Evidence-based Guidelines for the use of Stem Cell Therapy

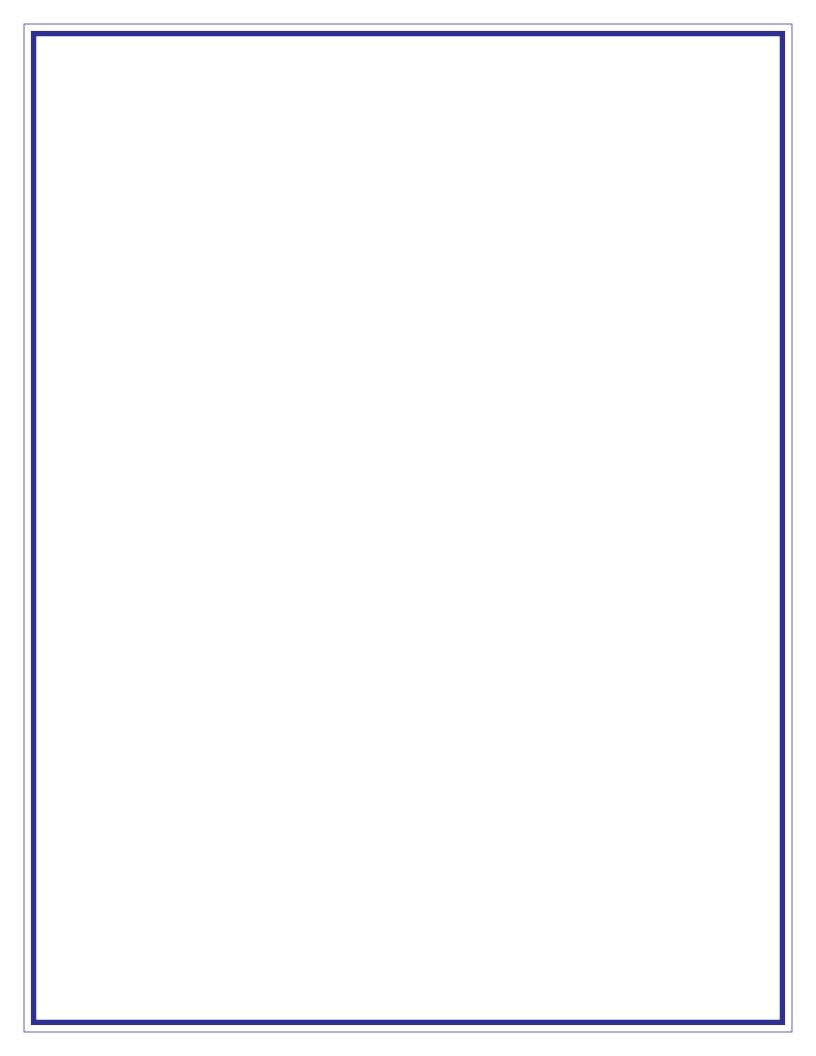
Neurological Conditions



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DISCLAIMER

The Evidence-based Guidelines for the use of Stem Cell Therapy published by the MoHFW/DHR-DGHS provides recommendations made after careful consideration of the available evidence. This evidence has been synthesized by collation of systematic reviews (SR) and meta-analysis (MA) of 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 All MoHFW guidelines are subject to regular review and may be updated or withdrawn.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 immense excitement and hope. Keeping the highest quality of evidence as the foundational base for formulating 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.

Kajn Ball

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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 Living
ADMSCs	:	Adipose Tissue-Derived Mesenchymal Stem Cells
AEs	:	Adverse Events
AHSCT	:	Autologous Hematopoietic Stem Cell Transplantation
ALS	:	Amyotrophic Lateral Sclerosis
ALSFRS-R score	:	Amyotrophic Lateral Sclerosis Functional Rating Scale-
		Revised
BI	:	Barthel Index
BM	:	Bone Marrow
BMA	:	Bone Marrow Aspiration
BMAC	:	Bone Marrow Aspirate Concentrate
BM-MNCs	:	Bone Marrow Mononuclear Cells
BM-MSCs	:	Bone Marrow Derived Mesenchymal Stem/Stromal Cells
BMSCs	:	Bone Marrow Stromal Cells
CBSCs	:	Cord Blood Stem Cells
CD	:	Cluster of Differentiation
CI	:	Confidence Interval
CoI	:	Conflict of Interest
CSF	:	Cerebrospinal Fluid
DMT	:	Disease Modifying Therapy
EDSS	:	Expanded Disability Status Scale
ERG	:	External Review Group
EPC	:	Epithelial Progenitor Cell
EQ-5D	:	Euro-QoL- 5D
ESCs	:	Embryonic Stem Cells
F/U	:	Follow-Up
FVC	:	Forced Vital Capacity
GDG	:	Guideline Development Group
GRADE	:	Grading of Recommendations Assessment, Development and
		Evaluation
haMPCs	:	Human Autologous Adipose-Derived Mesenchymal
		Progenitor Cells
hESCs	:	Human Embryonic Stem Cells
HMSCs	:	Human Mesenchymal Stem Cells
HSCs	:	Hematopoietic Stem Cells
hUC	:	Human Umbilical Cord
HuCNS-SCs	:	Human Central Nervous System Neural Stem Cells
IA	:	Intraarterial
ICA	:	Internal Carotid Artery
IM	:	Intramuscular
iPSCs	:	Induced Pluripotent Stem Cells

IS		Ischemic Stroke
IS IT	:	Intrathecal
I I IV	:	Intravenous
	:	
MCID	:	Minimal Clinical Important Difference Mean Difference
MD Mad	:	
Med	:	Median
MNCs	:	Mononuclear Cells
MPCs	:	Mesenchymal Progenitor Cells
mRS	:	Modified Rankin Scale
MS	:	Multiple Sclerosis
MSCs	:	Mesenchymal Stem Cells
MSC-NTFs	:	Mesenchymal Stem Cell Induced to Secrete High Levels of
		Neurotrophic Factors
NIHSS	:	National Institute of Health Stroke Scale
NR	:	Not Reported
NSAID	:	Non-Steroid Anti-Inflammatory Drug
NSCs	:	Neural Stem Cells
PET	:	Positron Emission Tomography
PRISMA	:	Preferred Reporting Items for Systematic Reviews and Meta-
		Analysis
РТ	:	Physical Therapy
RCT	:	Randomized Controlled Trial
RoB 2	:	Risk of Bias 2
RPMS	:	Rapidly Progressive Multiple Sclerosis
RR	:	Relative Risk
RRMS	:	Relapsing Remitting Multiple Sclerosis
SAEs	:	Severe Adverse Events
SCI	:	Spinal Cord Injury
SCIM	:	Spinal Cord Independence Measure
SCL	:	Spinal Cord Lesions
SD	:	Standard Deviation
SE	:	Standard Error
SF-36	:	36-Item Short-form Health Survey
SMD	:	Standardized Mean Difference
SPMS	:	Secondary Progressive Multiple Sclerosis
SR/MA	:	Systematic Review/Meta-Analysis
SVC	:	Slow Vital Capacity
UCMSCs	:	Umbilical Cord Mesenchymal Stem Cells

EXECUTIVE SUMMARY

1. Background & Rationale:

Neurological disorders are a major cause of disability and mortality worldwide. As per the recent Global burden of disease (GBD) estimates, nervous system disorders are the leading cause of overall disease burden globally.¹ Most of the neurological conditions run a chronic course with limited curative treatment options. Current therapeutic options focus on prevention, delaying symptoms and rehabilitative strategies and hence there is an unmet need for therapies with curative intent. Stem cell therapy is one such 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 neurological diseases. 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 evidence-based recommendations for the use of stem cell therapy in four neurological conditions namely stroke, spinal cord injury, multiple sclerosis and amyotrophic lateral sclerosis.

2. Target audience:

The recommendations in this guideline are intended to inform the policy makers, patients and health care professionals especially neurologists and neurosurgeons practicing in secondary and tertiary care centers as well as researchers and scientists working in the field of regenerative medicine regarding the efficacy and safety of stem cell therapy in the aforementioned neurological 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 systematic review teams. Briefly, the process involved: (i) Identifying priority review questions (PICOs), (ii) Evidence synthesis by systematic review & meta-analysis, (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 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 wording of the final recommendations. This was followed by external peer review before the final release of guidelines.

4. Summary of Recommendations:

S. No	Key Question	Recommendation	Rationale/Justification
1.	In patients with stroke, 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 stroke*. Strength: Conditional# Certainty of Evidence: Very Low <i>#It may be used only in the context</i> of rigorously conducted randomized controlled trials.	There is very low certainty evidence of trivial reduction in mortality and trivial improvement in function and disability. The undesirable effects are variable and heterogenous.
2.	In patients with spinal cord injury (SCI), 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 spinal cord injury. Strength: Conditional [#] Certainty of Evidence: Very Low <i>#It may be used only in the context</i> of rigorously conducted randomized controlled trials.	The evidence is inadequate in quantity and quality to determine the efficacy of stem cell therapy in patients with spinal cord injury. The incidence of undesirable effects including mortality are variable.
3.	In patients with amyotrophic lateral sclerosis (ALS), 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 amyotrophic lateral sclerosis. Strength: Conditional [#] Certainty of Evidence: Very Low <i>#It may be used only in the context</i> <i>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 ALS.
4.	Inpatientswithmultiple sclerosis(MS),a)What is the efficacyandsafetyofhematopoieticstemcelltransplantation	a) Autologous hematopoietic stem cell transplantation (AHSCT) is <u>recommended</u> for the treatment of highly active	There is very low certainty evidence of a large benefit and known harms associated with AHSCT. The committee decided

*The evidence comes from RCTs that included patients with ischemic stroke only. Whether stem cell therapy can be used in patients with haemorrhagic stroke is not known as there are no RCTs in patients with haemorrhagic stroke.

**The evidence overwhelmingly comes from Relapsing Remitting Multiple Sclerosis. It is not known, whether AHSCT is effective in other forms of MS (relapsing progressive, secondary progressive).

##

- A. Highly active treatment-resistant relapsing MS, defined as ≥ 2 episodes of disease activity in the 36 months prior to the assessment for AHSCT. The two disease activity episodes will be a clinical MS relapse or MRI evidence of MS disease activity and must meet all the criteria described below: 1. At least one episode of disease activity must occur following \geq 1 month of treatment with one of the following: (i) a DMT approved for the treatment of relapsing MS, or (ii) a monoclonal antibody approved for the treatment of relapsing MS, or (iii) rituximab. Qualifying DMTs include: dimethyl fumarate, diroximel fumarate, monomethyl fumarate, teriflunomide, cladribine, daclizumab, ponesimod, siponimod, ozanimod, fingolimod, rituximab, ocrelizumab, natalizumab, alemtuzumab, ublituximab, and ofatumumab, and
 - 2. At least one episode of disease activity must have occurred within the 12 months prior to the AHSCT, and
 - 3. At least one episode of disease activity must be a clinical MS relapse confirmed by a neurologist. The other episode(s) must occur at least one month before or after the onset of the clinical MS relapse, and must be either another clinical MS relapse or MRI evidence of disease activity in the form of a gadolinium-enhancing lesion, or a new non-enhancing T2 lesion compared to a reference scan obtained not more than 36 months prior to the time of evaluation.
- B. Expanded Disability Status Scale (EDSS) ≤ 6

C. No contraindications to AHSCT

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 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).

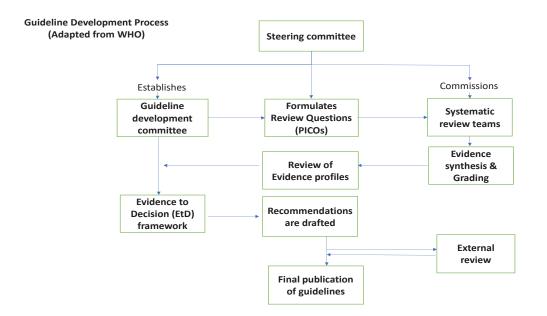


Figure 1: Guideline Development Process -adapted from WHO1

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 informed decisions.

As per the GBD estimates, diseases affecting the nervous system have been ranked as the leading group cause of DALYs in 2021.² Neurological disorders often have a chronic disease course with limited curative treatment options. The disease conditions included for review in the present guidelines are stroke, spinal cord injury, multiple sclerosis and amyotrophic lateral sclerosis. These were selected based on the directives from the MoHFW and a review of literature on the therapeutic use of stem cell therapy in neurological disorders. 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 neurologists and neurosurgeons 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 aforementioned neurological conditions.

4. Contributors:

The guideline was developed using standard methodology as described by international agencies like WHO and NICE.^{1,3} This involved the creation of a steering group, a guideline development group and systematic review teams (List 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 for the guidelines for conducting systematic reviews for addressing the question, decide on the critical outcomes and formulate recommendations based upon evidence generated by the systematic 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 systematic reviews, 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 meetings using the GRADEpro 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 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 technical and administrative support in the entire process of guideline development.

5. Management of Conflict of Interests (CoIs):

All the GDG members need to be free from any conflict of interest in order to formulate 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 were asked to fill up the Declaration of Interests form that was adapted from the WHO.¹These declarations were then reviewed by the steering group and managed appropriately. A summary of the Declaration of interests (DoIs) and how they were managed is provided in Annexure 2.

6. Defining the Scope and Key Questions:

The steering group held a meeting on 11th April 2023 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 neurological conditions included four diseases- stroke, multiple sclerosis, spinal cord injury and amyotrophic lateral sclerosis.

Thereafter, the GDG held a meeting 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 EoI inviting experts in the field from all over the country to conduct systematic reviews and meta-analysis in July 2023. Out of a total of 130 applications received, 28 teams were selected. Criteria for evaluation included methodological expertise, subject expertise, quality of systematic reviews published, database access, strength of team and conflict of interests, if any. The systematic reviews were thus commissioned in September 2023. 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 uniformity and transparency in the entire process of guideline development.

Literature search strategy: To maintain a uniform methodology, all the systematic review teams were instructed to design 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 of relevant review articles was done. 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 that include well characterized stem cells or stem cell-derived products were included.

In addition, few conditions precluded the trial from being included in the final body of evidence in the evidence to decision framework. They were as follows:

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

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

Data extraction methods: Data extraction was conducted by the systematic review 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 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.⁴ While doing meta-analysis, the use of standardized mean difference (SMD) was to be 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 following terms of reference were agreed upon by the GDG 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 systematic review teams was monitored monthly and queries were resolved by the secretariat after discussion with the methodologists.

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

The minimal clinically important difference (MCID) 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 that 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 deliberated and finalized one threshold for each outcome. Wherever 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 can 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. If the studies were less than 10, it was considered in-evaluable. 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.⁵

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 frameworks. 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 domain of the EtD framework based on the evidence presented to them. 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 discussions and deliberation was 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. 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.⁶

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 (randomized controlled trials 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 for any factual errors and thereafter the document was finalized.

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II. RECOMMENDATIONS

1. STROKE

A. BACKGROUND:

Stroke is a leading cause of morbidity and mortality worldwide, with very large direct, indirect and intangible healthcare costs resulting in a major economic burden on the patient, family and society. The Global Burden of Disease study found that globally, stroke remained the second-leading cause of death [11.6% (95% UI: 10.8-12.2) of total deaths] and the third-leading cause of death and disability combined [5.7% (95% UI: 5.1-6.2) of total disability-adjusted life-years] in 2019.¹ In India, stroke is now the fourth leading cause of death and the fifth leading cause of disability.² Despite the availability of numerous medical innovations, interventions and therapeutic approaches, it continues to be one of the leading causes of disability worldwide.

B. RECOMMENDATIONS:

Stem cell therapy is **not recommended** in routine clinical practice for the treatment of stroke*.

Strength: Conditional[#] Certainty of Evidence: Very Low

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

* The evidence comes from RCTs that included patients with ischemic stroke only. Whether stem cell therapy can be used in patients with haemorrhagic stroke is not known as there are no RCTs in patients with haemorrhagic stroke.

Rationale/Justification:

This recommendation has been made as there is very low certainty evidence of trivial reduction in mortality and trivial improvement in functional and disability scale. The undesirable effects are variable and heterogenous. The subgroup analysis based on stem cell type, route of administration and timing of administration and onset of stroke did not reveal any statistically significant and clinically important benefit. In addition, there is uncertainty on the long-term safety of stem cell therapy in patients with stroke. Results should be interpreted with caution, in view of various study limitations like high risk of bias, small number of participants and/or events in the included studies and different sources of stem cell use.

C. SUMMARY OF EVIDENCE:

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

Included Studies: Literature search was done for the articles published up to 31st January 2024. A total of 4550 records from electronic databases and additional 13 from reference lists were

identified. Of the 4563 identified records, 810 duplicates were removed. Further title and abstract screening resulted in exclusion of irrelevant 3654 records. Full text review was done for 99 articles and a total of 15 articles were selected for this systematic review after applying inclusion and exclusion criteria. *The body of evidence comprises RCTs of ischemic stroke only as we could not find any RCTs in patients with hemorrhagic stroke fulfilling the inclusion criteria. Therefore, the recommendations are applicable only to ischemic stroke.*

Type of stem cell: All the fifteen trials used adult non-neural stem cells. Eight studies used bone-marrow derived mesenchymal or mononuclear cells.^{3,4,10-14,16} Two studies used multipotent adult progenitor cells.^{8,9} Peripheral blood stem cells⁶ adipose-tissue derived mesenchymal stem cells⁵, bone marrow-derived ALD-401 cells¹⁷ were used in one study each. Allogenic multilineage-differentiating stress enduring (Muse) cells were used in one study.¹⁵ One study included both epithelial progenitor cells and bone marrow stromal cells as intervention.⁷

Phase of stroke: Three studies were conducted in acute phase^{8,9,14}, six in subacute phase^{4,5,7,15-17}, and six in chronic phase of stroke.^{3,6,10-12}

Route of administration: The cells were transfused intravenously in 10 studies^{3,5,7-10,12,13,15-17}, intraarterially in two^{4,14}, and one in Lumber subarachnoid space.¹¹In one study, the cells were transplanted intracerebrally.⁶

Duration of follow-up: Included studies had a wide range of follow ups, which ranged from 6 months^{4,14} to 1 year^{3,6,8,9,12,15-17}, 2 years^{5,10}, 4 years⁷, 5 years¹³ or 7 years.¹¹

Out of these 15 RCTs on ischemic stroke, 12 trials met the *'reliable body of evidence'* criteria as specified by the GDG and were used for synthesizing evidence.³⁻¹⁷ Studies that were excluded are given below with their respective reason for exclusion.

S. No.	Author	Reason for exclusion
1.	Bang et al. 2005 ³	More than 30 % deviated from allocated intervention post- randomization
2.	De Celis–Ruiz et al. 2022 ⁵	More than 30 % deviated from allocated intervention post- randomization
3.	Lee et al. 2010 ¹³	More than 30 % deviated from allocated intervention post- randomization

Critical outcomes reviewed and their MCID:

S. No.	Outcome reviewed	What does it measure?	MCID decided by the GDG
1.	All-cause mortality	Total number of deaths in a population over a specific period of time	-

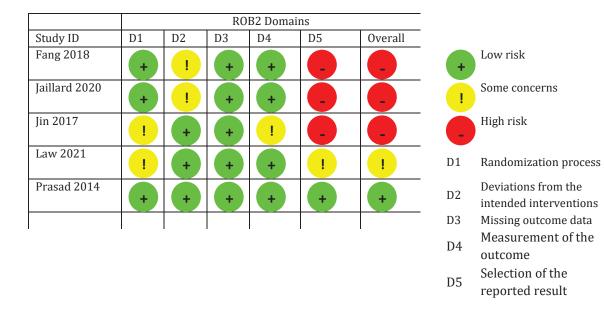
2.	Modified Rankin Scale Range: 0-6 Higher score is worse	Modified Rankin Scale measures degree of disability and dependence after stroke.	An absolute change in mRS score by 1.
3.	Barthel Index Range: 0-100 Higher score is better	TheBarthel Index for activities of daily livingis anordinal scalewhich measures a person's ability to complete activities of daily living.	An absolute change in Barthel Index by 10.
4.	SAEs	Serious Adverse Events	-

Risk of Bias Assessment:

1. Assessment for Modified Rankin scale:



2. Assessment for Barthel Index:



3. Assessment for All-cause mortality:

Study ID	D1	D2	D3	D4	D5	Overall		
Bhatia 2018	!	+	+	+	!	!	+	Low risk
Chen 2014	+	+	+	!	+	!	!	Some concerns
Fang 2018	+	!	+	+	+	!		High risk
Hess 2017	+	+	+	+	-			
Houkin 2024	+	+	+	+	+	+	D1	Randomization process
Jaillard 2020	+	!	+	+	+	!	D2	Deviations from the intende interventions
Jin 2017	!	+	+	+	!	!	D3	Missing outcome data
Law 2021	!	+	+	+	!	!	D4	Measurement of the outcon
Moniche 2023	+	+	+	+	+	+	D5	Selection of the reported result
Niizuma 2023	+	!	+	+	+	!		
Prasad 2014	+	+	+	+	+	+		

Desirable Effects:

1. Disability: Eleven trials, with a total of 697 participants, reported the Modified Rankin Scale (mRS) at the end of follow up. (Follow-up period ranged from 6 months to 7 years). The mean difference in mRS was -0.35 (95% CI: -0.51 to -0.19) in the stem cell arm as compared to usual care. There seems to be a trivial reduction in the disability with the use of stem cell therapy i.e. less than half of the MCID of one (dotted line). Therefore, the effect observed is statistically significant but unimportant clinically.

	Stemcell t	transplant	tation	Conventio	onal treat	ment		Mean Difference		Mean Difference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI		IV, Fixed, 95% CI	
Bhatia 2018	1.3	1.8	10	2.3	2.2	10	0.8%	-1.00 [-2.76, 0.76]	4		
Chen 2014	2.1	0.3	15	2.7	0.5	15	30.2%	-0.60 [-0.90, -0.30]			
Fang 2018*	1.46	0.9	6	1.75	0.9	3	1.7%	-0.29 [-1.54, 0.96]			
Hess 2017	2.8	1.3	67	2.8	1.3	62	13.1%	0.00 [-0.45, 0.45]		i —	
Houkin 2024	3.25	1.81	105	3.5	1.51	102	12.8%	-0.25 [-0.70, 0.20]			
Jaillard 2020	2.75	0.93	20	3.07	1.1	11	4.5%	-0.32 [-1.09, 0.45]		+	
Jin 2017	1.17	0.41	10	2.33	0.82	10	8.2%	-1.16 [-1.73, -0.59]			
Law 2021	2.16	1.11	9	2.83	1.85	8	1.2%	-0.67 [-2.14, 0.80]	←		
Moniche 2023	2.73	1.17	39	2.8	1.4	38	7.9%	-0.07 [-0.65, 0.51]			
Niizuma 2023	2.27	1.32	27	2.62	0.52	10	7.5%	-0.35 [-0.94, 0.24]			
Prasad 2014	3.6	1.4	60	3.4	1.2	60	12.1%	0.20 [-0.27, 0.67]			
Total (95% CI)			368			329	100.0%	-0.35 [-0.51, -0.19]		•	
Heterogeneity: Chi ² =	20.05, df = 1	0 (P = 0.0)	3); I ² = 50 [°]	%				- / -	F		-
Test for overall effect:									-2	-1 U 1	2
	(/								Favours stem cell Favours control	

1.1: mRS at last follow up (6 months to 7 years):

1.2: mRS at last follow-up, by phase of stroke:

	Stemcell	transplant	ation	Conventio	onal treat	ment		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
1.2.2 Acute									•
Hess 2017	2.8	1.3	67	2.8	1.3	62	38.7%	0.00 [-0.45, 0.45]	I —≑—
Houkin 2024	3,25	1.81	105	3.5	1.51	102	37.9%	-0.25 [-0.70, 0.20]	
Moniche 2023	2.73	1.17	39	2.8	1.4	38	23.4%	-0.07 [-0.65, 0.51]	
Subtotal (95% CI)			211			202	100.0%	-0.11 [-0.39, 0.17]	-
Heterogeneity: Chi ² =	0.61, df = 2 (P = 0.74);	I ² = 0%						
Test for overall effect:	Z = 0.78 (P =	0.44)							
1.2.3 Subacute									
Bhatia 2018	1.3	1.8	10	2.3	2.2	10	3.8%	-1.00 [-2.76, 0.76]	
Fang 2018*	1.46	0.9	6	1.75	0.9	3	7.7%	-0.29 [-1.54, 0.96]	
Niizuma 2023	2.27	1.32	27	2.62	0.52	10	33.8%	-0.35 [-0.94, 0.24]	
Prasad 2014	3.6	1.4	60	3.4	1.2	60	54.7%	0.20 [-0.27, 0.67]	
Subtotal (95% CI)			103			83	100.0%	-0.07 [-0.41, 0.28]	
Heterogeneity: Chi ^z =			l² = 10%						
Test for overall effect: .	Z = 0.40 (P =	: 0.69)							
1.2.4 Chronic									
Chen 2014	2.1	0.3	15	2.7	0.5	15	68.6%	-0.60 [-0.90, -0.30]	
Jaillard 2020	2.75	0.93	20	3.07	1.1	11	10.1%	-0.32 [-1.09, 0.45]	
Jin 2017	1.17	0.41	10	2.33	0.82	10	18.5%	-1.16 [-1.73, -0.59]	0
Law 2021 Subtotal (95% CI)	2.16	1.11	9 54	2.83	1.85	8 44	2.8% 100.0%	-0.67 [-2.14, 0.80] -0.68 [-0.92, -0.43]	
						44	100.0%	-0.68 [-0.92, -0.45]	
Heterogeneity: Chi ² =									
Test for overall effect:	z = 5.43 (P +	0.00001)							
									-2 -1 0 1 2
Toot for oubgroup diffe				0.000 13	00.00				Favours [stemcell] Favours [Conventional]

Test for subgroup differences: $Chi^2 = 12.23$, df = 2 (P = 0.002), $I^2 = 83.6\%$

1.3: mRS at last follow-up, by route of administration of stem cell:

	Stemcell t	ransplant	ation	Conventio	onal treati	nent		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% Cl
1.20.1 Intra-arterial									
Bhatia 2018	1.3	1.8	10	2.3	2.2	10	9.7%	-1.00 [-2.76, 0.76]	
Moniche 2023	2.73	1.17	39	2.8	1.4	38	90.3%	-0.07 [-0.65, 0.51]	
Subtotal (95% CI)			49			48	100.0%	-0.16 [-0.71, 0.39]	
Heterogeneity: Chi ² = I	0.97, df = 1 (l	P = 0.33);	l² = 0%						
Test for overall effect: .	Z = 0.57 (P =	0.57)							!
1.20.2 Intravenous									
Fang 2018*	1.46	0.9	6	1.75	0.9	3	3.2%	-0.29 [-1.54, 0.96]	- +
Hess 2017	2.8	1.3	67	2.8	1.3	62	24.7%	0.00 [-0.45, 0.45]	· · · · · · · · · · · · · · · · · · ·
Houkin 2024	3.25	1.81	105	3.5	1.51	102	24.2%	-0.25 [-0.70, 0.20]	
Jaillard 2020	2.75	0.93	20	3.07	1.1	11	8.5%	-0.32 [-1.09, 0.45]	
Law 2021	2.16	1.11	9	2.83	1.85	8	2.3%	-0.67 [-2.14, 0.80]	
Niizuma 2023	2.27	1.32	27	2.62	0.52	10	14.2%	-0.35 [-0.94, 0.24]	I
Prasad 2014	3.6	1.4	60	3.4	1.2	60	22.9%	0.20 [-0.27, 0.67]	I
Subtotal (95% CI)			294			256	100.0%	-0.12 [-0.34, 0.11]	•
Heterogeneity: Chi ² = 3	3.84, df = 6 (l	P = 0.70);	I ² = 0%						
Test for overall effect: .	Z = 1.02 (P =	0.31)							i
1.20.3 Intracerebral									I
Chen 2014	2.1	0.3	15	2.7	0.5			-0.60 [-0.90, -0.30]	
Subtotal (95% CI)			15			15	100.0%	-0.60 [-0.90, -0.30]	
Heterogeneity: Not ap	plicable								
Test for overall effect: .	Z = 3.99 (P <	0.0001)							
1.20.4 Lumber subar	cahnoid spa	ce							<u> </u>
Jin 2017	1.17	0.41	10	2.33	0.82			-1.16 [-1.73, -0.59]	
Subtotal (95% CI)			10			10	100.0%	-1.16 [-1.73, -0.59]	•
Heterogeneity: Not ap									
Test for overall effect: .	Z = 4.00 (P <	0.0001)							
								-4	
								-	Favours stemcell Favours control

Test for subgroup differences: Chi² = 15.24, df = 3 (P = 0.002), l² = 80.3%

1.4: mRS at last follow-up, by type of stem cell:

		erimen			ontrol			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
1.23.1 Mesenchyma									
Jaillard 2020		0.93	20	3.07	1.1	11	78.7%	-0.32 [-1.09, 0.45]	
Law 2021	2.16	1.11	9 29	2.83	1.85	8	21.3% 100.0%	-0.67 [-2.14, 0.80]	
Subtotal (95% CI)						19	100.0%	-0.39 [-1.08, 0.29]	
Heterogeneity: Chi ² =				; I~ = 0%	>				i
Test for overall effect		F (P = 0	1.26)						
1.23.2 BM MNCs									
Bhatia 2018	1.3	1.8	10	2.3	2.2	10	1.4%	-1.00 [-2.76, 0.76]	
Chen 2014	2.1	0.3	15	2.7	0.5	15	49.6%		i-=
Fang 2018*	1.46	0.9	6	1.75	0.9	3	2.8%	-0.29 [-1.54, 0.96]	_
Jin 2017	1.17	0.41	10	2.33	0.82	10	13.4%	-1.16 [-1.73, -0.59]	
Moniche 2023	2.73	1.17	39	2.8	1.4	38	13.0%	-0.07 [-0.65, 0.51]	I
Prasad 2014	3.6	1.4	60	3.4	1.2	60	19.8%	0.20 [-0.27, 0.67]	
Subtotal (95% CI)			140			136	100.0%	-0.44 [-0.65, -0.24]	•
Heterogeneity: Chi ² =					70%				
Test for overall effect	: Z = 4.19	9 (P < 0).0001)						i
1.23.3 Progenitor ce	ells								
Hess 2017	2.8	1.3	67	2.8	1.3	62	50.5%	0.00 [-0.45, 0.45]	! -# -
Houkin 2024	3.25	1.81	105	3.5	1.51	102	49.5%	-0.25 [-0.70, 0.20]	
Subtotal (95% CI)			172			164	100.0%	-0.12 [-0.44, 0.20]	i 🔶
Heterogeneity: Chi ² =	= 0.59, df	= 1 (P	= 0.44)	$ ^{2} = 0\%$	5				
Test for overall effect	: Z = 0.76	6 (P = 0).45)						
1.23.4 Muse cell									
Niizuma 2023	2.27	1.32	27	2.62	0.52	10	100.0%	-0.35 [-0.94, 0.24]	
Subtotal (95% CI)			27				100.0%	-0.35 [-0.94, 0.24]	· · · · · · · · · · · · · · · · · · ·
Heterogeneity: Not a	pplicable								
Test for overall effect	:Z=1.16	6 (P = 0).25)						
									1
									-4 -2 0 2
									Favours stemcell Favours control

Test for subaroup differences: $Chi^2 = 2.74$, df = 3 (P = 0.43), $l^2 = 0\%$

1.5: mRS 0-2 at last follow-up (dichotomized data: events represent participants with good clinical outcome-mRS between 0-2):

	Stemcell transpla	Intation	Conventional tre	atment		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Hess 2017	33	65	27	61	31.6%	1.15 [0.79, 1.66]	-#-
Houkin 2024	38	105	27	102	31.1%	1.37 [0.91, 2.06]	+=
Law 2021	4	9	2	8	2.4%	1.78 [0.44, 7.25]	
Moniche 2023	18	38	14	36	16.3%	1.22 [0.72, 2.07]	- -
Niizuma 2023	15	27	3	10	5.0%	1.85 [0.68, 5.06]	-
Prasad 2014	8	60	12	60	13.6%	0.67 [0.29, 1.51]	
Total (95% CI)		304		277	100.0%	1.21 [0.97, 1.52]	•
Total events	116		85				
Heterogeneity: Chi ² =	3.43, df = 5 (P = 0.6	3); I ² = 0%				ŀ	
Test for overall effect	Z = 1.66 (P = 0.10)					, i	0.01 0.1 1 1 10 100 Favours control Favours stemcell

2. Dependency: Five trials, with a total of 197 participants, reported the Barthel Index (BI) score as a continuous variable at the end of follow up. (Follow-up period ranged from 1 year to 7 years). The mean difference in BI was 12.1 (95% CI: -2.19 to 26.38) in stem cell arm compared to usual care. The difference was statistically non-significant in the pooled analysis.

2.1: BI at last-follow up (range: 1 year to 7 years):

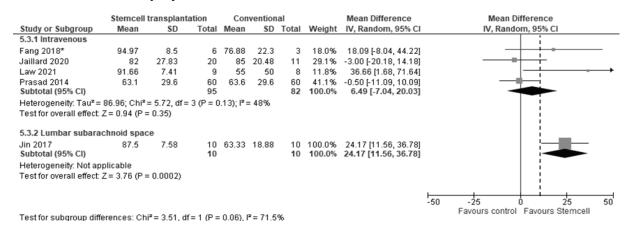
Stemcell	transplant	ation	Con	vention	al		Mean Difference		Mean Difference	
Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI		IV, Random, 95% CI	
94.97	8.5	6	76.88	22.3	3	15.3%	18.09 [-8.04, 44.22]			_
82	27.83	20	85	20.48	11	21.6%	-3.00 [-20.18, 14.18]			
87.5	7.58	10	63.33	18.88	10	25.3%	24.17 [11.56, 36.78]			
91.66	7.41	9	55	50	8	10.9%	36.66 [1.68, 71.64]			\rightarrow
63.1	29.6	60	63.6	29.6	60	26.8%	-0.50 [-11.09, 10.09]			
		105			92	100.0%	12.10 [-2.19, 26.38]			
		lf=4 (P:	= 0.010)	; I² = 70	%			-50	-25 0 25 Favours control Favours stemcell	50
	Mean 94.97 82 87.5 91.66 63.1 168.63; Chi	Mean SD 94.97 8.5 82 27.83 87.5 7.58 91.66 7.41 63.1 29.6	94.97 8.5 6 82 27.83 20 87.5 7.58 10 91.66 7.41 9 63.1 29.6 60 105 168.63; Chi [#] = 13.38, df = 4 (P	Mean SD Total Mean 94.97 8.5 6 76.88 82 27.83 20 85 87.5 7.58 10 63.33 91.66 7.41 9 55 63.1 29.6 60 63.6 105 168.63; Chi ^a = 13.38, df = 4 (P = 0.010) 105	Mean SD Total Mean SD 94.97 8.5 6 76.88 22.3 82 27.83 20 85 20.48 87.5 7.58 10 63.33 18.88 91.66 7.41 9 55 50 63.1 29.6 60 63.6 29.6 105 105 105 105 105	Mean SD Total Mean SD Total 94.97 8.5 6 76.88 22.3 3 82 27.83 20 85 20.48 11 87.5 7.58 10 63.33 18.88 10 91.66 7.41 9 55 50 8 63.1 29.6 60 63.6 29.6 60 105 92 168.63; Chi [#] = 13.38, df = 4 (P = 0.010); I [#] = 70% 92 168.63; Chi [#] = 13.38, df = 4 (P = 0.010); I [#] = 70%	Mean SD Total Mean SD Total Weight 94.97 8.5 6 76.88 22.3 3 15.3% 82 27.83 20 85 20.48 11 21.6% 87.5 7.58 10 63.33 18.88 10 25.3% 91.66 7.41 9 55 50 8 10.9% 63.1 29.6 60 63.6 29.6 60 26.8% 105 92 100.0% 168.63; Chi [#] = 13.38, df = 4 (P = 0.010); I [#] = 70% 92 100.0%	Mean SD Total Mean SD Total Weight IV, Random, 95% CI 94.97 8.5 6 76.88 22.3 3 15.3% 18.09 [-8.04, 44.22] 82 27.83 20 85 20.48 11 21.6% -3.00 [-20.18, 14.18] 87.5 7.58 10 63.33 18.88 10 25.3% 24.17 [11.56, 36.78] 91.66 7.41 9 55 50 8 10.9% 36.66 [1.68, 71.64] 63.1 29.6 60 63.6 29.6 60 26.8% -0.50 [-11.09, 10.09] 105 92 100.0% 12.10 [-2.19, 26.38] 168.63; Chi ² = 13.38, df = 4 (P = 0.010); I ² = 70% 12.10 [-2.19, 26.38]	Mean SD Total Mean SD Total Weight IV, Random, 95% CI 94.97 8.5 6 76.88 22.3 3 15.3% 18.09 [-8.04, 44.22] 82 27.83 20 85 20.48 11 21.6% -3.00 [-20.18, 14.18] 87.5 7.58 10 63.33 18.88 10 25.3% 24.17 [11.56, 36.78] 91.66 7.41 9 55 50 8 10.9% 36.66 [1.68, 71.64] 63.1 29.6 60 63.6 29.6 60 26.8% -0.50 [-11.09, 10.09] 105 92 100.0% 12.10 [-2.19, 26.38] 168.63; Chi² = 13.38, df = 4 (P = 0.010); i² = 70% 150 50	Mean SD Total Mean SD Total Weight IV, Random, 95% CI IV, Random, 95% CI 94.97 8.5 6 76.88 22.3 3 15.3% 18.09 [-8.04, 44.22]

2.2: BI at last-follow up, by phase of disease:

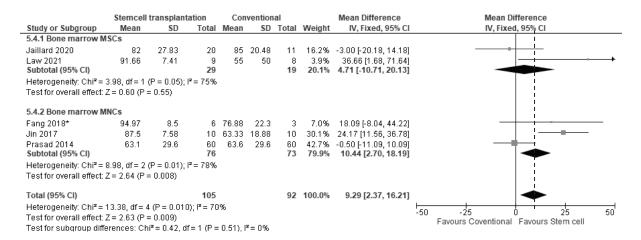
	Stemcell	transplanta	ation	Con	vention	al		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
5.2.2 Subacute									
Fang 2018*	94.97	8.5	6	76.88	22.3	3	28.5%	18.09 [-8.04, 44.22]	
Prasad 2014	63.1	29.6	60	63.6	29.6	60	71.5%	-0.50 [-11.09, 10.09]	
Subtotal (95% CI)			66			63	100.0%	4.80 [-11.65, 21.25]	
Heterogeneity: Tau ² =	= 69.29; Chi²	= 1.67, df =	1 (P = 0)).20); I ²÷	= 40%				i
Test for overall effect:	Z = 0.57 (P =	= 0.57)							
5.2.3 Chronic									
Jaillard 2020	82	27.83	20	85	20.48	11	37.0%	-3.00 [-20.18, 14.18]	
Jin 2017	87.5	7.58	10	63.33	18.88	10	41.3%	24.17 [11.56, 36.78]	
Law 2021	91.66	7.41	9	55	50	8	21.7%	36.66 [1.68, 71.64]	
Subtotal (95% CI)			39			29	100.0%	16.82 [-5.20, 38.83]	
Heterogeneity: Tau ² =	263.91; Chi	² = 7.64, df	= 2 (P =	0.02); P	= 74%				
Test for overall effect:									
									-50 -25 0 25 50
									Favours control Favours Stemcell
Test for submers diff	faranaa Oh	2 - 0 70 de	- 1 (D -	0.000	2 000				Favours control Favours Sterricen

Test for subgroup differences: Chi² = 0.73, df = 1 (P = 0.39), l² = 0%

2.3: BI at last follow-up, by route of administration:



2.4: BI at last follow-up, by type of stem cell:



3. All-cause mortality: Twelve studies with a total of 745 participants and 67 events reported mortality. Pooled analysis yielded a risk ratio of 0.83 (95% CI: 0.54 to 1.28) in the stem cell arm as compared to usual care, which was statistically non-significant.

3.1 Forest plot showing the effect of stem cell therapy on all-cause mortality:

	Stem cell transpla	ntation	Conventional tre	atment		Risk Ratio		Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H, Fixed, 95% CI	
Bhatia 2018	1	10	2	10	5.1%	0.50 [0.05, 4.67]			
Chen 2014	0	15	0	15		Not estimable			
Fang 2018*	0	6	2	3	8.1%	0.11 [0.01, 1.84]	←		
Hess 2017	5	67	9	62	23.8%	0.51 [0.18, 1.45]			
Houkin 2024	13	105	10	102	25.9%	1.26 [0.58, 2.75]			
Jaillard 2020	0	20	1	11	4.9%	0.19 [0.01, 4.32]	•		
Jin 2017	1	10	1	10	2.6%	1.00 [0.07, 13.87]			
Law 2021	1	9	1	8	2.7%	0.89 [0.07, 12.00]			
Moniche 2023	2	39	3	38	7.8%	0.65 [0.11, 3.67]			
Niizuma 2023	1	27	0	10	1.8%	1.18 [0.05, 26.79]			_
Prasad 2014	8	60	5	60	12.8%	1.60 [0.56, 4.61]			
Savitz 2019	0	29	1	19	4.6%	0.22 [0.01, 5.19]	•		
Total (95% CI)		397		348	100.0%	0.83 [0.54, 1.28]		•	
Total events	32		35					_	
Heterogeneity: Chi ² =	7.25, df = 10 (P = 0.7	70); I2 = 0%	5				L		
	est for overall effect: Z = 0.84 (P = 0.40)						0.02	0.1 1 10	50
	, -··-,							Favours Stem cell Favours conventional	I

3.2 Forest plot showing the effect of stem cell therapy on all-cause mortality based on cell type:

	Stem cell transpla	ntation	Conventional tre	atment		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
7.7.1 Mesenchymal							
Jaillard 2020	0	20	1	11	64.3%	0.19 [0.01, 4.32]	←
Law 2021	1	9	1	8	35.7%	0.89 [0.07, 12.00]	
Subtotal (95% CI)		29		19	100.0%	0.44 [0.07, 2.85]	
Total events	1		2				
Heterogeneity: Chi ² = 0		5); I ² = 0%					
Test for overall effect: Z	(= 0.86 (P = 0.39)						
7.7.2 BM MNCs							
Bhatia 2018	1	10	2	10	12.5%	0.50 [0.05, 4.67]	
Chen 2014	0	15	0	15		Not estimable	
Fang 2018*	0	6	2	3	19.9%	0.11 [0.01, 1.84]	•
Jin 2017	1	10	1	10	6.2%	1.00 [0.07, 13.87]	
Moniche 2023	2	39	3	38	19.0%	0.65 [0.11, 3.67]	
Prasad 2014	8	60	5	60	31.2%	1.60 [0.56, 4.61]	
Savitz 2019	0	29	1	19	11.2%	0.22 [0.01, 5.19]	·
Subtotal (95% CI)		169		155	100.0%	0.80 [0.40, 1.58]	-
Total events	12		14				
Heterogeneity: Chi ² = 4 Test for overall effect: Z		3); I² = 0%					
7.7.3 Progenitor cell							
Hess 2017	5	67	9	62	48.0%	0.51 [0.18, 1.45]	— B —
Houkin 2024	13	105	10	102	52.0%	1.26 [0.58, 2.75]	
Subtotal (95% CI)		172		164	100.0%	0.90 [0.49, 1.66]	
Total events	18		19				
Heterogeneity: Chi ² = 1		7); I ^z = 46%	6				
Test for overall effect: Z	(= 0.33 (P = 0.74)						
7.7.4 Muse cell							
Niizuma 2023	1	27	0	10	100.0%	1.18 [0.05, 26.79]	
Subtotal (95% CI)		27			100.0%	1.18 [0.05, 26.79]	
Total events	1		0				
Heterogeneity: Not app	licable						
Test for overall effect: Z	(= 0.10 (P = 0.92)						
							0.01 0.1 1 10 100
To at fair and an and store		-16 - 2 (D	0.000 17 .000				Favours stem cell Favours conventional
Test for subgroup diffe	rences: Chif = 0.58	, at = 3 (P	= 0.90), I* = 0%				

Undesirable effects:

4. Serious Adverse Events: Below is a tabulated description of the serious adverse events reported by the trials:

Outcomes	No of	Total events	Total events	Risk ratio (95 % CI)
	studies	in stem cell	in	
	reporting	arm	conventional	
	SAE		arm	
All-cause mortality	12	32	35	0.83 (0.54 to 1.28)
Recurrent stroke	7	11	7	0.95 (0.42 to 2.14)
Infection	7	52	43	0.89 (0.64 to 1.24)
Seizure	5	11	7	0.84 (0.39 to 1.81)
Worsening of	4	11	5	2.09 (0.80 to 5.46)
neurological deficits				
Development of any	5	0	4	0.20 (0.03 to 1.11)
neoplasm				
Recurrent vascular	4	13	4	1.85 (0.67 to 5.08)
events				

4.1 Recurrent stroke: Seven studies with 251 participants reported recurrent stroke. Pooled analysis yielded a risk ratio of 0.95 (95% CI: 0.42 to 2.14) in the stem cell arm as compared to usual care, which was statistically non-significant.

4.1.1. Recurrent stroke at last follow-up:

	Stem cell transpla	ntation	Conventional trea	tment		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Bhatia 2018	1	10	0	10	4.6%	3.00 [0.14, 65.90]	
Fang 2018*	0	12	1	6	18.0%	0.18 [0.01, 3.85]	<
Jaillard 2020	0	20	2	11	29.4%	0.11 [0.01, 2.19]	← ■
Jin 2017	0	10	1	10	13.9%	0.33 [0.02, 7.32]	
Moniche 2023	2	39	1	38	9.4%	1.95 [0.18, 20.61]	
Niizuma 2023	3	27	1	10	13.5%	1.11 [0.13, 9.48]	
Savitz 2019	5	29	1	19	11.2%	3.28 [0.41, 25.90]	
Total (95% CI)		147		104	100.0%	0.95 [0.42, 2.14]	•
Total events	11		7				
Heterogeneity: Chi ² =	5.84, df = 6 (P = 0.44); I ^z = 0%					
Test for overall effect:	Z = 0.12 (P = 0.90)						0.01 0.1 1 10 100 Favours stem cell Favours conventional

4.2 Infection: Seven studies with 402 participants reported infection. Pooled analysis yielded a risk ratio of RR=0.89 (95% CI: 0.64 to 1.24) in the stem cell arm as compared to usual care, which was statistically non-significant.

4.2.1 Infection at last follow-up:

	Stem cell transpla	ntation	Conventional t	herapy		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% Cl
Bhatia 2018	0	10	0	10		Not estimable	
Hess 2017	25	67	29	62	62.5%	0.80 [0.53, 1.20]	-#-
Jaillard 2020	5	20	6	11	16.1%	0.46 [0.18, 1.16]	
Law 2021	0	9	1	8	3.3%	0.30 [0.01, 6.47]	
Niizuma 2023	11	27	2	10	6.1%	2.04 [0.54, 7.63]	
Prasad 2014	1	60	1	60	2.1%	1.00 [0.06, 15.62]	
Savitz 2019	10	29	4	19	10.0%	1.64 [0.60, 4.47]	
Total (95% CI)		222		180	100.0%	0.89 [0.64, 1.24]	•
Total events	52		43				
Heterogeneity: Chi ² =	5.64, df = 5 (P = 0.34	l); l ² = 119	6				
Test for overall effect:	Z = 0.69 (P = 0.49)						0.01 0.1 1 10 100 Favours stem cell Favours control

4.3 Seizure: Five studies with 202 participants reported seizure. Pooled analysis yielded a risk ratio of RR=0.84 (95% CI: 0.39 to 1.81) in the stem cell arm as compared to usual care, which was statistically non-significant.

4.3.1 Seizure at last follow-up:

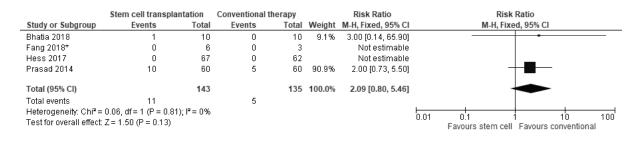
	Stemcell transpla	ntation	Convent	ional		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
Fang 2018*	0	6	1	3	18.3%	0.19 [0.01, 3.66]	· · · · · · · · · · · · · · · · · · ·
Jaillard 2020	6	20	5	11	61.9%	0.66 [0.26, 1.67]	
Moniche 2023	0	39	0	38		Not estimable	
Niizuma 2023	1	27	1	10	14.0%	0.37 [0.03, 5.38]	•
Savitz 2019	4	29	0	19	5.8%	6.00 [0.34, 105.45]	
Total (95% CI)		121		81	100.0%	0.84 [0.39, 1.81]	-
Total events	11		7				
Heterogeneity: Chi ² =	3.40, df = 3 (P = 0.33	3); I ^z = 12 ⁴	%				
Test for overall effect:	Z = 0.44 (P = 0.66)						0.01 0.1 1 10 100 Favours stem cell Favours Conventional

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4.4 Worsening of neurological deficits: Four studies with 278 participants reported worsening of neurological deficits. Pooled analysis yielded a risk ratio of RR=2.09 (95% CI: 0.80 to 5.46) in the stem cell arm as compared to usual care, which was statistically non-significant.

4.4.1 Worsening of neurological deficits at last follow-up:



4.5 Development of any neoplasm: Four studies with 185 participants reported neoplasm development/tumour formation. Pooled analysis yielded a risk ratio of RR=0.20 (95% CI: 0.03 to 1.11) in the stem cell arm as compared to usual care, which was statistically non-significant.

4.5.1 Development of any neoplasm at last follow-up:

	Stem cell transplan	tation	Convent	tional		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% CI
Bhatia 2018	0	10	0	10		Not estimable	
Fang 2018*	0	6	1	3	29.7%	0.19 [0.01, 3.66]	<
Jaillard 2020	0	20	0	11		Not estimable	
Moniche 2023	0	39	1	38	23.6%	0.33 [0.01, 7.74]	
Savitz 2019	0	29	2	19	46.7%	0.13 [0.01, 2.63]	<
Total (95% CI)		104		81	100.0%	0.20 [0.03, 1.11]	
Total events	0		4				
Heterogeneity: Chi ² =	0.16, df = 2 (P = 0.92)	² = 0%					
Test for overall effect:	Z = 1.85 (P = 0.07)						0.01 0.1 1 10 100 Favours stem cell Favours placebo

4.6 Recurrent vascular events: Four studies with 171 participants reported recurrent vascular events. Pooled analysis yielded a risk ratio of RR=1.85 (95% CI: 0.67 to 5.08) in the stem cell arm as compared to usual care, which was statistically non-significant.

4.6.1 Recurrent vascular events at last follow-up:

	Stem cell transpla	Intation	Conventional t	herapy		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% Cl
Fang 2018*	1	6	0	3	11.1%	1.71 [0.09, 32.93]	
Moniche 2023	3	39	3	38	53.0%	0.97 [0.21, 4.53]	
Niizuma 2023	4	27	1	10	25.4%	1.48 [0.19, 11.71]	
Savitz 2019	5	29	0	19	10.5%	7.33 [0.43, 125.42]	
Total (95% CI)		101		70	100.0%	1.85 [0.67, 5.08]	-
Total events	13		4				
Heterogeneity: Chi ² =	: 1.62, df = 3 (P = 0.65	5); I ^z = 0%					
Test for overall effect:	Z = 1.19 (P = 0.23)						0.01 0.1 1 10 100 Favours stem cell Favours conventional

patedabsoluteeffects' (95% effects' (95% cl)cellRelative evidenceeffect frudies)Relative of chantsdefCertainty of chantsof trainsplantationwithRisk with Sisk with Stem cellRelativeeffect (0.51 lower to 0.19 (0.51 lower to 0.19)Relative (0.51 lower to 0.26.38 higher)Relative (0.51 lower to 0.26.38 higher)r 1,000R3R81.21 lower to 0.26.38 lower (0.51 lower to 0.26.31 lower to 0.26.38 lowerRelative (0.57 lowerRelative (0.57 lowerr 1,000 </th <th>Patient or population: Ischemic stroke Setting: Hospital Intervention: Stem cell transplantation</th> <th>pared to convent c stroke mtation</th> <th>stem cell transplantation compared to Conventional treatment for Iscnemic stroke Patient or population: Ischemic stroke Setting: Hospital Intervention: Stem cell transplantation</th> <th>schemic stroke</th> <th></th> <th></th> <th></th>	Patient or population: Ischemic stroke Setting: Hospital Intervention: Stem cell transplantation	pared to convent c stroke mtation	stem cell transplantation compared to Conventional treatment for Iscnemic stroke Patient or population: Ischemic stroke Setting: Hospital Intervention: Stem cell transplantation	schemic stroke			
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Idency ted with: BI at last follow bed with: BI at last follow inge: 1 years 0 7 years) erMD12.1 higher (2.19 lower to 26.38 higher) erMD12.1 higher (5 RCTs)MOMa bolute hidex by 10 Wery lowcdeer=better) (5 non: 0 to 100101 per 1,00083 per 1,00083 745 (0.54 to 129) $\Theta \odot \odot$ $\Theta \oplus \odot \odot$ lity mRS 0-2 (mRS 0-2 at follow with: Modified rankin307 per 1,00081 per 1,000 $(0.54 to 1.28)$ $(12 RCTs)$ $\Theta \oplus \odot \odot$ sed with: Modified rankin $307 per 1,000$ RR $1.21 581$ $\Theta \oplus \odot$	Disability assessed with: mRS at last follow up (6 months to 7 years) (higher =worse) Scale from: 0 to 6		MD 0.35 lower (0.51 lower to 0.19 lower)		697 (11 RCTs)	⊕⊕⊖⊖ Low³b	An absolute change in mRS score by 1 was considered as MCID.
use mortality 101 per 1,000 83 per 1,000 RR 0.83 745 ility mRs 0-2 (mRs 0-2 at follow 101 per 1,000 54 to 129 (0.54 to 1.28) (12 RCTs) 12 RCTs follow up 371 per 1,000 RR 1.21 581 sed with: Modified rankin 307 per 1,000 (298 to 466) RR 1.21 581	Dependency assessed with: BI at last follow up (range: 1 year to 7 years) (higher = better) Scale from: 0 to 100		12.1 high 9 lower 8 higher)		197 (5 RCTs)	⊕⊖⊖⊖ Very lowcde	An absolute change in Barthel Index by 10 was considered as MCID.
ility mRS 0-2 (mRS 0-2 at 371 per 1,000 follow up) 307 per 1,000 (298 to 466) RR 1.21 581 sed with: Modified rankin ³⁰⁷ per 1,000 (0.97 to 1.52) (6 RCTs)	All-cause mortality	101 per 1,000	per to 129)	54 to 1.28)	3 745 (12 RCTs)	⊕⊕⊖⊖ Low ^{fg,h}	
	Disability mRS 0-2 (mRS 0-2 at last follow up) assessed with: Modified rankin scale		per 8 to 466)	17 to 1.52)	1 581 (6 RCTs)	⊕⊕⊕⊖ Moderate ⁱ	

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Anticipated absolute effects'(95% anticipates	Anticipated absolute CI) Risk with Risk Risk with Risk with Risk Conventional treatment cell trans trianty: We are very confident that the true effect lies clos cell trans trianty: We are wordence the effect estimate is limited: the the trainty: We have very little confidence in the effect estimates is limited: the the tainty: We have very little confidence in the effect estimates (and one level for risk of bias as less than 2/3 nd - studies (and one level as the point estimates vary widely across the one level as the point estimates vary widely across the one level as the confidence level crossed the null eff to one level as the confidence level crossed the null eff to one level as the confidence level crossed the null eff to one level as the confidence level crossed the null eff to one level as the confidence interval crosses the studie of to one level as the confidence interval crosses the null	Patient or population: Ischemic stroke Setting: Hospital Intervention: Stem cell transplantation Comparison: Conventional treatment	mic stroke plantation eatment						
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IRADE Working Group grades of evidence ligh certainty: We are very confident that the true effect lies close to that of the effect. In coderate certainty: We are wory confident that the true effect lies close to the effect. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially fiferent. ow certainty: Our confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of the effect. ery 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. ery 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. ery 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.	BADE Working Group grades of evidence Construct Sequence Construct Sequence Construct Set of evidence Construct Set of the effect lies close to that of the effect. Construct Set are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect. Construct Set are working for up and the intervention of the effect estimate in the rule effect estimate of the effect is likely to be substantially different from the estimate of friet. Construct Set are working for up the effect estimate: the true effect is likely to be substantially different from the estimate of friet. Construct Set are substantially and the effect estimate: Construct Set are substantially different from the estimate of friet. Construct Set are substantially and the effect estimate: Construct Set are are substantially different from the estimate of friet. Construct Set are and the effect estimate: Construct Set are and the point estimate: Construct Set are and the confidence in the effect and the estimate of the estimate and the estimate of the estimate and the estimate of the estimate and the estimate and the estimate and the estimate of the estice and the estimate and the estimate and the estimat	Outcomes	entiona	Risk with cell transplanta	Relative (95% CI)	t Nº of participant (studies)			
lifferent. ow certainty: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect. ertainty: Our confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect. erty 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. cplanations cplanations conv graded one level for risk of bias as less than2/3 nd . studies (by wt.) were at low risk of bias. Downgraded one level for risk of bias as less than2/3 nd . studies (by wt.) were at low risk of bias. Downgraded one level for risk of bias as proximately 2/3 nd of studies (by wt.) were at low risk of bias. Downgraded one level as the point estimates vary widely across the studies (by wt.) were at low risk of bias. Downgraded one level as the confidence level crossed the null effect. Downgraded one level as 4 out of 12 included studies had high risk of bias. The cumulative weight of studies with low risk of bias was 45.6%. Downgraded one level as the Confidence interval crossed the null effect. Downgraded one level as the Confidence interval crossed the null effect.	Ilferent: any ecretainty: Our confidence in the effect estimates is limited, the true effect using the substantially different from the estimate of the effect. <i>Explow ecretainty:</i> We have very little confidence in the effect estimates the true effect is likely to be substantially different from the estimate of effect. <i>Explore ecretainty:</i> No have very little confidence in the effect estimates the true effect is likely to be substantially different from the estimate of effect. <i>Explore and the effect estimates substantial of the effect estimates in the effect estimates substantial between the estimates are staticable by wt.</i> We est on the rest of the effect estimates wary widely across the studies (by wt.) were at low risk of bias. Downgraded one level for risk of bias as approximately 2/3* of studies (by wt.) were at low risk of bias. Downgraded one level as the point estimates wary widely across the studies. There is substantial heterogeneity with 1 ² of 70%. Downgraded one level as the point estimates wary widely across the studies. There is substantial heterogeneity with 1 ² of 70%. Downgraded one level as the onit estimates wary widely across the studies but the confidence interval overlap. Downgraded one level as the onit estimates wary widely across the studies but the confidence interval overlap. Downgraded one level as the confidence interval crossed the null effect. Downgraded one level as the Confidence interval crosses the null effect.	GRADE Working Group grades o High certainty: We are very confi Moderate certainty: We are mode	of evidence ident that the true effe erately confident in the	effect estimate: the true	estimate of the effect. : effect is likely to be clo	ose to the estimate of	the effect, but there	e is a possibility that it is substa	mtially
Downgraded one level for risk of bias as less than 2/3 rd - studies (by wt.) were at low risk of bias Downgraded one level for risk of bias as approximately 2/3 rd of studies (by wt.) were at low risk of bias. Downgraded one level for risk of bias as approximately 2/3 rd of studies (by wt.) were at low risk of bias. Downgraded one level as the point estimates vary widely across the studies. There is substantial heterogeneity with I ² of 70% Downgraded one level as the point estimates vary widely across the studies. There is substantial heterogeneity with I ² of 70% Downgraded one level as the confidence level crossed the null effect. Downgraded one level as 4 out of 12 included studies had high risk of bias. The cumulative weight of studies with low risk of bias was 45.6%. Although I ² was 0%, Point estimates vary widely across the studies but the confidence interval overlap. Downgraded one level as CI of effect estimate crossed the line of Null effect.	Downgraded one level for risk of bias as less than 2/3 ^{-nt} studies (by wt.) were at low risk of bias Downgraded one level for risk of bias as approximately 2/3 ^{-nd} fstudies (by wt.) were at low risk of bia. Downgraded one level for risk of bias as approximately 2/3 ^{-nd} fstudies (by wt.) were at low risk of bias. Downgraded one level for risk of bias as approximately 2/3 ^{-nd} fstudies (by wt.) were at low risk of bias. Downgraded one level as the point estimates vary widely across the studies. There is substantial heterogeneity with I ² of 70% Downgraded one level as the point estimates vary widely across the studies. There is substantial heterogeneity with I ² of 70% Downgraded one level as the confidence level crossed the mull effect. Ibowngraded one level as 4 u of 12 included studies had high risk of bias. The cumulative weight of studies with low risk of bias was 45.6%. Downgraded one level as the Confidence interval crossed the line of Null effect. Downgraded one level as the Confidence interval crosses the null effect.	Low certainty: Our confidence in Very low certainty: We have very Explanations	the effect estimate is li y little confidence in th	imited: the true effect ma e effect estimate: the true	y be substantially diffe e effect is likely to be su	erent from the estimat ubstantially different	te of the effect. from the estimate of	of effect.	
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Evidence Profile:

Stem cell transplantation compared to Usual Care for Ischemic stroke

Certainty assessment	ssment						Summary of findings	of findings			
							Study event rates (%)	t rates (%)		Anticipated absolute effects	solute effects
Participants (studies) Follow-up	Risk of bias	f Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty Wit of evidence nal tre:	With Conventio nal treatment	With Stem cell trans plantation	Relative effect (95% Cl)	Risk with Conventional treatment	with Risk difference mal with Stem cell t transplantation
Disability asse	ssed with	Disability assessed with: mRS at last follow up (6 mont	ow up (6 mont	ths to 7 years)	hs to 7 years) (higher =worse); Scale from: 0 to 6	se); Scale f	rom: 0 to 6				
697 (11 RCTs)	Serious ^a	Serious ^b	Not serious	Not serious	Not detected	⊕⊕⊖⊖ Low		1	I	329	MD 0.35 lower (0.51 lower to 0.19 lower)
Dependency as	ssessed w	Dependency assessed with: Blat last follow up (range:	ow up (range:		l year to 7 years) (higher = better); Scale from: 0 to 100	better); Sc	ale from: 0	to 100			
197 (5 RCTs)	Serious ^c	Serious ^d	Not serious	Serious ^e	Inevaluable	⊕⊖⊖⊖ Very low		1	I	92	MD 12.1 higher (2.19 lower to 26.38 higher)
All-cause mortality	ality										
745 (12 RCTs)	Serious ^f	Not serious ^g	Not serious	Serious ^h	Not detected	⊕⊕⊖⊖ Low	35/348 (10.1%)	32/397 (8.1%)	RR 0.83 (0.54 to 1.28)	to (10.1%)	17 fewer per 1,000 (from 46 fewer to 28 more)
Disability mRS	: 0-2 (mRS	Disability mRS 0-2 (mRS 0-2 at last follow up) assessed with: Modified rankin scale	w up) assessed	d with: Modifie	ed rankin scal	e					
581 (6 RCTs)	Not serious	Not serious	Not serious	Serious	Inevaluable	⊕⊕⊕⊖ Moderate	85/277 (30.7%)	116/304 (38.2%)	RR 1.21 (0.97 to 1.52)	21 85/277 to (30.7%)	64 more per 1,000 (from 9 fewer to 160 more)
CI: confidence	interval; MI	CI: confidence interval; MD: mean difference; RR: risk ratio	RR: risk ratio								
Explanations a. Downgraded b. Downgraded c. Downgraded	l one level fi l one level a l one level fo	Explanations a. Downgraded one level for risk of bias as less than 2/3 ^m . studies (by wt.) were at low risk of bias. b. Downgraded one level as the point estimates vary widely across the studies although the confidence intervals (CI) show overly c. Downgraded one level for risk of bias as approximately 2/3 ^m of studies (by wt.) were at low risk of bias.	s than 2/3 ^{rd-} stuc es vary widely ac proximately 2/3 ^{rr}	lies (by wt.) werg ross the studies a of studies (by w	e at low risk of bi although the conf t.) were at low ri	as. ìdence interv sk of bias.	als (CI) show	overlap. There	: is moderate	Explanations a. Downgraded one level for risk of bias as less than 2/3 ^m - studies (by wt.) were at low risk of bias. b. Downgraded one level as the point estimates vary widely across the studies although the confidence intervals (CI) show overlap. There is moderate heterogeneity with I ² of 50%. c. Downgraded one level for risk of bias as approximately 2/3 ^m of studies (by wt.) were at low risk of bias.	1² of 50%.

d. Downgraded one level as the point estimates vary widely across the studies. There is substantial heterogeneity with I² of 70%.
e. Downgraded one level as the confidence level crossed the null effect.
f. Downgraded one level as 4 out of 12 included studies had high risk of bias. The cumulative weight of studies with low risk of bias was 45.6%.
g. Although I² was 0%, Point estimates vary widely across the studies but the confidence interval overlap.
h. Downgraded one level as Cl of effect estimate crossed the line of Null effect.
i. Downgraded one level as the Confidence interval crosses the null effect.

Evidence-based Guidelines for the Use of Stem Cell Therapy: Neurological 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
Decommendations, Cham call the many is	not recommended in reuting clinical practice for the

Recommendations: Stem cell therapy is <u>not recommended</u> in routine clinical practice for the treatment of stroke[#]. 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 mortality and trivial improvement in function and disability.

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

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

The evidence comes from RCTs that included patients with ischemic stroke only. Whether stem cell therapy can be used in patients with haemorrhagic stroke is not known as there are no RCTs in patients with haemorrhagic stroke.

E. CAVEATS IN EXISTING EVIDENCE:

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

- 1. Lack of sufficient number of RCTs with low risk of bias
- 2. Small number of participants and/or events in included trials
- 3. Heterogeneity in the type of stem cell therapy used, ranging from bone marrow mononuclear cells to mesenchymal stem cells and endothelial progenitor cells, cell dosage, route of administration and time of administration which though increases generalisability and applicability but decreases the probability of finding effect with small number of participants
- 4. Lack of long term follow up of patients in most studies, thus providing insufficient evidence on the safety of this experimental therapy
- 5. Lack of cost effectiveness data

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2. SPINAL CORD INJURY

A. BACKGROUND:

Spinal cord injury (SCI) is a debilitating neurological condition with tremendous socioeconomic impact on affected individuals and their families. The Global Burden of Disease Study 2019 yielded an incidence of 134 (95% UI:104 to 174) (in thousands) cases in India in 2019.¹ As it has no effective treatment available, spinal cord injury continues to be associated with long-term disability, decreased life expectancy, reduced quality of life, and a great financial burden to health-care systems and the individuals who are affected.^{1,2}

B. RECOMMENDATIONS:

Stem cell therapy is **<u>not recommended</u>** in routine clinical practice for the treatment of spinal cord injury.

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 the evidence is inadequate in quantity and quality to determine the efficacy of stem cell therapy in patients with spinal cord injury. The incidence of undesirable effects including mortality are variable. In addition, the reported follow up period is too small to comment on the side effect profile and long-term safety is not known.

C. SUMMARY OF EVIDENCE:

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

Included Studies: The final search dated 18th November 2023 yielded 164 studies from EMBASE, Web of Sciences, Cochrane Central and PubMed. Studies were screened based on their eligibility criteria. Eleven studies were included in the systematic review and meta-analysis after satisfying the inclusion and exclusion criteria. Out of these 11 RCTs, 5 trials met the *'reliable body of evidence'* criteria, as specified by the GDG and were used for synthesizing evidence.³⁻¹³

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.	Abdelaziz et al. 2010 ³	Absence of stem cell characterization
2.	Cheng et al. 2014 ⁷	Absence of stem cell characterization
3.	Ghobrial et al. 2017 ⁸	Insufficient data for inclusion in analysis
4.	Yang et al. 2020 ¹¹	Absence of stem cell characterization
5.	Song et al. 2020 ¹²	Absence of stem cell characterization
6.	Srivastava et al. 2019 ⁹	Outcome not of interest

The type of participants and the nature of intervention in the included studies are as follows:

Study	Phase of disease	Type of stem cell used	Route of
			administration
Albu et al. 2021 ⁴	Chronic SCI	Wharton jelly derived	Intrathecal
		mesenchymal stem cells	
Dai et al. 2013 ⁵	Chronic SCI	BM derived mesenchymal	Local (at site of injury)
		stem cells	
El Kheir et al.	Chronic SCI	BM derived mesenchymal	Intrathecal
20146		stem cells	
Levi et al. 2019 ¹⁰	Chronic SCI	Neural stem cells (allogenic)	Intramedullary
Saini et al.	Acute SCI (within	CD34+ BM derived stem cells	Intramedullary
202213	21 days)		

Critical outcomes reviewed and their MCID:

S. No.	Outcome reviewed	What does it measure?	MCID decided by
			the GDG
1.	SpinalCordIndependenceMeasureScale (SCIM)Range: 0-100Higher score is better	The SCIM is a comprehensive rating scale that measures the ability of patients with spinal cord lesions (SCL) to accomplish various functional activities.	An absolute change in SCIM scale by 10
2.	Wexner Score Range: 0-20 Higher score is worse	The Wexner score is a scoring system used to assess fecal incontinence.	An absolute change in Wexner score by 2

3.	Qualiven questionnaire (Bladder function)	It is a 30 items questionnaire for urodynamic studies and measures the specific impact of urinary symptoms on quality of life.	-
4.	WHO Quality of Life- BREF Range: 0-100	The WHOQOL-BREF is a 26-item questionnaire that measures quality of life in four domains: physical health, psychological health, social relationships, and environment.	-
5.	SAEs	Serious Adverse Events	-
6.	All-cause mortality	Total number of deaths in a population over a specific period of time	-

D1 D2 D3 D4 D5 Study Overall (+)+ + + Low risk Saini et al, 2022 + (\mathbf{I}) Albu et al, 2021 Some concerns + + Dai et al, 2013 High risk (+) (\mathbf{I}) + D1 El Kheir et al, 2014 Randomisation process + + Levi et al, 2019 D2 Deviations from the intended interventions D3 Missing outcome data D4 Measurement of the outcome D5 Selection of the reported result

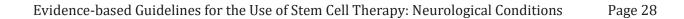
Risk of Bias Assessment:

Desirable effects:

There is insufficient evidence to draw firm conclusions regarding the desirable effects of stem cell therapy in patients with spinal cord injury.

1. Dependency: Evidence from one RCT* with 21 participants of acute complete spinal cord injury reported a mean difference of 9.76 (95% CI: -2.14 to 21.66) in the SCIM Score in the stem cell therapy arm (intramedullary route) as compared to usual care at the end of six months. The difference was statistically non-significant.

* More than 30% of patients in each arm died. Their data was incorporated in the analysis assuming the worst outcome.

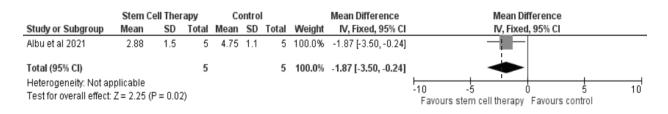


1.1 SCIM scale at the end of six months:

	Stem 0	cell ther	ару	C	control			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% Cl	I IV, Fixed, 95% CI
Saini et al 2022	18.76	15.9	10	9	11.28	11	100.0%	9.76 [-2.14, 21.66]	Ŋ ₩
Total (95% CI)			10			11	100.0%	9.76 [-2.14, 21.66]	a, , 🔶 , ,
Heterogeneity: Not ap Test for overall effect:		(P = 0.11	1)						-100 -50 0 50 100 Favours control Favours stem cell therapy

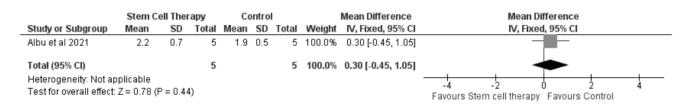
2. Bowel Function: Evidence from one RCT with 10 participants of chronic complete spinal cord injury reported a reduction in the Wexner Score with a mean difference of -1.87 (95% CI: -3.50 to - 0.24) in the stem cell therapy arm (intrathecal route) as compared to usual care at the end of six months. The difference was statistically significant but unimportant clinically as it was less than the MCID of 2.

2.1 Wexner score at the end of six months:



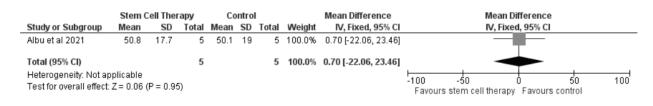
3. Bladder Function: Evidence from one RCT with 10 participants of chronic complete spinal cord injury reporting the Qualiven questionnaire (subscale- specific impact of urinary symptoms on quality of life) observed a mean difference of 0.30 (95% CI: -0.45 to 1.05) in the stem cell arm (intrathecal route) as compared to usual care at the end of six months. The difference was statistically non-significant.

3.1 Bladder function at the end of six months:



4. Quality of Life: Evidence from one RCT with 10 participants of chronic complete spinal cord injury reporting WHOQOL-BREF observed a mean difference of 0.70 (95% CI: -22.06 to 23.46) in the stem cell therapy arm (intrathecal route) as compared to usual care at the end of six months. The difference was statistically non-significant.

4.1 Quality of life at the end of six months:



5. Undesirable effects:

Serious Adverse Events: Albu et al⁴, Dai et al⁵ and El Kheir et al⁶ did not report any SAEs in either of the arms. The SAEs reported by Levi et al¹⁰ included sepsis, posterior reversible encephalopathy syndrome, seizure, wound hematoma and autonomic dysreflexia in the stem cell arm and urinary tract infection in the usual care arm.

All-cause mortality: Saini et al¹³ reported all-cause mortality, 5 patients in the usual care arm and 3 patients in the stem cell arm expired during the follow up period due to ventilation associated pneumonia. This difference was statistically not significant (p = 0.31).

Injury Injury Relative Rel	Relative Name Of Certainty of the 95% 95% participants evidence evidence evidence (1 RCT) Very lowabs evidence evidence evidence er) - 21 0 0 evidence evidence er) - 21 0 0 evidence evidence er) - 10 0 0 evidence evidence er) - 10 0 0 evidence evidence evidence her) - - 10 0 0 evidence							
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Explanations a. Cochrane's Risk of Bias tool found a high risk of bias in the studies, which leads to downgrading the Risk of Bias grade by two levels. b. Single study was downgraded one level for inconsistency as it was inevaluable. c. Downgraded one level for imprecision as effect estimate is crossing the line of no effect.	Explanations a. Cochrane's Risk of Bias tool found a high risk of bias in the studies, which leads to downgrading the Risk of Bias grade by two levels. b. Single study was downgraded one level for inconsistency as it was inevaluable. c. Downgraded one level for imprecision as effect estimate is crossing the line of no effect. d. Downgraded one level for imprecision as OIS not met.	*The risk in the intervention group CI: confidence interval; MD: mean diffe GRADE Working Group grades of evi High certainty: We are very confident Moderate certainty: Our confidence in the e Low certainty: Our confidence in the e Very low certainty: We have very little	(and its 95% confidence erence; RR: risk ratio idence t that the true effect lies ely confident in the effe effect estimate is limited le confidence in the effe.	e interval) is based on the assumed close to that of the estimate of the ct estimate: the true effect is likely it: the true effect may be substantial ct estimate: the true effect is likely	risk in the effect. So be close 1 Jy different to be substi	comparison gro o the estimate from the estim ntially differer	oup and the relative of the effect, but there are of the effect, but there are of the estimate of	ffect of the intervention (and its 95% CI). is a possibility that it is substantially different.
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Stem cell the	erapy con	Stem cell therapy compared to usual care in patients with Spinal Cord Injury:	care in patien	its with Spina.	Cord Injury:						
Certainty assessment	sessment						Summary of findings	of findings			
Participants (studies)	Risk of hias	Inconsistency Indirectness Imprecision	Indirectness		Publication hias	Overall certainty of	Study event rates (%) With With ster	E	Relative effect	Anticipated abso Risk with Risk	lute effect differe
Follow-up	COLO					or evidence	standard of care	cell therapy	(95% CI)	standard of care	with stem cell therapy
SCIM at 6 months	onths										
21 (1 RCT)	Very serious ^a	Inevaluable ^b	Not serious	Serious ^c	Inevaluable	⊕⊖⊖⊖ Very low				1	MD 9.76 higher (2.14 lower to 21.66 higher)
Wexner Score at 6 months	e at 6 mo	onths									
10 (1 RCT)	Very serious ^a	Inevaluable ^b	Not serious	Serious ^d	Inevaluable	⊕⊖⊖⊖ Very low			1	1	MD 1.87 lower (3.50 lower to 0.24 lower)
Qualiven qu	estionnai	Qualiven questionnaire (specific impact of urinary symptoms on QoL) at 6 months	oact of urinary	symptoms or	1 QoL) at 6 moi	nths					
10 (1 RCT)	Very serious ^a	Inevaluable ^b	Not serious	Serious ^c	Inevaluable	⊕⊖⊖⊖ Very low	,	1	1		MD 0.30 higher (0.45 lower to 1.05 higher
WHOQoL- BREF at 6 months	EF at 6 m	onths								_	
10 (1 RCT)	Very serious ^a	Inevaluable ^b	Not serious	Serious ^c	Inevaluable	⊕⊖⊖⊖ Very low				1	MD 0.70 higher (22.06 lower to 23.46 higher)
CI: confidence Explanations:	ce interval; 1S:	CI: confidence interval; MD: mean difference; RR: risk ratio Explanations:	nce; RR: risk rati	0							
a. Cochrane b. Single stu c. Downgrac d. Downgrae	s Risk of Bi dy was dov led one lev łed one lev	a. Cochrane's Risk of Bias tool found a high risk of bias in the studies, which leads to downgrading the Risk of Bias grade by two levels. b. Single study was downgraded one level for inconsistency as it was inevaluable. c. Downgraded one level for imprecision as effect estimate is crossing the line of no effect. d. Downgraded one level for imprecision as OIS not met.	gh risk of bias in tl I for inconsistenc as effect estimate as OIS not met.	he studies, whic y as it was ineva is crossing the l	ı leads to downgr luable. ine of no effect.	ading the Risk	of Bias grade t	oy two levels.			

Evidence-based Guidelines for the Use of Stem Cell Therapy: Neurological 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:

Desirable Effects	Don't Know*
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 clinical practice for the treatment of spinal cord injury. It may be used only in the context of rigorously conducted RCTs.

* This judgment was made as the evidence is inadequate in quantity and quality to determine the efficacy of stem cell therapy in patients with spinal cord injury.

** This judgment was made as the incidence of undesirable effects including mortality are variable.

*** 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 limitations:

- 1. Very few high quality RCTs with lack of explicit sequence generation and allocation concealment leading to a high risk of bias
- 2. Small number of participants and/or events in the included trials
- 3. Heterogeneity in the type of patients included in terms of the level of spinal cord injury, the severity of patients and the level of disability which though increases generalisability and applicability but decreases the probability of finding effect with small number of participants
- 4. Heterogeneity in the outcomes assessed by the RCTs
- 5. Heterogeneity in the type of stem cell therapy used ranging from mononuclear cells to mesenchymal stem cells
- 6. Lack of appropriate characterization and standardization of stem cells
- 7. Lack of long term follow up of patients thus providing insufficient evidence on the safety of this experimental therapy
- 8. Lack of cost effectiveness data

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3. AMYOTROPHIC LATERAL SCLEROSIS

A. BACKGROUND:

Amyotrophic lateral sclerosis (ALS) is a type of motor neuron disease characterized by progressive degeneration of neurons in the brain and spinal cord and is more common in men. The illness is relentlessly progressive, leading to death from respiratory paralysis and the median survival is between 3–5 years. The incidence of ALS is approximately 1-2.6 cases per 100000 persons annually, whereas the prevalence is approximately 6 cases per 100000.¹ None of the current disease modifying therapies reverse disease progression. The treatment is mainly supportive and the clinical care is associated with high costs for the patients and their families.

B. RECOMMENDATIONS:

Stem cell therapy is **not recommended** in routine clinical practice for the treatment of amyotrophic lateral sclerosis.

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 the evidence is inadequate in quantity and quality to determine the safety and efficacy of stem cell therapy in patients with ALS. The difference in the Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS) score between the two arms was statistically non-significant. The difference in the forced vital capacity and slow vital capacity between both arms was also statistically non-significant. The difference in all-cause mortality and serious adverse events in the stem cell arm as compared to usual care was also statistically non-significant. In addition, the follow up period of one year is too small to comment on the side effect profile and long-term safety is not known. Results should be interpreted with caution, in view of very few studies with small number of participants and/or events.

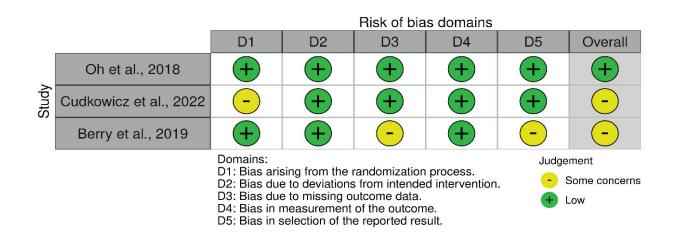
C. SUMMARY OF EVIDENCE:

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

Included Studies: After conducting a thorough literature search upto 15th March 2024 using prespecified databases, a total of 320 articles were identified. These articles were then screened based on the inclusion and exclusion criteria. Out of the 320 articles, only three studies met the criteria to be included in the current meta-analysis.²⁻⁴ All the 3 reported studies used autologous bone marrow derived mesenchymal stem cells as the intervention via intrathecal route. Critical outcomes reviewed and their MCID:

S.	Outcome reviewed	What does it measure?	MCID decided by
No			the GDG
1.	Revised Amyotrophic	It is a disease-specific severity score that	An absolute change
	Lateral Sclerosis	reflects motor impairment and functional	in ALSFRS score by
	Functional Rating	deterioration in people with amyotrophic	3.24
	Scale ALSFRS-R	lateral sclerosis (ALS). The ALSFRS-R measures	
	Range:0-48	12 aspects of physical function, and each	
	Higher score is better	function is scored from 4 (normal) to 0 (no	
		ability).	
2.	Forced Vital Capacity	It is a spirometry marker of lung function. It is	An absolute change
	(FVC)	the maximum amount of air a person can	in FVC by 2-6%
	Higher score is better	forcefully exhale after a deep breath.	
3.	SAEs	Serious adverse events	-
4.	All-cause mortality	Total number of deaths in a population over a	-
		specific period of time	

Risk of Bias Assessment:



Desirable effects:

1. Revised Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS-R) score: Two trials with 248 participants reported the ALSFRS-R score. The mean difference for change from baseline in ALSFRS-R score between the stem cell therapy arm as compared to usual care at 6 months follow up was 1.82 (95% CI: -1.14 to 4.77), which was statistically non-significant.

1.1 Change in ALSFRS-R score at the end of 6 months:

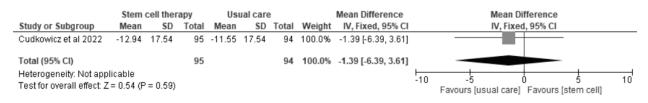
	Stem of	cell ther	apy	Usu	ial car	е		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% Cl	IV, Random, 95% Cl
Cudkowicz et al 2022	-5.52	6.53	95	-5.88	6.49	94	51.8%	0.36 [-1.50, 2.22]	
Oh et al 2018	-3.1	3.51	31	-6.48	4.53	25	48.2%	3.38 [1.22, 5.54]	
Total (95% CI)			126			119	100.0%	1.82 [-1.14, 4.77]	
Heterogeneity: Tau ² = 3 Test for overall effect: Z				P = 0.04)); l² = 7	7%			-10 -5 0 5 10 Favours (usual care) Favours (stem cell)

2. Vital Capacity: Oh et al² reported the mean difference of change from baseline in FVC between the stem cell arm and the usual care to be -0.53 (95 % CI: -5.37 to 4.31) at the end of four months, which was statistically not significant. Cudkowicz et al³ reported the mean difference of change in Slow Vital Capacity (SVC) to be -1.39 (95% CI: -6.39 to 3.61), which was statistically non-significant.

2.1 Change in FVC at the end of 4 months:

	Stem	cell ther	ару	Usu	al car	e		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% Cl
Oh et al 2018	-11.28	10.06	31	-10.75	8.4	25	100.0%	-0.53 [-5.37, 4.31]	
Total (95% CI)			31			25	100.0%	-0.53 [-5.37, 4.31]	
Heterogeneity: Not ap	pplicable								
Test for overall effect	: Z = 0.21	(P = 0.83	3)						-10 -5 0 5 10 Favours (usual care) Favours (stem cell)

2.2 Change in SVC at the end of 6 months:



Undesirable effects:

3. Serious adverse events: Three RCTs with 301 participants reported serious adverse events and the pooled analysis yielded a risk ratio of 1.15 (95% CI: 0.72 to 1.85) in the stem cell group as compared to usual care, which was statistically non-significant. Three RCTs with 301 participants reported all-cause mortality and the pooled analysis yielded a risk ratio of 1.20 (95% CI: 0.51 to 2.79) in the stem cell group as compared to usual care, which was statistically non-significant.

3.1 Serious adverse events at the end of 6 months:

	Stem cell the	erapy	Usual	care		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Berry et al 2019	9	36	2	12	11.4%	1.50 [0.38, 6.00]	
Cudkowicz et al 2022	23	95	17	94	65.0%	1.34 [0.77, 2.34]	
Oh et al 2018	3	33	6	31	23.5%	0.47 [0.13, 1.72]	
Total (95% CI)		164		137	100.0%	1.15 [0.72, 1.85]	-
Total events	35		25				
Heterogeneity: Chi ² = 2.	.26, df = 2 (P =	0.32); I ^z	= 11%				
Test for overall effect: Z	= 0.59 (P = 0.5	6)					0.1 0.2 0.5 1 2 5 10 Favours [experimental] Favours [control]

3.2 All-cause mortality at the end of 6 months:

	Stem cell the	erapy	Usual o	are		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% Cl
Berry et al 2019	0	36	0	12		Not estimable	
Cudkowicz et al 2022	10	95	6	94	66.1%	1.65 [0.62, 4.36]	
Oh et al 2018	1	33	3	31	33.9%	0.31 [0.03, 2.85]	
Total (95% CI)		164		137	100.0%	1.20 [0.51, 2.79]	
Total events	11		9				
Heterogeneity: Chi ² = 1	.83, df = 1 (P =	0.18); P	² = 45%			0.1	
Test for overall effect: Z	2 = 0.42 (P = 0.	68)				0.1	Favours [stem cell] Favours [usual care]

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Stem cell therapy compared to usual care for Amyotrophic Lateral Sclerosis

Patient or population: Amyotrophic Lateral Sclerosis Setting: Hospital/ Tertiary care Intervention: Stem cell therapy Comparison: Usual care

Anti	iicipated absolut	Anticipated absolute effects*(95% CI)	5	Nº of		
Outcomes Risk	Risk with control	Relative Reserved Risk with Stem cell therapy (95% Cl)	Kelative effect participants (95% CI) (studies)	participants (studies)	evidence (GRADE)	Comments
ALS Function rating Scale-R (ALSFRS-R) at 6 months; Scale from: 0 to 48 (Higher is better)		MD 1.82 ALSFRS-R higher (1.14 lower to 4.77 higher)		248 (2 RCTs)	⊕⊖⊖⊖ Very low ^{a.b.c}	
Serious adverse events at 6 months 182 per 1,000	: per 1,000	210 per 1,000 (131 to 338)	1,000 RR 1.15 (0.72 to 1.85)	301 (3 RCTs)	⊕⊖⊖⊖ Very lowa.b.c	
All-cause mortality: at 6 months 66 pe	66 per 1,000	79 per 1,000 RR (34 to 183) (0.5)	RR 1.20 301 (0.51 to 2.79) (3 RCTs)	301 (3 RCTs)	⊕⊖⊖⊖ Very low ^{a,b,c}	
Forced Vital Capacity (FVC) at 4 months -		MD 0.53 lower (5.37 lower to 4.31 higher)		56 (1 RCT)	⊕⊖⊖⊖ Very Low ^{d,e}	
Slow Vital Capacity (SVC) at 6 months -		MD 1.39 lower (6.39 lower to 3.61 higher)		189 (1 RCT)	⊕⊖⊖⊖ Very low ^{a,d,e}	
*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). Confidence interval; MD : mean difference; RR : risk ratio	nterval) is based on	the assumed risk in the compariso	n group and the re	lative effect of	the intervention (and	lits 95% CI).

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. One study had some concerns in the randomization process. Another study has some concerns in missing outcome data and selection of reported outcomes

b. Downgraded one level for inconsistency as the results were not consistent.

c. Downgraded one level for imprecision as the 95% CI crossed the null effect line; OIS not met.

e. Downgraded two levels for imprecision as the 95% CI crossed the null effect line and was very wide; OIS not met. d. Single study was downgraded one level for inconsistency as it was inevaluable.

Evidence-based Guidelines for the Use of Stem Cell Therapy: Neurological Conditions

GRADE Evidence Profile

Certainty assessment	essment						Summary	Summary of findings				
Participants						Overall	Study ev (%)	Study event rates (%)	Relative	Anticipated al	Anticipated absolute effects	
(studies) Follow-up	bias	—	nconsistency Indirectness	Imprecision	rublication certainty bias of evidence		With control	With Stem cell (effect (95% CI)	Risk with control	with Risk difference with Stem cell therapy	Stem

ALS Function rating Scale-R (ALSFRS-R) at 6 months; Scale from: 0 to 48 (higher is better)

MD 1.82 ALSFRS-R higher (1.14 lower to 4.77 higher)	
⊕⊖⊖⊖ Very low	
Inevaluable	
Serious ^c	
Not serious	
Serious ^b	
Serious ^a	
248 (2 RCTs)	

Serious Adverse Events at 6 months

301	Serious ^a	berious ^a Serious ^b	Not serious	Serious ^c	Inevaluable $\oplus \bigcirc \bigcirc \bigcirc$ 25/137 35/164	000⊕	25/137	35/164	RR 1.	1.15 23/137	3/137	27 more per	per 1,	1,000
(3 RCTs)						Very low	(18.2%) (21.3%)	(21.3%)	(0.72	to (16.8%)	6.8%)	(from 51 fewer to 155 more)	r to 155 m	lore)
								_	1.85)					
All-cause m	ortality: a	All-cause mortality: at 6 months												

301 (3 RCTs)	Serious ^a	erious ^a Serious ^b	Not serious Serious ^c	Serious ^c	Inevaluable	eevaluable ⊕○○○ 9/137 Very low (6.6 %)	9/137 11/164 (6.6 %) (6.7%)	RR (0.51 2.79)	1.20 to	$\begin{array}{c c} 1.20 \\ \text{to} \\ \text{to} \end{array} \left[\begin{array}{c} 9/137(6.6\%) \\ \text{(fr} \end{array} \right] 13$	13 (from	13 more per 1,000 (from 32 fewer to 118 more)	per 1 to 118 r	1,000 more)
Forced Vita	l Capacity	Forced Vital Capacity at 4 months												

	•										
56 (1 RCT)	Not serious	Inevaluable ^d	Not serious	Very serious ^e	Inevaluable	⊕⊖⊖⊖⊖ Very Low	-		MD (5.37 low	0.53 ver to 4.31 hig	lower higher)
Slow Vital C	apacity at	slow Vital Capacity at 6 months									

189 (1 RCT)	Serious ^a	Inevaluable ^d	Not serious	Very serious ^e	Inevaluable	⊕⊖⊖⊖⊖ Very low			MD 1.39 lower (6.39 lower to 3.61 higher)
CI: confider	ence interva	d; MD: mean differ	rence; RR: risk rati	tio		-			

Explanations

a. One study had some concerns in the randomization process. Another study has some concerns in missing outcome data and selection of reported outcomes

b. Downgraded one level for inconsistency as the results were not consistent.

c. Downgraded one level for imprecision as the 95% CI crossed the null effect line; OIS not met.

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

e. Downgraded two levels for imprecision as the 95% CI crossed the null effect line and was very wide; OIS not met.

Evidence-based Guidelines for the Use of Stem Cell Therapy: Neurological 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 no	t recommended in routine clinical practice for
the treatment of amyotrophic lateral sclerosis	It may be used only in the context of rigorously

the treatment of amyotrophic lateral sclerosis. It may be used only in the context of rigorously conducted randomized controlled trials.

* This judgment was made as the evidence is inadequate in quantity and quality to determine the safety and efficacy of stem cell therapy in patients with ALS.

** 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
- 2. Small number of participants and/or events in the included trials
- 3. Motor outcomes that matter to the patients not assessed
- 4. Lack of long term follow up of patients thus providing insufficient evidence on the safety of this experimental therapy

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4. MULTIPLE SCLEROSIS

A. BACKGROUND:

Multiple sclerosis (MS) is one of the leading causes of neurological disability in young adults with symptom onset generally occurring between the ages of 20 to 40 years. It is an autoimmune inflammatory disorder characterized by demyelination of nerve fibers in the central nervous system and affects women more commonly than men. Initially the episodes are reversible, that are followed by progressive neurological deterioration over time. The prevalence of MS in our country has increased from 1.33/100,000 in 1985 to 8.35/100,000 in 2014.¹ There is no cure for MS and the current disease modifying therapies do not provide satisfactory and cost-effective treatment options.

B. RECOMMENDATIONS:

a) Autologous hematopoietic stem cell transplantation (AHSCT) is **recommended** for the treatment of highly active relapsing remitting multiple sclerosis^{*}, if there is no satisfactory improvement with disease modifying therapies.

Strength: Conditional** Certainty of Evidence: Very Low

* The evidence overwhelmingly comes from Relapsing Remitting Multiple Sclerosis. It is not known, whether AHSCT is effective in other forms of MS (relapsing progressive, secondary progressive).

- A. Highly active treatment-resistant relapsing MS, defined as \geq 2 episodes of disease activity in the 36 months prior to the assessment for AHSCT. The two disease activity episodes will be a clinical MS relapse or MRI evidence of MS disease activity and must meet all the criteria described below:
 - At least one episode of disease activity must occur following ≥ 1 month of treatment with one of the following: (i) a DMT approved for the treatment of relapsing MS, or (ii) a monoclonal antibody approved for the treatment of relapsing MS, or (iii) rituximab. Qualifying DMTs include: dimethyl fumarate, diroximel fumarate, monomethyl fumarate, teriflunomide, cladribine, daclizumab, ponesimod, siponimod, ozanimod, fingolimod, rituximab, ocrelizumab, natalizumab, alemtuzumab, ublituximab, and ofatumumab, and
 - 2. At least one episode of disease activity must have occurred within the 12 months prior to the AHSCT, and
 - 3. At least one episode of disease activity must be a clinical MS relapse confirmed by a neurologist. The other episode(s) must occur at least one month before or after the onset of the clinical MS relapse, and must be either another clinical MS relapse or MRI evidence of disease activity in the form of a gadolinium-enhancing lesion, or a new non-enhancing T2 lesion compared to a reference scan obtained not more than 36 months prior to the time of evaluation.
- B. Expanded Disability Status Scale (EDSS) ≤ 6
- C. No contraindications to AHSCT

b) Mesenchymal stem cell therapy is **not recommended** in routine clinical practice for the treatment of multiple sclerosis.

Strength: Conditional[#] Certainty of Evidence: Very Low

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

Rationale/Justification

a. Autologous Hematopoietic Stem Cell Transplantation: This recommendation has been made as there is very low certainty evidence of a large benefit and known harms associated with autologous HSCT. The committee decided that benefits clearly outweigh harms. There seems to be a clinically important improvement in EDSS score at 6 months (greater than two times of MCID) and at one year (greater than three times of MCID) that was statistically significant. The proportion of patients free of relapse was higher in the HSCT group as compared to usual care and the results were statistically significant. There was a statistically non-significant difference in disease progression between the stem cell arm as compared to usual care. Serious adverse events were higher in the HSCT group, but the results were highly imprecise. No deaths were reported in either group.

b. Mesenchymal Stem Cell Therapy: This recommendation has been made as there is very low certainty evidence of small benefit in terms of disability and relapse rate. There seems to be statistically non-significant change in EDSS score at 6 months and at one year. There seems to be a small improvement in annual relapse rate (just crossing the MCID of 0.6), which is important clinically. There is little to no difference in undesirable effects between stem cell therapy and usual care. In addition, the follow up period of one year is too small to comment on the side effect profile and long-term safety is not known.

C. SUMMARY OF EVIDENCE:

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

Included Studies: Of the 1144 records identified through the pre-specified databases till 30th November 2023, eight studies involving 360 participants were included in the meta-analysis. Three studies used the mesenchymal stem cell as intervention derived from bone marrow, one study used adipose derived mesenchymal stem cell, one study used Umbilical cord blood cell derived mesenchymal stem cell, one study used placenta derived mesenchymal stem cell and two used autologous hematopoietic stem cell transplantation. The year of study conduct for the included studies ranged from 2014 to 2023.²⁻⁹ For trails using AHSCT as intervention, the study by Burt et al² included patients with relapsing remitting multiple sclerosis (RRMS) only and the study by Mancardi et al³ included patients with relapsing remitting multiple sclerosis, secondary progressive multiple sclerosis and relapsing progressive multiple sclerosis.

The type of participants and the nature of intervention given in included studies for AHSCT are as follows:

Author	Type of MS -no. of participants	Dose of stem cell	Source & type of Stem Cell	Route
Mancardi et. al.	SPMS-13/ RRMS-	3 and 8 x 10^{6} CD34 ⁺ /kg	AHSC	iv
2015 ³	7/RPMS-1	cells		
Burt et al. 2019 ²	RRMS-110(all)	Not mentioned	bone marrow HSC	iv

The type of participants and the nature of intervention given in included studies for MSC are as follows:

Author	Type of MS- no. of participants	Dose of stem cell	Source & type of Stem Cell	Route
Liufriu et al. 2014 ⁶	RRMS-9	1.87x10 ⁶ MSCs/Kg bwt	BM-MSCs	iv
Li et al. 2014 ⁵	RRMS-16 SPMS-7	4x10 ⁶ cells/kg	human umbilical cord-MSCs	iv
Lublin et al. 2014 ⁷	RRMs-10/ SPMS- 6	low dose 150 x 10 ⁶ cells high dose 600 x 10 ⁶ cells PDA	human placenta- MSCs	iv
Fernandez et al. 2018 ⁹	SPMS-30(all)	low dose 1 x 10 ⁶ cells/kg high dose 4 x 10 ⁶ cells/kg	AdMSCs	iv
Ucelli et al. 2021 ⁸	RRMS-94/SPMS- 33/PPMS-17	1-2x10 ⁶ cells/kg bwt	BM MSCs	iv
Nabavi et al. 2023 ⁴	RRMS-14/ SPMS- 5/ PPMS-2	2x10 ⁶ cells/kg cell	BM MSCs	iv

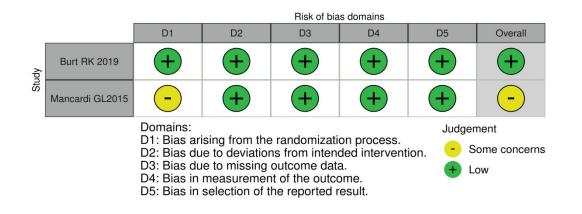
Critical outcomes reviewed and their MCID:

S. No	Outcome	What does it measure?	MCID decided by
	reviewed		the GDG
1.	The Expanded	The Expanded Disability Status Scale (EDSS)	An absolute change
	Disability Status	is a method of quantifying disability in	in EDSS score by 0.5
	Scale (EDSS)	multiple sclerosis and monitoring changes in	
	Range: 0-10	the level of disability over time. The EDSS	
	Higher score is	scale ranges from 0 to 10 in 0.5 unit	
	worse	increments that represent higher levels of	
		disability.	
2.	Annualized	ARR is computed as the total number of	A difference of 0.6
	relapse rate	relapses in a given period divided by the total	for Annualized
	(ARR)	number of person-years in that period.	relapse rate (ARR)
3.	Proportion free	The proportion of patients who did not have	A difference of
	of relapse	a single relapse episode in a given period of	20/100 (20%)
		time	
4.	Serious adverse	Mortality, non-hematopoietic grade 3	-
	events	toxicities & grade 4 toxicities	
	411		
5.	All-cause	Total number of deaths in a population over	-
	mortality	a specific period of time	

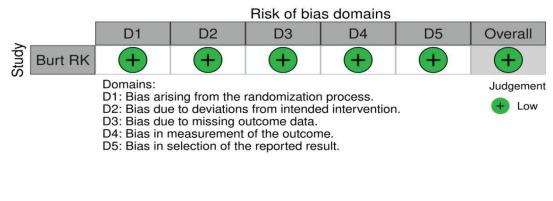
a. AUTOLOGOUS HEMATOPOIETIC STEM CELL TRANSPLANTATION (AHSCT)

Risk of Bias Assessment:

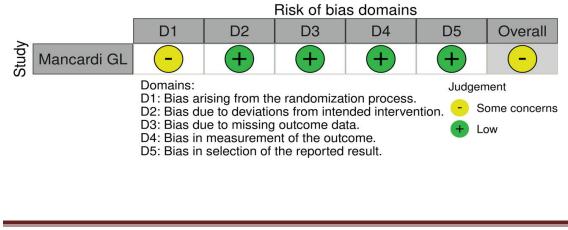
RoB -2 Disease progression and EDSS:



RoB-2 for outcome proportion free from relapse comparison HSCT vs Usual care:



RoB -2 for outcome ARR between HSCT and usual care:



Desirable Effects (AHSCT):

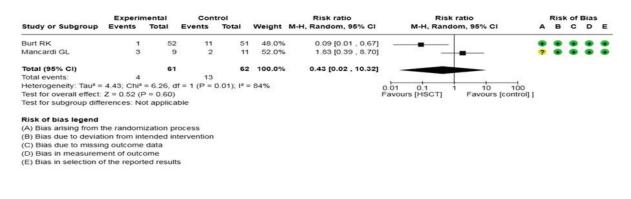
1. Disability: One trial with 103 participants reported EDSS score at six months and at one year of follow up. The mean difference in EDSS score was -1.20 (95% CI: -1.76 to -0.64) at six months and - 1.60 (95% CI: -2.20 to -1.00) at one year in the HSCT arm as compared to usual care. There is a statistically significant improvement in EDSS score both at six months (two times the MCID-dotted line) and at one year (three times the MCID-dotted line), which is important clinically.

1.1 EDSS score at six months:

	Exp	erimenta	1		Control			Mean difference	Mean difference	1	Risk	ofE	Bias	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI	A	в	C	D	E
Burt RK	2.5	1.4	52	3.7	1.5	51	100.0%	-1.20 [-1.76 , -0.64]	-	٠	•	٠	•	4
Total (95% CI)			52			51	100.0%	-1.20 [-1.76 , -0.64]	•					
Heterogeneity: Not ap	plicable													
Test for overall effect:	Z = 4.20 (P	< 0.0001)					-4	-2 0 2 4					
Test for subgroup diffe	erences: Not	t applicab	le					Favours [e:	xperimental] Favours [control]					
Risk of bias legend														
(A) Bias arising from t	he randomiz	zation pro	cess											
(B) Bias due to deviati	ion from inte	ended inte	rvention											
(C) Bias due to missin	g outcome	data												
(D) Bias in measurem	-													
(E) Bias in selection of														
2 EDSS agos	no at or	20110	- 24.											
.2 EDSS scor	re at oi	ne yea	ar:											
.2 EDSS scor	Ex	periment	al		Control			Mean difference	Mean difference		Ris	k of		-
.2 EDSS scoi		5		Mean	Control SD	Total	Weight		Mean difference IV, Fixed, 95% Cl	A	Ris	k of C		s
Study or Subgroup	Ex	periment	al		SD		-			A	Ris			-
	Ex Mean	periment SD	al Total	4	SD		100.0%	IV, Fixed, 95% CI		A	Ris B			-
Study or Subgroup Burt RK	Ex Mean 2.4	periment SD	al Total 52	4	SD	51	100.0%	IV, Fixed, 95% CI		A	Ris B			-
Study or Subgroup Burt RK Total (95% CI)	Exp Mean 2.4	sD 1.4	al Total 52 52	4	SD	51	100.0%	IV, Fixed, 95% Cl -1.60 [-2.20 , -1.00]	IV, Fixed, 95% Cl	A	Ris			-
Study or Subgroup Burt RK Total (95% CI) Heterogeneity: Not aj Test for overall effect	Exp Mean 2.4 pplicable : Z = 5.21 (F	2 periment SD 1.4 P < 0.0000	al Total 52 52 01)	4	SD	51	100.0%	IV, Fixed, 95% Cl -1.60 [-2.20 , -1.00]	IV, Fixed, 95% Cl	•	Ris B			-
Study or Subgroup Burt RK Total (95% CI) Heterogeneity: Not aj Test for overall effect Test for subgroup diff	Exp Mean 2.4 pplicable : Z = 5.21 (F	2 periment SD 1.4 P < 0.0000	al Total 52 52 01)	4	SD	51	100.0%	IV, Fixed, 95% Cl -1.60 [-2.20 , -1.00]	IV, Fixed, 95% Cl	A •••	Ris B			-
Study or Subgroup Burt RK Total (95% CI) Heterogeneity: Not aj Test for overall effect Test for subgroup diff Risk of bias legend (A) Bias ansing from	Ex Mean 2.4 pplicable : Z = 5.21 (F erences: No the random	1.4 periment SD 1.4 P < 0.0000 ot applicat ization pro-	al Total 52 52 01) ble	4	SD	51	100.0%	IV, Fixed, 95% Cl -1.60 [-2.20 , -1.00]	IV, Fixed, 95% Cl	A •	Ris B			-
Study or Subgroup Burt RK Total (95% CI) Heterogeneity: Not aj Test for overall effect Test for subgroup diff Risk of bias legend (A) Bias arising from (B) Bias due to devia	Ex Mean 2.4 pplicable : Z = 5.21 (F erences: No the random tion from int	1.4 periment SD 1.4 0 < 0.0000 ot applicat ization pro- tended int	al Total 52 52 01) ble	4	SD	51	100.0%	IV, Fixed, 95% Cl -1.60 [-2.20 , -1.00]	IV, Fixed, 95% Cl	A •	Ris B			-
Study or Subgroup Burt RK Total (95% CI) Heterogeneity: Not aj Test for overall effect Test for subgroup diff Risk of bias legend (A) Bias arising from (B) Bias due to devia (C) Bias due to missis)	Exp Mean 2.4 pplicable : Z = 5.21 (F erences: No the random the random ing outcome	1.4 > < 0.0000 ot applicat ization pro- tended int	al Total 52 52 01) ble	4	SD	51	100.0%	IV, Fixed, 95% Cl -1.60 [-2.20 , -1.00]	IV, Fixed, 95% Cl	A	Ris B			-
Study or Subgroup Burt RK Total (95% CI) Heterogeneity: Not aj Test for overall effect Test for subgroup diff Risk of bias legend (A) Bias arising from (B) Bias due to devia	Exp Mean 2.4 pplicable : Z = 5.21 (F erences: No the random tion from int ng outcome ent of outco	1.4 > < 0.0000 bt application pro- tization pro-	al Total 52 52 01) ble pocess ervention	4	SD	51	100.0%	IV, Fixed, 95% Cl -1.60 [-2.20 , -1.00]	IV, Fixed, 95% Cl	A	Ris B			-

2. Disease progression: Two trials with 123 participants reported the disease progression to be lower at one year in the HSCT group as compared to the usual care group. The risk ratio for disease progression was 0.43 (95% CI: 0.02 to 10.32) in the HSCT arm as compared to usual care which was statistically non-significant.

2.1 Disease progression measured by EDSS at one year:



3. Proportion free from relapse: One trial with 103 participants reported that proportion of patients free of relapse at one year was higher in the HSCT group as compared to usual care with a risk ratio of 3.13 (95% CI: 2.08 to 4.70) and the results were statistically significant and important clinically.

3.1 Proportion free from relapse:

Risk Ratio

	Experin	nental	Cont	trol		Risk ratio	Risk ratio	Ri	isk (of Bi	as
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI	A	в	C I	E
Burt RK	51	52	2 16	51	100.0%	3.13 [2.08 , 4.70]		• •	•	• •	
Total (95% CI)		52	2	51	100.0%	3.13 [2.08 , 4.70]	•				
Total events:	51		16				•				
Heterogeneity: Not ap	plicable						0.01 0.1 1 10 100				
Test for overall effect:	Z = 5.48 (F	> < 0.000	001)				avours [Control] Favours [HSCT]				
Test for subgroup diffe	erences: No	ot applica	able								
Risk of bias legend											
(A) Bias arising from t	the random	ization p	rocess								
(B) Bias due to deviat	ion from int	tended in	tervention								
(C) Bias due to missin	ng outcome	data									
(D) Bias in measurem	ent of outco	ome									
(E) Bias in selection of	of the report	ted result	ts								

Risk Difference

	HSC	ст	Cont	rol		Risk difference	Risk difference		R	isk	of E	Bias	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	M-H, Fixed, 95% Cl	A	в	C	D	Е	F
Burt RK	51	52	16	51	100.0%	0.67 [0.53 , 0.80]	•	•	4	•	•	•
Total		52		51	100.0%	0.67 [0.53 , 0.80	n ¦∔						
Total events:	51		16										
Test for overall effect:	Z = 9.85 (F	< 0.000	01)				-4 -2 0 2 4	11					
Test for subgroup diffe	erences: No	ot applica	ble				Favours [Control] Favours [HS0	CT]					
Heterogeneity: Not ap	plicable												

Risk of bias legend

(A) Random sequence generation (selection bias)

(B) Allocation concealment (selection bias)

(C) Blinding of participants and personnel (performance bias)

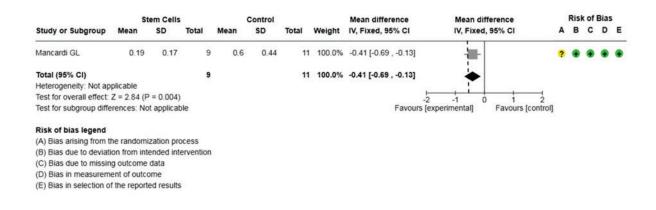
(D) Blinding of outcome assessment (detection bias)

(E) Incomplete outcome data (attrition bias)

(F) Selective reporting (reporting bias)

4. Annualized relapse rate: One trial with 20 participants reported a lower annualized relapse rate in the patients with HSCT as compared to usual care. The mean difference was -0.41 (95% CI: -0.69 to -0.13), which is statistically significant but unimportant clinically (less than MCID of 0.6).

4.1 Annualized relapse rate:



Undesirable Effects:

5. Serious adverse events: Two trials with 123 participants reported serious adverse events however, no deaths were reported. Pooled analysis revealed a risk ratio of 21.46 (95% CI: 2.99 to 154.08) in the AHSCT arm as compared to the usual care. There is an increase in serious adverse events with AHSCT therapy as compared to usual care but the results had very serious imprecision.

5.1 Serious adverse events

	Experin	nental	Cont	rol		Risk ratio	Risk r	atio		Risk	of	Bias	1
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Rando	m, 95% Cl	A	в	С	D	E
Burt RK	21	52	0	51	50.4%	42.19 [2.62 , 678.43]		∎ →	•		•	•	4
Mancardi GL	4	9	0	11	49.6%	10.80 [0.66 , 177.36]	+		?	•	•	•	•
Total (95% CI)		61		62	100.0%	21.46 [2.99 , 154.08]							
Total events:	25		0										
Heterogeneity: Tau ² =	0.00; Chi2	= 0.52, d	f = 1 (P = (0.47); l ² =	0%		0.01 0.1 1	10 100					
Test for overall effect:	Z = 3.05 (F	P = 0.002)				Favours HSCT	Favours Control					
Test for subgroup diffe	erences: No	ot applica	ble										

Risk of bias legend

(A) Bias arising from the randomization process

(B) Bias due to deviation from intended intervention

(C) Bias due to missing outcome data

(D) Bias in measurement of outcome

(E) Bias in selection of the reported results

No deaths and non-hematopoietic grade 4 toxicities (such as myocardial infarction, sepsis, or other disabling or potential life-threatening events or transfer to intensive care unit) were reported by Burt et al.² However, the following Grade 3 toxicities reported by Burt et al² were taken as serious adverse events in this analysis: febrile neutropenia (n=13), atrial fibrillation (n=1), Infection (n=4), engraftment bone pain(n=1), serum sickness (n=1), seizure (n=1).

SUMMARY OF FINDINGS:

Safety and efficacy of HSCT as compared to usual care in patients with MS

Patient or population: Patients with MS Setting: Hospital/ Tertiary care Intervention: HSCT

	Anticipated absolute effects* (95% CI)	e effects* (95% CI)		Nº of	Certainty of	
Outcomes	Risk with placebo Risk with HSCT	Risk with HSCT	Kelauve errect (95% CI)	participants (studies)	the evidence (GRADE)	Comments
EDSS at six months	1	MD 1.2 lower (1.76 lower to 0.64 lower)		103 (1 RCT)	⊕⊕⊖⊖ Low ^{a,b}	A change in EDSS score by 0.5was considered as MCID.
EDSS at one year	ı	MD 1.6 lower (2.2 lower to 1 lower)	1	103 (1 RCT)	⊕⊕⊖⊖ Low ^{a,b}	
Disease Progression at one year	210 per 1,000	90 per 1,000 (4 to 1,000)	RR 0.43 (0.02 to 10.32)	123 (2 RCTs)	⊕⊖⊖⊖ Very low ^{f,c,d}	
Serious Adverse Event	0 per 1000		RR 21.46 (2.99 to 154.08)	123 (2 RCTs)	⊕⊕⊖⊖ Lowfie	
Proportion free from relapse at one year	314 per 1,000	982 per 1,000 (653 to 1,000)	RR 3.13 (2.08 to 4.70)	103 (1 RCT)	⊕⊕⊖⊖ Low ^{a,b}	The committee considered the MCID for Population free of relapse as difference of 20/100 (20%).
Annual Relapse rate	,	MD 0.41 lower (0.69 lower to 0.13 lower)		20 (1 RCT)	⊕⊖⊖⊖ Very Low ^{g,a,b}	A change in Annual relapse rate by 0.6 was considered as MCID.

Evidence based Guidelines for the use of Stem Cell Therapy: Neurological conditions

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

Preter or population: Patients with MS Setting Hondray (Pretray carse interval mission: IBCT Comparison: IBCT Compar	an a bour of familie and a comp	and any any and in a many or an any indiana and any any france				
Anterparted absolute effects* (95% CI) No of Buttingparted Cartainity of purficipants Cartainity of the evidence MORE Working Group grades of evidence Risk with JBCT Risk with JBCT Commons Cartainity of the evidence MORE Working Group grades of evidence Risk with JBCT Cartainity of Groups Cartainity of Cartainity ware and evidence of evidence Cartainity of Cartainity ware Cartainity of Cartainity ware MORE Working Group grades of evidence Risk with JBCT Cartainity ware Cartainity ware Group of evidence Risk with JBCT Cartainity ware Cartainity ware Group of evidence Risk with JBCT Cartainity ware Cartainity ware Commons of evidence Risk with JBCT Cartainity ware Cartainity ware Commons of evidence Risk with JBCT Cartainity ware Cartainity ware Commons of evidence of the effect still selve to be done to the effect. Cartainity ware Cartainity ware Commons of the confidence in the effect still selve to be anothered to the effect. Cartainity ware Cartainity ware Commons of the confidence in the effect still selve to be anothered to the effect. Cartaininininitianity different from the effect still selve to	Patient or population: Patients w Setting: Hospital/ Tertiary care Intervention: HSCT Comparison: Placebo/usual care	ith MS				
Interview Relative effect Data place Relative effect Data place Condents Interview ADIE Marking Group grades of evidence gip cartainty, we are very confident that the true effect estimates of the effect. Condition Co	Antic			Nº of	Certainty of	
RADE Working Group grades of evidence determiny: we are very confident that the true effect lies close to that of the effect. More certainty: we are wery 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. We certainty: we need the effect estimate is limited: the true effect may be substantially different from the estimate of the effect. The effect is likely to be substantially different from the estimate of the effect. The value pairs of compared one level for inconsistency as it was inevaluable. The value pairs of compared are level for inconsistency as it was inevaluable. The value of the effect estimate is limited. The value of comfidence interval is to wate. The value of the effect risk of time of no effect. The value of the effect risk of time of no effect. The value of the effect risk of time of no effect. The value of the effect risk of this to wate. Downgraded two levels for risk of this	Outcomes Risk		Relative effect (95% CI)	participants (studies)	the evidence (GRADE)	Comments
Ifferent. ever stainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect. ery buy certainty: we have very little confidence in the effect estimate the true effect is likely to be substantially different from the estimate of effect. plantum Single study was downgraded one level for inconsistency as it was inevaluable. Single study was downgraded one level for inconsistency as it was inevaluable. The width inconsistence interval as to may be a substantially all the estimate of effect. The width of the confidence interval as to was inevaluable. The width of the confidence interval is too widt. The width of the confidence interval as too widt. The width of the confidence interval as too widt. The width of the confidence interval as too width of the confidence interval as the confidence interval a	GRADE Working Group grades of evi High certainty: we are very confident Moderate certainty: we are moderate	dence t that the true effect lies close to that of the estimate of sly confident in the effect estimate: the true effect is like	the effect. ely to be close to the estimate c	of the effect, but the	e is a possibility th	at it is substantially
planations Single study was downgraded one level for inconsistency as it was inevaluable. Sinall sample size, OIS not met Highly inconsistent results on opposite side of fine of no-effect The width of the confidence interval is too wide. Very wide confidence interval and OIS not met Jourgraded too levels for risk of bias Downgraded two levels for risk of bias	different. Low certainty: our confidence in the (Very low certainty: we have very littl.	effect estimate is limited: the true effect may be substa e confidence in the effect estimate: the true effect is lik	intially different from the estim cely to be substantially differen	nate of the effect. t from the estimate	of effect.	
	Explanations a. Single study was downgraded one le b. Small sample size, OIS not met c. Highly inconsistent results on oppos d. The width of the confidence interval and O f. Downgraded one level for risk of bia g. Downgraded two levels for risk of bi	evel for inconsistency as it was inevaluable. site side of line of no-effect 1 is too wide. Sis not met ias				

GRADE EVIDENCE PROFILE:

Safety and efficacy of HSCT as compared to usual care in patients with MS

Certainty assessment	essment						Summary of findings	f findings			
,							,	þ			
Participants	Diclo				Dublication	Overall	Study event rates (%)	t rates (%)	Relative	Anticipated	Anticipated absolute effects
(studies) Follow-up	bias	Inconsistency	Indirectness	Imprecision	r uurcauon bias	certainty of evidence	With placebo	With HSCT	effect (95% CI)	Risk with placebo	Risk difference with HSCT
EDSS at Six months	nonths										
103 (1 RCT)	Not serious	Inevaluable ^a	Not serious	Serious ^b	Inevaluable	⊕⊕⊖⊖ Low		1	1	ı	MD 1.2 lower (1.76 lower to 0.64 lower)
EDSS at One year	year										
103 (1 RCT)	Not serious	Inevaluable ^a	Not serious	Serious ^b	Inevaluable	⊕⊕⊖⊖ Low					MD 1.6 lower (2.2 lower to 1 lower)
Disease Progression at one year	gression at	one year									
123 (2 RCTs)	Serious ^f	Very serious ^c	Not serious	Very serious ^d	Inevaluable	⊕⊖⊖⊖ Very low	13/62 (21.0%)	4/61 (6.6%)	RR 0.43 (0.02 to 10.32)	13/62 (21.0%)	120 fewer per 1,000 (from 205 fewer to 1,000 more)
Serious Adverse Event	erse Event										
123 (2 RCTs)	Serious ^f	Not serious	Not serious	Very serious ^e	Inevaluable	⊕⊖⊖⊖ Very low	0/62 (0.0%)	25/61 (41.0%)	RR 21.46 (2.99 to 154.08)	0/62 (0.0%)	ı
Proportion f	ree from re	Proportion free from relapse at one year	ar								
103 (1 RCT)	Not serious	Inevaluable ^a	Not serious	Serious ^b	Inevaluable	⊕⊕⊖⊖ Low	16/51 (31.4%)	51/52 (98.1%)	RR 3.13 (2.08 to 4.70)	16/51 (31.4%)	668 more per 1,000 (from 339 more to 1,000 more)

Evidence based Guidelines for the use of Stem Cell Therapy: Neurological conditions

Safety and efficacy of HSCT as compared to usual care in patients with MS

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Summary of findings

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20	Very	Inevaluable ^a	Not serious	Serious ^b	Inevaluable	⊕ 000	1	 ,	-	MD 0.41 lower
(1 RCT)	serious					Very Low				(0.69 lower to
										0.13 lower)
CI. confidonco	Interval MD	T: confidence interval: MD: mean difference: BB: risk ratio	D. rich ratio							

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

Explanations

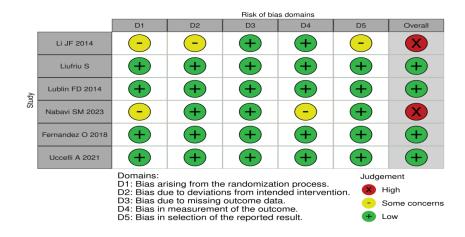
- a. Single study was downgraded one level for inconsistency as it was inevaluable.
 - b. Small sample size, OIS not met
- c. Highly inconsistent results on opposite side of line of no-effect
 - d. The width of the confidence interval is too wide.
 - e. Very wide confidence interval and OIS not met
 - f. Downgraded one level for risk of bias g. Downgraded two levels for risk of bias

Evidence based Guidelines for the use of Stem Cell Therapy: Neurological conditions

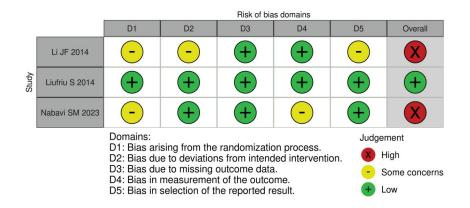
b. MESENCHYMAL STEM CELL THERAPY:

Risk of Bias assessment:

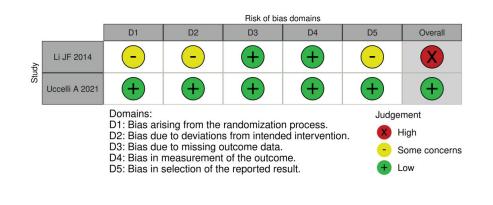
Risk of bias using RoB-2 tool for outcome EDSS of studies using Mesenchymal stem cells:



Risk of bias for the outcome proportion free from relapse of studies using mesenchymal stem cells:



RoB-2 for annual relapse rate of studies using mesenchymal stem cells:



Desirable Effects (MSCs):

1. EDSS score: Six trials with 237 participants reported the EDSS score at 6 months. There appears to be no improvement in EDSS score at 6 months in the MSC therapy group as compared to the usual care group. The mean difference reported was -0.05 (95% CI: -0.37 to 0.28), which was statistically non-significant. Two trials with 52 participants reported the EDSS score at 12 months. The mean difference reported was -0.55 (95% CI: -2.38 to 1.27), which was statistically non-significant.

1.1 EDSS score at 6 months:

MSC			Control			Mean difference	Mean difference		Risk of Bias					
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI	A	в	С	D	E
Fernanadez O	7.63	0.46	19	7.45	0.98	10	25.8%	0.18 [-0.46 , 0.82]	-					
LIJF	5.68	1.07	13	6.57	1.03	10	14.3%	-0.89 [-1.75 , -0.03]		?	?			?
Llufriu S	4.5	1.06	5	4.125	1.03	4	5.6%	0.38 [-1.00 , 1.75]						
Lublin FD	4.35	1.8	12	3.77	0.22	4	9.8%	0.58 [-0.46 , 1.62]	·					
Nabavi SM	4.75	1.76	12	4.89	1.56	9	5.2%	-0.14 [-1.56 , 1.28]		?			?	
Uccelli A	4.5	1.57	68	4.6	1.56	71	39.2%	-0.10 [-0.62 , 0.42]	te-	۲	•	•	•	
Total (95% CI)			129			108	100.0%	-0.05 [-0.37 , 0.28]						
Heterogeneity: Chi2 =	5.95, df = 5	(P=0.3	1); l ² = 16	%										
Test for overall effect:	Z = 0.29 (P	= 0.77)							-4 -2 0 2 4					
Test for subgroup diffe	erences: No	t applicat	ble					Favours	[stem cells] Favours [cont	trol]				
Risk of bias legend														
(A) Bias arising from t	he randomi	zation pro	cess											
(B) Bias due to deviat	ion from inte	ended inte	ervention											
(C) Bias due to missin	ng outcome	data												
(D) Bias in measurem	ent of outco	ome												
(E) Bias in selection of	f the report	ed results												

(E) Bias in selection of the reported results

1.2 EDSS score at one year:

Stem Cells			Control			Mean difference	Mean difference		Risk of Bias					
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI	A	в	C	D	E
Fernanadez O	7.75	0.62	19	7.4	1.04	10	51.4%	0.35 [-0.35 , 1.05]						
LIJF	5.93	1.13	13	7.44	1.14	10	48.6%	-1.51 [-2.45 , -0.57]		?	?	٠	•	?
Total (95% CI)			32			20	100.0%	-0.55 [-2.38 , 1.27]						
Heterogeneity: Tau ² =	1.55; Chi2 =	= 9.70, df	= 1 (P =)	0.002); I* =	90%									
Test for overall effect:	Z = 0.60 (P	= 0.55)							-4 -2 0 2 4					
Test for subgroup diffe	erences: No	t applicat	ole					Favours	[experimental] Favours [contro	n i				

Risk of bias legend

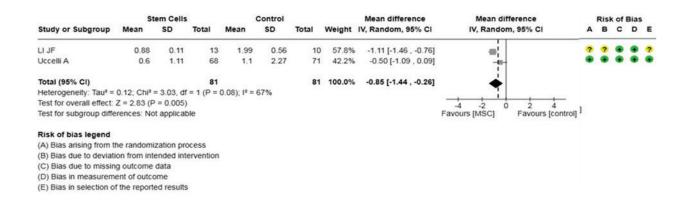
(A) Bias arising from the randomization process

- (B) Bias due to deviation from intended intervention
- (C) Bias due to missing outcome data (D) Bias in measurement of outcome

(E) Bias in selection of the reported results

2. Annual relapse rate: Two trials with 162 participants reported annual relapse rate. The mean difference for annual relapse rate was -0.85 (95% CI: -1.44 to -0.26) in the MSC therapy arm as compared to the usual care. There seems to be a small clinically important reduction in average or annual relapse rate in the MSC therapy arm, which was crossing the MCID of 0.6.

Average/annual relapse rate at one year:



3. Proportion free from relapse: Three trials with 53 participants reported the proportion free from relapse. Pooled analysis yielded a risk ratio of 1.76 (95% CI: 0.44 to 7.06) in the stem cell arm as compared to usual care, which was statistically non-significant.

3.1 Proportion free from relapse at last follow-up:

	Experimental Control					Risk ratio	Ris	k ratio		Risk of Bias				
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% C	M-H, Ran	dom, 95% Cl	Α	в	с	D	E	
LI JF	4	13	1	10	24.1%	3.08 [0.40 , 23.44	·]		?	?	•	•	?	
Llufriu S	4	5	1	4	27.8%	3.20 [0.55 , 18.47	- I		•	•	•	÷	•	
Nabavi SM	10	12	8	9	48.1%	0.94 [0.67 , 1.32	2]	+	?	•	•	?	÷	
Total (95% CI)		30		23	100.0%	1.76 [0.44 , 7.06								
Total events:	18		10											
Heterogeneity: Tau ² =	1.02; Chi2	= 6.23, d	f = 2 (P = 0	0.04); 12 =	68%		0.01 0.1	1 10 10	0					
Test for overall effect:	Z = 0.79 (F	^o = 0.43)					Favours [control]	Favours [MSC						
Test for subgroup diffe	erences: No	ot applica	ble											

Risk of bias legend

(A) Bias arising from the randomization process

(B) Bias due to deviation from intended intervention

(C) Bias due to missing outcome data

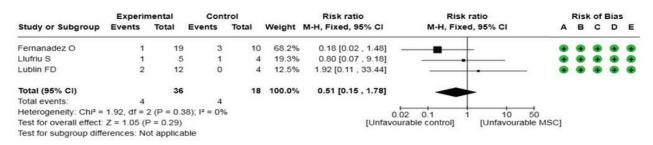
(D) Bias in measurement of outcome

(E) Bias in selection of the reported results

Undesirable Effects:

4. Serious adverse events: Three studies with a total of 54 participants reported serious adverse events. Pooled analysis revealed a risk ratio of 0.51 (95% CI: 0.15 to 1.78) in the mesenchymal stem cell arm as compared to usual care, which was statistically non-significant.

4.1 Serious adverse events: (Risk ratio):



Risk of bias legend

(A) Bias arising from the randomization process

(B) Bias due to deviation from intended intervention

(C) Bias due to missing outcome data

(D) Bias in measurement of outcome

(E) Bias in selection of the reported results

The type of serious adverse events reported by Lublin et al⁷ in the above analysis were choking, respiratory infection, urinary infection, Grade I Anaphylactoid reaction and Grade 2 superficial thrombophelebitis.

Efficacy and safety of mesenchymal stem cell therapy as compared to usual care in patients with Multiple Sclerosis	ymal stem cell th	ierapy as compared to usua	ıl care in patients with M	ultiple Sclerosis		
	Anticipated a	Anticipated absolute effects*(95% CI)			Contrainter of the	
Outcomes	Risk with placebo	Risk with Stem cell (MSC)	Relative effect (95% CI)	Nº of participants (studies)	certainty of the evidence (GRADE)	Comments
EDSS at Six Months (EDSS 0-10, 0 good 10 worse)		MD 0.05 lower (0.37 lower to 0.28 higher)		237 (6 RCTs)	⊕⊕⊕⊖ Moderate ^{a,b}	An absolute change in EDSS score by 0.5was considered as MCID.
EDSS at one year (EDSS 0-10, 0 good 10 worse)	1	MD 0.55 lower (2.38 lower to 1.27 higher)	1	52 (2 RCTs)	⊕⊖⊖⊖ Very low ^{cde}	
Annual relapse rate	1	MD 0.85 lower (1.44 lower to 0.26 lower)	1	162 (2 RCTs)	⊕⊖⊖⊖ Very lowcef	An absolute change in Annual relapse rate by 0.6was considered as MCID.
Proportion free from relapse- at last follow up	435 per 1,000	765 per 1,000 (191 to 1,000)	RR (0.44 to 7.06)	1.76 53 (3 RCTs)	⊕⊖⊖⊖ Very lowcgh	A Population free of relapse difference of 20/100 (20%) was considered as MCID.
Serious Adverse Events (SAEs)	222 per 1,000	113 per 1,000 (33 to 396)	RR (0.15 to 1.78)	0.51 ⁵⁴ (3 RCTs)	⊕⊕⊖⊖ Low ^h	
*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).	roup (and its 95%	6 confidence interval) is base	d on the assumed risk in tl	ie comparison groui	o and the relative e	effect of the
UI: CONNGENCE INTERVAL; MU: MEAN QUITERENCE; KK: MSK FAUO	n anterence; KK:	risk ratio				

Summary of Findings: GRADE

...:

Evidence based Guidelines for the use of Stem Cell Therapy: Neurological conditions

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Risk with OutcomesRisk with Stem cell placeboRelative effect (MSC)Nº of participants (Studies)Comments evidenceGRADE 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.Nº of participants (Studies)OutcomesComments evidenceHigh certainty: We are very confident that the true effect lies close to that of the estimate of the effect.Nº of participants (Studies)OutcomesComments evidenceHigh certainty: We are very confident in the effect setimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.Nº of participantsOutcomesCommentsLow certainty: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.Nº of participantsCommentsExplanationsExplanationsNoteNoteNoteNoteNoteExplanationsNoteNoteNoteNoteNoteNoteExplanationsNoteNoteNoteNoteNoteNoteExplanationsNoteNoteNoteNoteNoteNoteExplanationsNoteNoteNoteNoteNoteNoteExplanationsNoteNoteNoteNoteNoteNoteExplanationsNoteNoteNoteNoteNoteNoteExplanationsNoteNoteNoteNoteNoteNoteExplanatio	o th				Cartainty of the	
GRADE Working Group grades of evidence High certainty: We are very confident that the Moderate certainty: We are moderately confi is substantially different. Low certainty: Our confidence in the effect es Very low certainty: We have very little confid Sxplanations		Kisk with Stem cell (MSC)	Relative effect (95% CI)	Nº of participants (studies)	evidence (GRADE)	Comments
is substantially different. Low certainty: Our confidence in the effect es Very low certainty: We have very little confid Explanations	he true (Ifident in	effect lies close to that of the 1 the effect estimate: the true	estimate of the effect. 9 effect is likely to be clc	ose to the estimate of t	he effect, but there i	is a possibility tha
xplanations	stimate idence ii	: is limited: the true effect may be substantially different from the estimate of the effect. n the effect estimate: the true effect is likely to be substantially different from the estimate of effect.	iy be substantially diffe e effect is likely to be su	rent from the estimate ubstantially different fi	of the effect. om the estimate of e	effect.
a. Less than $1/3^{rd}$ of studies by weight are at risk of blas	bias					
b. OIS not met						
c. One study had high risk of bias d. Downgraded one level for inconsistency as CI not overlapping e. Sample size is underpowered and confidence interval cross the minimally clinical important difference	: overlapp rval cross	oing s the minimally clinical importa	nt difference			
f. Downgraded one level for inconsistency g. Overlapping confidence intervals, therefore no serious inconsistency	rious inco	onsistency				
וו. דוופ כטווונופווכפ ווונפרעמו וא עפרץ אונופ, טוא ווטר ווופר						

GRADE EVIDENCE PROFILE:

Efficacy and safety of mesenchymal stem cell therapy as compared to usual care in patients with Multiple Sclerosis

Certainty assessment	ssment						Summary	Summary of findings			
Participants Risk of	Risk of	-	T solitoot		Publication	Overall certainty	Study event rates (%)	nt rates	Relative effect	Anticipated absolute effects	
(suures) Follow-up	bias	-		umprecision	bias	of evidence	With placebo	With Stem cell (MSC)	(95% CI)	Risk with Risk difference with Stem placebo cell (MSC)	item
EDSS at Six N	onths (ED	EDSS at Six Months (EDSS 0-10, 0 good 10 worse)	10 worse)								

237 (6 RCTs)	Not serious ^a	Not serious	Not serious	Serious ^b	None	⊕⊕⊕⊖ Moderate	ı	1	ı	'	MD 0.05 lower (0.37 lower to 0.28 higher)
EDSS at one	year (EDSS	EDSS at one year (EDSS 0-10, 0 good 10 worse)	worse)								
52 (2 RCTs)	Serious ^c Serious ^d	Serious ^d	Not serious Serious ^e	Serious ^e	None	⊕⊖⊖⊖ Very low	ı	-	ı	1	MD 0.55 lower (2.38 lower to 1.27 higher)
Annual relapse rate	ose rate										

Proportion free from relapse at last follow up

53	Very	Not serious ^g	Not serious	Serious ^h	None			18/30	RR 1.76 10/23	10/23	330 more per 1,000	
(3 RCTS)	serious ^c					Very low	(43.5%) $(60.0%)$	(60.0%)	(0.44 to (43.5%))	(43.5%)	(from 243 fewer to 1,000	
									7.06)		more)	
	1											1

MD 0.85 lower (1.44 lower to 0.26 lower)

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⊕⊖⊖⊖ Very low

None

Serious^e

Not serious

Serious^f

Serious^c

(2 RCTs) 162

Serious Adverse Events

,000 • to 173	
109 fewer per 1,000 (from 189 fewer to 173 more)	
4/18 (22.2%)	
RR 0.51 (0.15 to 1.78)	
4/36 (11.1%)	
4/18 (22.2%)	
⊕⊕⊖⊖ Low	
None	
Very serious ^h	
Not serious	
Not serious	
Not serious	
54 (3 RCTs)	

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

Explanations

a. Less than $1/3^{rd}$ of studies by weight are at risk of bias

b. OIS not met

c. One study had high risk of bias

d. Downgraded one level for inconsistency as CI not overlapping e. Sample size is underpowered and confidence interval cross the minimally clinical important difference

f. Downgraded one level for inconsistency

g. Overlapping confidence intervals, therefore no serious inconsistency h. The confidence interval is very wide, OIS not met

Evidence based Guidelines for the use of Stem Cell Therapy: Neurological conditions

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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:

a. AUTOLOGOUS HEMATOPOIETIC STEM CELL TRANSPLANTATION

Desirable Effects	Large*	
Undesirable Effects	Moderate*	
Certainty of evidence	Very low	
Values	Probably no important uncertainty or variability	
Balance of effects	Probably favors the intervention	
Resources required	Large costs**	
Certainty of evidence of required resources	Moderate	
Cost effectiveness	Does not favor either the intervention or the	
	comparison	
Equity	Probably reduced	
Acceptability	Probably yes	
Feasibility	Probably yes	

Recommendations: Autologous Hematopoietic Stem Cell Transplantation is **recommended (Conditional#)** for the treatment of highly active relapsing remitting multiple sclerosis##, if there is no satisfactory improvement with disease modifying therapies.

* This judgment has been made as there is very low certainty evidence of a large benefit and known harms associated with autologous HSCT. The committee decided that benefits clearly outweigh harms.

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

The evidence overwhelmingly comes from Relapsing Remitting Multiple Sclerosis. It is not known, whether aHSCT is effective in other forms of MS (relapsing progressive, secondary progressive).

#

A. Highly active treatment-resistant relapsing MS, defined as ≥ 2 episodes of disease activity in the 36 months prior to the assessment for AHSCT. The two disease activity episodes will be a clinical MS relapse or MRI evidence of MS disease activity and must meet all the criteria described below:

 At least one episode of disease activity must occur following ≥ 1 month of treatment with one of the following: (i) a DMT approved for the treatment of relapsing MS, or (ii) a monoclonal antibody approved for the treatment of relapsing MS, or (iii) rituximab. Qualifying DMTs include: dimethyl fumarate, diroximel fumarate, monomethyl fumarate, teriflunomide, cladribine, daclizumab, ponesimod, siponimod, ozanimod, fingolimod, rituximab, ocrelizumab, natalizumab, alemtuzumab, ublituximab, and ofatumumab, and

2. At least one episode of disease activity must have occurred within the 12 months prior to the AHSCT, and

3. At least one episode of disease activity must be a clinical MS relapse confirmed by a neurologist. The other episode(s) must occur at least one month before or after the onset of the clinical MS relapse, and must be either another clinical MS relapse or MRI evidence of disease activity in the form of a gadolinium-enhancing lesion, or a new non-enhancing T2 lesion compared to a reference scan obtained not more than 36 months prior to the time of evaluation.

B. Expanded Disability Status Scale (EDSS) ≤ 6

C. No contraindications to AHSCT

b. MESENCHYMAL STEM CELL THERAPY

Desirable Effects	Small*	
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: Mesenchymal Stem Cell T	herapy is not recommended in routine clinical practice	

for the treatment of multiple sclerosis. It may be used only in the context of rigorously conducted randomized controlled trials.

*This judgment has been made as there is very low certainty evidence of small benefit in terms of disability and relapse rate.

** This judgment has been made as there is little to 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:

a. AUTOLOGOUS HEMATOPOIETIC STEM CELL TRANSPLANTATION:

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

1. Lack of sufficient number of RCTs

2. Small number of participants and/or events in the included RCTs

b. MESENCHYMAL STEM CELL THERAPY

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

1. Lack of sufficient number of RCTs

2. Small number of participants and/or events in the RCTs

3. Lack of long term follow up of patients thus providing insufficient evidence on the safety of this experimental therapy

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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 neurological conditions, priority areas for future research were identified and are as follows:

- Stroke
- Multiple Sclerosis (Mesenchymal stem cell therapy)

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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Annexure 2: DECLARATION OF INTEREST (DoI)

Name	Declaration of 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. M Jeeva Sankar, All India Institute of Medical Sciences (AIIMS), New Delhi	None declared	Not applicable
Dr. Rakesh Lodha, All India Institute of Medical Sciences, 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

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Dr. Anura Aggamual Trivadi	None declared	Nataraliashla
Dr. Anurag Aggarwal, Trivedi	None declared	Not applicable
School of Biosciences, Ashoka		
University, Sonipat, Haryana	Nege de classe d	Net control
Dr. Alok Srivastava, Christian	None declared	Not applicable
Medical College, Vellore		
Dr. Sujata Mohanty, All India	She declared that she is a	The Steering Group did not see
Institute of Medical Sciences,	member of the Subject Expert	it as a potential CoI.
New Delhi	Committees of CDSCO & NMC.	NY
Dr. Maneesha Inamdar,	None declared	Not applicable
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Dr. Anupam Kumar, Institute of	None declared	Not applicable
Liver and Biliary Sciences, New		
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Dr. Naresh K, Sree Chitra	None declared	Not applicable
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(SCTIMST), Kerala		
Dr. M V Padma Srivastava, All	The member declared that she	The Steering Group did not see
India Institute of Medical	has received research support	it as a potential CoI.
Sciences, New Delhi	from DST with an interest	
	related to the subject matter	
	and is a member of the	
	Committee of DGHS related to	
	the subject matter.	
Dr. Jeyaraj D Pandian, Christian	The member declared that he	The Steering Group did not see
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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 Centers (TRCs) across the country to assist in evidence synthesis by conducting systematic reviews and meta-analyses, thereby enabling consistent, high-quality guideline development.

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