen et al 2012	82.4	9.6	26	77.4	17.0	25	19.7%	5.0 [-2.6; 12.6]				+	_	- 1	
Mao et al 2015	88.1	3.2	48	78.5	8.7	41	27.3%	9.6 [6.8; 12.4]					-		
Total (95% CI)			138			124		4.0 [-2.0; 10.0]						ł	
Heterogeneity: Tau	2 = 31.8	B; Ch	$i^2 = 85$.02, df =	= 3 (P	< 0.01); $I^2 = 96\%$			1	1	1	1	1	
									-30	-20	-10	0	10	20	30
										Co	ntrol		SC	Т	

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:

Study	SCT Mean	SD		Contro Mean	-	Total	Mean Difference IV, 95% CI		Diff 95%	erence 6 Cl	
Jayankura et al 2023	-22.4	30.8	25	-13.2	25.5	29	-9.2 [-24.4; 6.0]			-	
								 -10 SCT	0	10 Control	20

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.

Intervention: Stem Cell Therapy Comparison: Usual Care	Patient or population: Avascular Necrosis of Hip Setting: Hospital/Tertiary care Intervention: Stem Cell Therapy Comparison: Usual Care					
	Anticipated absolute	solute effects*(95% CI)				
Outcomes	Risk with Placebo/ Standard care	Risk with Stem Cell Therapy	Relative effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)	Comments
Harris Hip score (Quantitative analysis) (HHS) Assessed with: Radiography		MD 4 higher (2 lower to 10 higher)		262 (4 RCTs)	⊕OOO Very lowabc	
Visual Analogue Scale (Quantitative analysis) (VAS) Assessed with: Questionnaire		MD 0.6 lower (0.8 lower to 0.4 lower)		71 (2 RCTs)	⊕○○○ Very lowa.d	
Western Ontario and McMaster Universities Osteoarthritis Index (Quantitative analysis) (WOMAC) Assessed with: Questionnaire	ı	MD 9.2 lower (24.4 lower to 6 higher)	ı	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	p (and its 95% co fference; RR : risk 1	nfidence interval) is based ratio	on the assumed r	isk in the comparison	group and the relative effect	of the interventi
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 wordenately 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: We have very little confidence in the effect estimate: the true effect is likely to 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 the effect.	vidence nt that the true eff itely confident in t e effect estimate is ttle confidence in t	ect lies close to that of the e he effect estimate: the true limited: the true effect ma he effect estimate: the true	estimate of the effe effect is likely to b y be substantially (effect is likely to b	ect. be close to the estimate different from the estir be substantially differe	e of the effect, but there is a pos nate of the effect. In from the estimate of effect.	ssibility that it is
Explanations a. Downgraded by two levels as more than 2/3 rd 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.	n 2/3 rd of the studies on as wide CI crossin ncy as results are in	(by wt.) were at high risk of b g the line of null effect. consistent across studies.	ias.			

Evidence-based Guidelines for the use of Stem cell therapy: Orthopedic Conditions

EVIDENCE PROFILE:

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

	apy compan	occur den anertapy compared to contraction incertable on my	T ININGCOMULT	duri no cico non							
		Cer	Certainty assessment	int				Sun	Summary of findings	ndings	
						Overall	Study event rates (%)	t rates (%)	Dolotivo	Anticipat efi	Anticipated absolute effects
Fatucipants (studies) Follow-up	Risk of bias	Inconsistency	Inconsistency Indirectness	Imprecision	Publication bias	certainty of evidence	With Placebo/ Standard care	With Stem Cell Therapy	effect (95% CI)	With effect Risk with Stem Cell (95% CI) Standard Therapy care	Risk difference with Stem Cell Therapy
HHS (Quantital	tive analysi	HHS (Quantitative analysis) (assessed with: Radiography)	h: Radiography)								
262	Very	Serious ^c	Not serious	Serious ^b	Inevaluable $\oplus \bigcirc \bigcirc \bigcirc$	$\bigcirc \bigcirc $	ı				MD 4 higher
(4 RCTs)	serious ^a					Very low					(2 lower to 10

										higher)
Visual Analog	ue Scale (Qu	/isual Analogue Scale (Quantitative analysis) (assessed with: Questionnaire)	sis) (assessed w	vith: Questionna	ire)					
71	Very	Not Serious	Not serious	Serious ^d	Inevaluable $\oplus \bigcirc \bigcirc \bigcirc$	$\bigcirc \bigcirc $	·	-		MD 0.6 lower
(2 RCTs)	serious ^a					Very low				(0.8 lower to
										0.4 lower)
Western Ontai	rio and McM	Nestern Ontario and McMaster Universities Osteoarthritis Index (Quantitative analysis) (assessed with: Questionnaire)	es Osteoarthriti	is Index (Quanti	tative analysis) (assessed v	vith: Ouesti	onnaire)		

MD **9.2 lower** (24.4 lower to

Very low 0000

Inevaluable

Serious^b

Not serious

Inevaluable^e

Very serious^a

(1 RCT) 54

6 higher)

THR (Quantitative analysis) (assessed with: Questionnaire)

•	•										
311	Very	Not serious	Not serious	Serious ^b	Inevaluable	000Φ	40/148	30/163	RR 1.0	40/148	0 fewer per
(5 RCTs)	serious ^a					Very low (27.0%)	(27.0%)	(18.4%)	(0.7 to	(27.0%)	1,000
									1.5)		(from 81
											fewer to 135
											more)
	MD.	CI. confidence interval. MD. mass difference. DD. wich wete	DD. wals watio								

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

Explanations

a. Downgraded by two levels as more than $2/3^{rd}$ 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-based Guidelines for the use of Stem cell therapy: Orthopedic Conditions

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:

Trivial*
Trivial**
Very Low
Probably no important uncertainty or variability
Does not favor either the intervention or the
comparison
Large costs***
Moderate
Probably favors the comparison
Probably reduced
Probably yes
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.

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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 nonsurgical 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 <u>not recommended</u> 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:

				Risk of bia	s domains		
		D1	D2	D3	D4	D5	Overall
	Akgun 2015	+	+	+	+	-	-
	de Girolamo 2019	+	+	+	+	-	-
	Hashimoto 2019	-	X	+	X	-	X
	Hong 2019	+	+	+	+	+	+
	Kim 2022	-	-	+	+	+	-
	Koh 2016	-	+	-	+	-	-
Study	Lee 2019	X	+	+	+	-	X
Stl	Lim 2021	-	-	-	+	-	-
	Liu 2021	-	-	+	-	+	-
	Saw 2013	X	+	+	+	+	-
	Saw 2021	-	+	+	X	+	X
	Venosa 2022	+	+	-	+	-	-
	Won g 2013	-	+	+	X	-	X
	Zhou 2021	+	+	+	+	+	+
		Domains: D1: Bias aris D2: Bias due	sing from the r	andomization from intended	process. d intervention.	Judge	ment High

RoB2 assessment for subjective outcomes: VAS, WOMAC and KOOS

D2: Bias due to deviations from intended intervention.

D3: Bias due to missing outcome data.

D4: Bias in measurement of the outcome. D5: Bias in selection of the reported result.

Evidence-based Guidelines for the use of Stem cell therapy: Orthopedic Conditions

Some concerns

Low

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

	Stem 0	cell Ther	apy	Cont	Note Nean difference Mean difference Nean difference Nean difference Risk of Bias R B C D E F 9.7 13 20.2% 1.00 [-6.93, 8.93] 7.80 [-12.02, -3.58] 2											
Study or Subgroup	Mean	SD	Total	Mean			Weight	IV, Random, 95%	% CI	IV, Random, 95% CI	A	в	C	D	E	F
Kim 2022	17.9	10.9	13	16.9	9.7	13	20.2%	1.00 [-6.93 ,	8.93]		?	?		•	٠	?
Lim 2021	24.7	1.1	43	26.2	2.525	46	45.9%	-1.50 [-2.30 , -	0.70]	=	?	?	?	•	?	?
Zhou 2021	5.93	5.84	29	13.73	9.85	28	33.9%	-7.80 [-12.02 , -	3.58]		٠	٠	•	٠	٠	•
Total (95% CI)			85			87	100.0%	-3.13 [-7.87 ,	1.60]	•						
Heterogeneity: Tau ² =	12.58; Chi2	= 8.70, d	f = 2 (P =	0.01); l ² =	: 77%											
Test for overall effect:	Z = 1.30 (P	= 0.19)							-2	0 -10 0 10 20						
Test for subgroup diffe	rences: Not	applicab	ole					F	avours [experimental] Favours [control	ŋ					
Risk of bias legend																
(A) Bias arising from th(B) Bias due to deviation	ons from int	ended in		ns												
(C) Bias due to missing	-															
 (D) Bias in measurement (E) Bias in selection of 																
(F) Overall bias	ane reporte	o result														
(1) 0101010103																

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

	Stem	Cell Ther	ару	Cont	rol Thera	apy		Mean difference	Mean difference		Ri	sko	f Bi	35	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% Cl	A	в	c	D	E	F
Lim 2021	53.4	2.2	43	53.5	5	46	91.1%	-0.10 [-1.69 , 1.49		?	?	?	•	?	?
Liu 2021	78.2	15.4	10	63.5	11.6	5	1.2%	14.70 [0.75 , 28.65	1 T	?	?	•	?	•	?
Saw 2013	68.08	12.88	25	67.63	12.95	24	4.4%	0.45 [-6.78 , 7.68	1 - !		•		•		?
Saw 2021	57	17.9	36	52.8	17.17	33	3.4%	4.20 [-4.08 , 12.48	1 <u>+</u>	?	•	•	•	•	•
Total (95% CI)			114			108	100.0%	0.24 [-1.27 , 1.76]	1						
Heterogeneity: Chi2 =	5.19, df = 3	(P=0.10	5); 1 ² = 42	%											
Test for overall effect:	Z = 0.31 (P	= 0.75)							-20 -10 0 10 20						
Test for subgroup diffe	erences: No	t applicat	ble						Favours [control] Favours [expendence]	riment	tal]				
Risk of bias legend															
(A) Bias arising from t	he randomi	zation pro	cess												
(B) Bias due to deviati	ions from in	tended in	tervention	ns											

(C) Bias due to missing outcome data (D) Bias in measurement of the outcome

(E) Bias in selection of the reported result

(F) Overall bias

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

	Stem	Cell Ther	apy	Cont	rol Thera	py		Mean difference	Mean difference		Ri	sk o	f Bi	35
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI	A	в	c	D	Е
Akgun 2015	86.51	3.37	7	81.75	2.71	7	61.7%	4.76 [1.56 , 7.96]	- i	۲			•	?
Kim 2022	77.1	9.7	13	77.6	7.6	13	14.1%	-0.50 [-7.20 , 6.20]		?	?		•	
Koh 2016	36.6	11.9	40	30.1	14.7	40	18.4%	6.50 [0.64 , 12.36]	i	2		?	٠	?
Saw 2021	75	22.86	36	62.2	21.89	33	5.7%	12.80 [2.24 , 23.36]		?	۲	٠	•	٠
Total (95% CI)			96			93	100.0%	4.79 [2.28 , 7.31]	•					
Heterogeneity: Chi2 =	4.93, df = 3	(P = 0.18	8); 2 = 39	%					· .					
Test for overall effect:	Z = 3.73 (P	= 0.0002	2)						-20 -10 0 10 20	_				
Test for subgroup diffe	erences: No	t applicat	ble						Favours [control] Favours [ex	perimen	tal]			
Risk of bias legend														
(A) Bias arising from t	he randomi	zation pro	ocess											
(B) Bias due to deviat	ions from in	tended in	tervention	ns										
(A) Dias due to missis	g outcome	data												
(C) Bias due to missing		utcome												
	ent of the o													
 (C) Bias due to missir (D) Bias in measurem (E) Bias in selection o 														

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

	Stem	Cell Ther	ару	Cont	rol Thera	apy		Mean difference	Mean di	fference		Ri	sk o	f Bi	35	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed	I, 95% CI	A	в	С	D	E	F
Akgun 2015	85.29	1.7	7	82.35	1.47	7	86.3%	2.94 [1.28 , 4.60]	1	- ÷				•	?	?
Kim 2022	84.3	7.9	13	82	11.1	13	4.4%	2.30 [-5.11 , 9.71]	i —	- 1	?	?	•	•	٠	?
Koh 2016	38.5	12.8	40	37.6	12.9	40	7.5%	0.90 [-4.73 , 6.53]		- :	?		?		?	?
Saw 2021	75.9	25.2	36	67.5	24.12	33	1.8%	8.40 [-3.24 , 20.04]	ı –		?	•	٠	•	•	•
Total (95% CI)			96			93	100.0%	2.85 [1.31 , 4.40]	1	•						
Heterogeneity: Chi2 =	1.37, df = 3	(P=0.7	1); I ² = 09	6						·						
Test for overall effect:	Z = 3.62 (P	= 0.0003	3)						-20 -10	0 10 20						
Test for subgroup diffe	erences: No	t applicat	ble						Favours [control]		experimenta	al]				
Risk of bias legend																
(A) Bias arising from t	he randomi	zation pro	ocess													
(B) Bias due to deviat	ions from in	tended in	tervention	ns												
(C) Bias due to missin	ig outcome	data														
(D) Bias in measurem	ent of the o	utcome														
(E) Bias in selection o	f the report	ed result														
(E) Oussall bias																

(F) Overall bias

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

	Stem	Cell Ther	apy	Cont	rol Thera	py		Mean difference	Mean dif	ference		Ri	sko	f Bi	as	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed	, 95% CI	Α	в	c	D	E	F
Akgun 2015	81.43	2.44	7	75	2.89	7	64.7%	6.43 [3.63 , 9.23]		-8-				•	?	?
Kim 2022	30	12.2	13	29.2	7.9	13	8.1%	0.80 [-7.10 , 8.70]			! ?	?	٠	•	•	?
Koh 2016	33.9	10.3	40	31.6	11	40	23.3%	2.30 [-2.37 , 6.97]	-		1 ?		?	•	?	?
Saw 2021	45.3	24.78	36	43.9	23.7	33	3.9%	1.40 [-10.04 , 12.84]			2	•	•	•	٠	•
Total (95% CI)			96			93	100.0%	4.81 [2.56 , 7.07]		٠	i i					
Heterogeneity: Chi2 =	3.72, df = 3	(P = 0.29	9); l ² = 19	%						•	1					
Test for overall effect:	Z = 4.19 (P	< 0.0001)						-20 -10 0	10	20					
Test for subgroup diffe	rences: No	t applicat	ole						Favours [control]	Favours [e	experimenta	si]				
Risk of bias legend																
(A) Bias arising from t	he randomi	zation pro	cess													
(B) Bias due to deviati	ions from in	tended in	tervention	ns												
(C) Bias due to missin	g outcome	data														
(D) Bias in measurem	ent of the o	utcome														
(E) Bias in selection of	f the reporte	ed result														
(F) Overall bias																

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

	Stem	Cell Ther	apy	Cont	rol Thera	DV		Mean difference	Mean d	lifference		R	isk	of B	35	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixe	d, 95% CI	A	B	c	D	E	F
Akgun 2015	87.24	4.05	7	81.63	3.21	7	34.2%	5.61 [1.78 , 9.44]	í -		1				?	?
Kim 2022	84.9	11.5	13	83.8	11.4	13	6.5%	1.10 [-7.70 , 9.90]	· -		! ?	2				?
Koh 2016	32.3	7.2	40	27.8	6.8	40	53.3%	4.50 [1.43 , 7.57]	1	-8-	1 .		2	ā	-	
Saw 2021	73.1	19.7	36	60.7	18.9	33	6.0%	12.40 [3.29 , 21.51]	1		+ ?				÷	ē
Total (95% CI)			96			93	100.0%	5.14 [2.90 , 7.38]	1	•	1					
Heterogeneity: Chi2 =	3.47, df = 3	B (P = 0.3	2); 2 = 14	.%							1					
Test for overall effect:	Z = 4.50 (P	< 0.0000)1)						-20 -10	0 10	20					
Test for subgroup diffe	erences: No	t applicat	ble						Favours [control]	Favours	[experiment	al]				
Risk of bias legend																
(A) Bias arising from t	he randomi	zation pro	ocess													
(B) Bias due to deviati	ions from in	itended in	tervention	ns												
(C) Bias due to missin	g outcome	data														
(D) Bias in measurem	ent of the o	utcome														
(E) Bias in selection of	f the report	ed result														
(F) Overall bias																

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

	Stem	Cell Ther	ару	Cont	rol Thera	py		Mean difference	Mean difference		Risk	of	Bias	1
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI	A	B	0	E	F
Akgun 2015	83.04	4.72	7	76.79	5.94	7	39.4%	6.25 [0.63 . 11.87]					2	?
Kim 2022	52.9	17	13	47.6	12.1	13	9.7%	5.30 [-6.04 , 16.64]		2	2			?
Koh 2016	38.4	13.1	40	37.8	12	40	41.1%	0.60 [-4.91 , 6.11]		2 (? 9	?	?
Saw 2021	43.4	24.42	36	40.7	23.38	33	9.8%	2.70 [-8.58 , 13.98]		2	•			•
Total (95% CI)			96			93	100.0%	3.49 [-0.04 , 7.02]	•					
Heterogeneity: Chi2 =	2.10, df = 3	(P = 0.55	5); 12 = 0%	6					-					
Test for overall effect:	Z = 1.94 (P	= 0.05)							-20 -10 0 10 2	0				
Test for subgroup diffe	erences: No	t applicat	ble					F	avours [control] Favours [expe		0			
Risk of bias legend														
Risk of bias legend (A) Bias arising from t	he randomi	zation pro	cess											
				15										
(A) Bias arising from t	ions from in	tended in		15										
(A) Bias arising from t (B) Bias due to deviat	ions from in ig outcome	tended in data		15										
 (A) Bias arising from t (B) Bias due to deviat (C) Bias due to missir 	ions from in ig outcome ent of the o	tended in data utcome		15										

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 Commarison: IIsual Care

Comparison: Usual Care						
	Anticipate	Anticipated absolute effects*(95% CI)				
Outcomes	Risk with Control Therapy	Risk with Stem Cell Therapy	Relative effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)	Comments
KOOS - Activities of Daily Living at 12 months	ı	MD 2.85 higher (1.31 higher to 4.4 higher)	ı	189 (4 RCTs)	⊕⊖⊖⊖ Very low ^{ab}	
K00S Pain at 12 months		MD 4.79 higher (2.28 higher to 7.31 higher)	ı	189 (4 RCTS)	⊕⊖⊖⊖ Very low ^{ab}	
K00S QoL at 12 months	ı	MD 3.49 higher (0.04 lower to 7.02 higher)	ı	189 (4 RCTs)	⊕⊖⊖⊖ Very lowac	
KOOS Sports & Recreation at 12 months		MD 4.81 higher (2.56 higher to 7.07 higher)	·	189 (4 RCTs)	⊕⊖⊖⊖ Very low ^{ab}	
KOOS Symptom at 12 months	ı	MD 5.14 higher (2.9 higher to 7.38 higher)	·	189 (4 RCTs)	⊕⊖⊖⊖ Very low ^{ab}	
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	ı	MD 3.13 lower (7.87 lower to 1.6 higher)		172 (3 RCTs)	⊕⊖⊖⊖ Very low ^{a.c.d}	
IKDC Score at 12 months	ı	MD 0.24 higher (1.27 lower to 1.76 higher)	·	222 (4 RCTs)	⊕⊖⊖⊖ Very low ^{ab}	
*The risk in the intervention g	group (and its 95	*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	the assumed risk in	the comparison group	and the relative effect of th	le intervention

CI: confidence interval; MD: mean difference; OR: odds ratio (and its 95% CI).

Evidence-based Guidelines for the use of Stem cell therapy: Orthopedic Conditions

arient or population: Cartilage Defects etting: Terriary care/hospital momparison: Usual Care onparison: Usual Care Maticipated absolute effects'(95% CI) Robertice care Robertice care and the control of the effect absolute effects' (95% CI) RADE Working Group grades of evidence Igh certainty: we are very confident that the true effect the true effect the evidence (GADE) RADE Working Group grades of evidence Igh certainty: we are very confident that the true effect is likely to be close to the estimate of the effect. Note care and the effect estimate: the true effect is likely to be close to the estimate of the effect. Igh certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of the effect. In the confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of the effect. If the confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of the effect. If the confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of the effect. Comparated two levels for risk of bias as more than 2/3 rd of studies (by wt.) were at high risk of bias. Downgraded two levels for rinprecision as results are precise for no benefit but OIS not met. Downgraded by one level for imprecision as results are inconsistent across studies.	Preferent or population: Cartilage Defects Control of Therapy Comparison: Usual Care Multiparted absolute effects [95% CI] Multiparted absolute effects [95% CI] Multiparted absolute effects [95% CI] Risk with Risk with Stem Cell Therapy Risk Risk with Stem Cell Therapy Risk Risk With Stem Cell Therapy Risk Risk Risk Risk Risk Risk Risk Risk	Stern Cert Therapy compared to usual care for cartilage defects				
Anticipated absolute effects*(95% CI) Anticipated absolute effects*(95% CI) No of participants Carainty of the evidence Risk with Control Risk with Stem Cell Therapy Relative effect No of participants Carainty of the evidence ADBE Working Group grades of evidence Therapy Relative effect No of participants Carainty of the evidence Ligh certainty: we are very confident that the true effect lies close to that of the effect. Open effect. Comments Ligh certainty: we are noderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect. Control Comments Oderate certainty: our confidence in the effect estimate: the true effect is likely to be close to the estimate of the effect. Comments evertainty: our confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect. evertainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect. eventainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect. eventainty: Comments Comments for confidence in the effect estimate is limited. In the effect on the estimate of the effect. Comments eventainty: Comments	Anticipated abso Risk with Control Therapy Risk oup grades of evidence are very confident that the true effe- are very confident that the true effe- are very confidence in the th. Confidence in the effect estimate is l we have very little confidence in the the level for imprecision as more than 2 are level for imprecision as wide CI c are level for inconsistency as results and level for inconsistency as results.	Patient or population: Cartila, Setting: Tertiary care/hospital Intervention: Stem Cell Thera Comparison: Usual Care	ge Defects Jy			
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Not serious Not serious Serious ^b Inevaluable ⊕OOO Intervaluable Mot serious Serious ^b Inevaluable ⊕OOO	Serious ^b Inevaluable				MD 2.85 higher (1.31 higher to 4.4 higher)
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Not serious Not serious Serious ^c Inevaluable $\oplus \bigcirc \bigcirc \bigcirc$ Not serious Not serious Serious ^b Inevaluable $\oplus \bigcirc \bigcirc \bigcirc$ Not serious Not serious Serious ^b Inevaluable $\oplus \bigcirc \bigcirc \bigcirc$ not serious Not serious Serious ^b Inevaluable $\oplus \bigcirc \bigcirc \bigcirc$	Serious ^b Inevaluable	- 	· ·	1	MD 4.79 higher (2.28 higher to 7.31 higher)
Not serious Not serious Serious ^c Inevaluable ©OO Not serious Not serious Serious ^b Inevaluable ©OO	-	-	-	-	
Not serious Not serious Serious ^b Inevaluable $\oplus \bigcirc \bigcirc$ Very low very low not serious Not serious Serious ^b Inevaluable $\oplus \bigcirc \bigcirc$	Serious ^c Inevaluable (· ·		MD 3.49 higher (0.04 lower to 7.02 higher)
serious Not serious Serious ^b Inevaluable $\oplus \bigcirc \bigcirc \bigcirc$ Very low serious Not serious Serious ^b Inevaluable $\oplus \bigcirc \bigcirc \bigcirc$	-	-	-	-	
serious Not serious Serious ^b Inevaluable $\oplus \bigcirc \bigcirc \bigcirc$	Serious ^b Inevaluable	- 	1	· ·	MD 4.81 higher (2.56 higher to 7.07 higher)
very not serious Not serious Serious ^b Inevaluable OO					
	Serious ^b Inevaluable			,	MD 5.14 higher (2.9 higher to 7.38 higher)
Evidence-based Guidelines for the use of Stem cell therapy: Orthopedic Conditions	of Stem cell therapy: Orthopedic Cond	itions			Page 51

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-5--iii 4+7 EVIDENCE PROFILE:

					0	
			MD 0.81	lower	(1.67 lower to	0.04 higher)
	ndings					
	Summary of findings		ı			
	Sı		·			
			ı			
			000 0	Very low		
			Serious ^c Inevaluable $\oplus \bigcirc \bigcirc \bigcirc$			
age defects	ment		Serious ^c			
re tor cartila	Certainty assessment		Not	serious		
Stem Cell Therapy compared to usual care for cartilage defects	Cert		Serious ^d			
nerapy com		t 12 months	very	4 RCTs) serious ^a		
Stem Cell TI		VAS Score at 12 months	184	(4 RCTs)		

⊕⊖⊖⊖ Very low Inevaluable Serious^c Not serious Serious^d WOMAC Score at 12 months serious^a very (3 RCTs) 172

(7.87 lower to

MD **3.13** lower 1.6 higher)

IKDC Score at 12 months

MD 0.24	higher	(1.27 lower to	1.76 higher)
ı			
,			
000⊕	Very low		
Inevaluable			
Serious ^b			
Not serious			
not serious			
very	serious ^a		
222	(4 RCTs)		

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.

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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

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.

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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 weightbearing 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

	Stem	Cell T	herapy	Sta	ndard	of Care				
Study	Total	Mean	SD	Total	Mean	SD	Mean Difference in VAS Score	MD	95%-CI	Weight
Stem_Cell = Bone Marr	ow De	rived	Mesenc	hymal	Stem	Cell	(I			
Chun_2022	7	4.31	2.6500	8	4.37	2.7000		-0.06	[-2.77; 2.65]	10.2%
Rodas 2021	10	1.94	1.2400	10	3.06	2.8900		-1.12	[-3.07; 0.83]	19.8%
Rosario_2021	15	-3.50	1.5000	25	-1.60	1.8000			[-2.94; -0.86]	
Random effects model Heterogeneity $l^2 = 0\%$, τ^2	32 = 0, p =	= 0.41		43			¢		[-2.42; -0.69]	
Random effects model	32			43			-	-1.56	[-2.42; -0.69]	100.0%
Prediction interval									[-7.18; 4.06]	
Heterogeneity: $l^2 = 0\%$, τ^2	= 0, p =	= 0.41								
Test for subgroup difference	es: x0=	: 0.00, 0	df = 0 (p)	= NA)			-6 -4 -2 0 2 4 6			
	110				Fav	ours Ste	em Cell Therapy Favours Stand	ard of c	are	

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

Study			Therapy SD					Mean I AS	Differe ES Sc		MD	95%-CI
Chun_2022	7	48.50	26.0000	8	48.80	20.5000	╞	1	-	 	-0.30 [·	-24.23; 23.63]
					Fa	vours Ste		−10 Therap	-	 	ard of car	e

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.

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Patient or population: Tendinopathy Setting: Tertiary care Intervention: Stem cell Comparison: usual care Anticipa		occur comparied to occurrent a of care for remainsparity				
A	nopathy					
	Anticipated absolute effects*(95% CI)	te effects*(95% CI)				
Outcomes	Risk with standard of care	Risk with Stem cell	Relative effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)	Comments
ASES Scale from: 0 to 100 follow-up: mean 6 months	ı	MD 0.30 lower (24.23 lower to 23.63 higher)		15 (1 RCT)	⊕⊖⊖⊖ Very lowabc	
VAS Scale from 0 to 10 follow-up: mean 6 months	ı	MD 1.56lower (2.42 lower to 0.69lower)	ı	75 (3 RCTs)	⊕○○○ Very lowac	
*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). Cl: confidence interval; MD: mean difference; RR: Risk ratio	group (and its 959 ean difference; RR :	6 confidence interval Risk ratio) is based on the ass	sumed risk in the com	iparison group and the relat i	ve effect of the interventi
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. Low certainty: We have very little confidence in the effect estimate: the true effect is likely to be close to the estimate of the effect.	es of evidence onfident that the tru noderately confiden e in the effect estime very little confidenci	te effect lies close to t t in the effect estimat ate is limited: the true e in the effect estima	chat of the estimate te: the true effect is e effect may be subs te: the true effect is	of the effect. likely to be close to th tantially different fro likely to be substanti	he estimate of the effect, but t m the estimate of the effect. ally different from the estima	here is a possibility that it te of effect.
Explanations a. Downgraded by two levels for risk of bias as more than 2/3 rd 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	sk of bias as more than onsistency as it is inev precision as OIS not m	n 2/3 rd of the studies (b; ⁄aluable for single study et	y wt.) were at high risl	k of bias		

EVIDENCE PROFILE

Stem cell compared to standard of care for Tendinopathy

	\nticipated absolute effects	Risk difference with Stem cell						
ings	Anticipat ef	Risk with standard of care						
Summary of findings		(95% CI)						
v 3	Study event rates (%)	With Stem cell						
	Study even	With standard of care						
	Overall	certainty of evidence						
	Publication bias							
ment		Imprecision						
Certainty assessme	Risk of Inconsistency Indirectness Impr							
Ce		Inconsistency						
	ייני ביין ייני	bias						
	Participants n.	(studies) Follow-up						

ASES (follow-up: mean 6 months; Scale from: 0 to 100)

MD 0.30	lower	(24.23 lower	to 23.63	higher)	
-					
-					
I					
000⊕	Very low ^{a,b,c}				
none					
serious ^c					
not serious					
Inevaluable ^b not serious					
very	serious ^a				
15	(1 RCT)				

VAS (follow-up: mean 6 months)

MD 1.56	lower	(2.42 lower to	0.69 lower)	
ı				
000⊕	Very low ^{a,c}			
none				
Serious ^c				
not serious				
not serious				
very	serious ^a			
75	(3 RCTs)			

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.

Evidence-based Guidelines for the use of Stem cell therapy: Orthopedic Conditions

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.

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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 nonunion 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.	Included only infected cases of non-union, findings would be non-
	20186	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,	Questionnaire to measure physical	Absolute change of
	Shoulder & Hand	function and symptoms in people with	QDASH score by 20
	(QDASH) score	any or multiple musculoskeletal	points
	Range: 0-100	disorders of the upper limb	
	Higher score is worse		
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:



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

	Exp	erim en	tal	0	Control			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Toosi 2023 (1)	41	27.01	5	45	17.67	5	100.0%	-4.00 [-32.29, 24.29]	
Total (95% CI)			5			5	100.0%	-4.00 [-32.29, 24.29]	
Heterogeneity: Not ap Test for overall effect.		(P = 0.	78)						-100 -50 0 50 100 Favours [experimental] Favours [control]
<u>Footnotes</u> (1) Change in Mayow	rist 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.

Setting: Tertiary care Intervention: Any Stem cell and product derived from stem cells Comparison: Usual Care	Fortual OF population: Note union of both Setting: Tertiary care Intervention: Any Stem cell and product derived from stem Comparison: Usual Care	ı cells				
	Anticipated absolu	Anticipated absolute effects*(95% Cl)	Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
Outcomes	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 lowabc	
Mayo wrist score at 3 months		MD 4 lower (32.29 lower to 24.29 higher)		10 (1 RCT)	⊕⊖⊖⊖ Very low ^{ab.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).	ınd its 95% confiden	nce interval) is based o	on the assume	ed risk in the com	parison group and the relat	ive effect of the interventi
CI: confidence interval; MD: mean difference; RR: risk ratio	ence; 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.	lence hat the true effect lie y confident in the eff	es close to that of the fect estimate: the true	estimate of th e effect is likel	e effect. y to be close to th	e estimate of the effect, but	chere is a possibility that it
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.	fect estimate is limit confidence in the efi	ted: the true effect ma ffect estimate: the true	ly be substant e effect is likel	ially different fro y to be substanti	n the estimate of the effect. Illy different from the estim:	ate 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	is single study with und r as it was inevaluable f s OIS not met as verv wide CI	clear risk of bias for single study				

GRADE EVIDENCE PROFILE

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

	lute effects	Risk difference with any stem cell and product derived from stem cells
ings	Anticipated absolute effects	Risk withRiskUsual Care/differenceConventionalwith anyCareinstem cell andtreatment ofproductnonunion ofderived frombonestem cells
Summary of findings		Relative effect (95% CI)
Sı	rates (%)	With Any Stem cell and product derived from stem cells
	Study event rates (%)	PublicationOverall Care/ ConventionalWith Any Stem cellPublicationCare/ CareinStem cellbiasof CareinCarein productevidencetreatment of non-union of from stem
		Overall certainty of evidence
		Publication bias
nent		Imprecision
Certainty assessment		Indirectness
Сел		articipants Risk of Inconsistency Indirectness Follow-up
		Risk of bias
		Participants (studies) Follow-up

QDASH at 3 months

10	Very	Very Inevaluable ^b	Not serious	Serious ^c	Inevaluable $\oplus \bigcirc \bigcirc \bigcirc$	000⊕			MD 10.05
(1 RCT)	serious ^a					Very low ^{a,b,c}			lower
						1			(18.28 lower
									to 1.82 lower)
Mayo wris	t score	Mayo wrist score at 3 months							

MD 4 lower (32.29 lower to 24.29 higher)	
1	
,	
I	
⊕⊖⊖⊖ Very low ^{a,b,d}	
Inevaluable	
Very serious ^d	
Not serious	
Inevaluable ^b	
Very serious ^a	
10 (1 RCT)	

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.

Evidence based Guidelines for the use of Stem Cell Therapy: Orthopedics Conditions

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

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.

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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	Validated measure for measuring	Absolute change of
	(VAS)	intensity of pain	VAS score by
	Range: 0-100		20points
	Higher score is worse		
2.	Lysholm Knee Scale	Patient-reported outcome measure used	Absolute change of
	Score (LKSS)	to evaluate the functional status of the	LKSS by 20 points
	Range:0-100	knee joint.	
	Higher score is better		
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	hMSCs		Control = s	odium hyal	uronate		Mean difference	Mean difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Vangsness Jr. et al 150 million cells	40.09	8.54	18	22.4	19.3	10	58.4%	17.69 [5.09 , 30.29	1
Vangsness Jr. et al 50 million cells	35.63	16.81	17	22.4	19.3	9	41.6%	13.23 [-1.70 , 28.16	1
Total (95% CI)			35			19	100.0%	15.84 [6.21 , 25.46	ı 📥
Heterogeneity: Tau ² = 0.00; Chi ² = 0.2	20, df = 1 (F	e = 0.65);	I² = 0%						· · · · · · · · · · · · · · · · · · ·
Test for overall effect: Z = 3.22 (P = 0	.001)								-100 -50 0 50 100
Test for subgroup differences: Not ap	plicable								Favours [control] Favours [experimental]

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

	1	hMSCs		Control = s	odium hyal	uronate		Mean difference	Mean difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Vangsness Jr. et al 150 million cells	47.82	15.01	18	26.2	16.85	10	80.0%	21.62 [9.08 , 34.16	3]
Vangsness Jr. et al 50 million cells	37.47	47.38	17	26.2	16.85	9	20.0%	11.27 [-13.80 , 36.34	4) –
Total (95% CI)			35			19	100.0%	19.55 [8.34 , 30.76	a 👗
Heterogeneity: Tau ² = 0.00; Chi ² = 0.5	52, df = 1 (F	P = 0.47);	I ² = 0%						- •
Test for overall effect: Z = 3.42 (P = 0	.0006)								-100 -50 0 50 100
Test for subgroup differences: Not ap	plicable								Favours [control] Favours [experimental]

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

	1	hMSCs		Control = s	odium hyal	uronate		Mean difference	Mean difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Vangsness Jr. et al 150 million cells	28.1	31.81	18	31.3	19.5	10	53.8%	-3.20 [-22.23 , 15.83	
Vangsness Jr. et al 50 million cells	20.6	33.9	17	31.3	19.5	9	46.2%	-10.70 [-31.24 , 9.84	1 -=+
Total (95% CI)			35			19	100.0%	-6.66 [-20.62 , 7.30	
Heterogeneity: Tau ² = 0.00; Chi ² = 0.2	28, df = 1 (F	P = 0.60);	I ² = 0%						
Test for overall effect: Z = 0.94 (P = 0.	.35)								-100 -50 0 50 100
Test for subgroup differences: Not app	plicable								Favours [control] Favours [experimen

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

		hMSCs		Control = s	odium hyal	uronate		Mean difference	Mean difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Vangsness Jr. et al 150 million cells	34.1	22.02	18	34.4	19.34	10	62.6%	-0.30 [-16.02 , 15.42	1 -
Vangsness Jr. et al 50 million cells	22.9	33.52	17	34.4	19.34	9	37.4%	-11.50 [-31.84 , 8.84	i _=-
Total (95% CI)			35			19	100.0%	-4.49 [-16.93 , 7.95	
Heterogeneity: Tau ² = 0.00; Chi ² = 0.7	'3, df = 1 (F	= 0.39);	$I^{2} = 0\%$						1
Test for overall effect: Z = 0.71 (P = 0.	.48)								-100 -50 0 50 100
Test for subgroup differences: Not ap	plicable								Favours [control] Favours [experimenta

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.

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SUMM

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

Comnarison: Ilsual care

	Anticipated absolute effects*(95% CI)	Relative effect	Nº of participants	Certainty of the evidence	
Outcomes	Risk with placebo Risk with Outcomes	(95% CI)	(studies)	(GRADE)	Comments
Visual Analogue Scale (post scores) - At 6 months	MD 15.84 higher - (6.21 higher to 25.46 higher)		54 (1 RCT)	$\oplus \bigcirc \bigcirc$	
Visual Analogue Scale (post scores) - At 12 months	MD 19.55higher - (8.34 higher to 30.76 higher)	ı	54 (1RCT)	⊕⊖⊖⊖ Very Low ^{ab,c}	
Lysholm knee scale score- 6 months	MD 6.66 lower - (20.62 lower to 7.30 higher)		54 (1 RCT)	⊕⊖⊖⊖ Very Low ^{ab.d}	
Lysholm knee scale score- 12 months	MD 4.49 lower - (16.93 lower to 7.95 higher)	,	54 (1 RCT)	⊕⊖⊖⊖ Very Low ^{abd}	

CI: confidence interval; MD: mean difference; RR: risk ratio; SMD: standardized mean difference

GRADE Working Group grades of evidence

(and its 95% CI).

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

Evidence based Guidelines for the use of Stem Cell Therapy: Orthopedics Conditions

GRADE EVIDENCE PROFILE

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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.

Evidence based Guidelines for the use of Stem Cell Therapy: Orthopedics Conditions

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.

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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

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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:

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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:

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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