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 Ministry of Health & Family Welfare (MoHFW)/ Department of Health Research (DHR)- Directorate General of Health Services (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.

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MESSAGE





In this evolving and promising landscape of modern medicine, stem cell therapy stands as one of the most dynamic areas of scientific enquiry. Its potential to revolutionize the treatment of a wide array of conditions, from degenerative diseases to traumatic injuries, has generated 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.

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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
IT	:	Intrathecal
IV	:	Intravenous
MCID	:	Minimal Clinical Important Difference
MD	:	Mean Difference
Med	:	Median
MNCs	:	Mononuclear Cells
MoHFW	:	Ministry of Health & Family Welfare
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
PT	:	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
UI	:	Uncertainty Interval

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 therapies. 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 World Health Organization (WHO) and National Institute for Care and Health Excellence (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, (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 (balance between benefits and harms) 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 **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.*	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 *#It may be used only in the context of rigorously conducted randomized controlled trials.*	The evidence is inadequate in quantity and quality to determine the 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 *#It may be used only in the context of rigorously conducted randomized controlled trials.*	The evidence is inadequate in quantity and quality to determine the safety and efficacy of stem cell therapy in patients with ALS.
4.	In patients with multiple sclerosis (MS), a) What is the efficacy and safety of hematopoietic stem cell transplantation	a) Autologous hematopoietic stem cell transplantation (AHSCT) is **recommended** 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

	compared to usual care?	relapsing remitting multiple sclerosis**, if there is no satisfactory improvement with disease modifying therapies. Strength: Conditional## Certainty of Evidence: Very Low	that benefits clearly outweigh harms.
	b) What is the efficacy and safety of mesenchymal stem cell therapy compared to usual care?	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.*	There is very low certainty evidence of small benefit in terms of disability and relapse rate. There is little to no difference in undesirable effects between stem cell therapy and usual care.

*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).

#For RCTs using stem cells with less than minimal manipulation, approval from a registered Institutional Ethics Committee (IEC) is required before initiating the study and this therapy/procedure/product should demonstrate the type and number of stem cells administered. For RCTs involving stem cells that have undergone more than minimal manipulation, prior regulatory approval from the Central Drugs Standard Control Organization (CDSCO) is mandatory, in addition to IEC approval. The levels of manipulation for stem cell therapy have been defined by CDSCO (Annexure-1).

##

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 ≥ 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 are being jointly developed by Department of Health & Family Welfare (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 includes collation of evidence from SR and MA of existing literature on well-defined review questions. Finally, the evidence obtained from SR & MA is graded for its certainty using the GRADE Approach. This grading is 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).

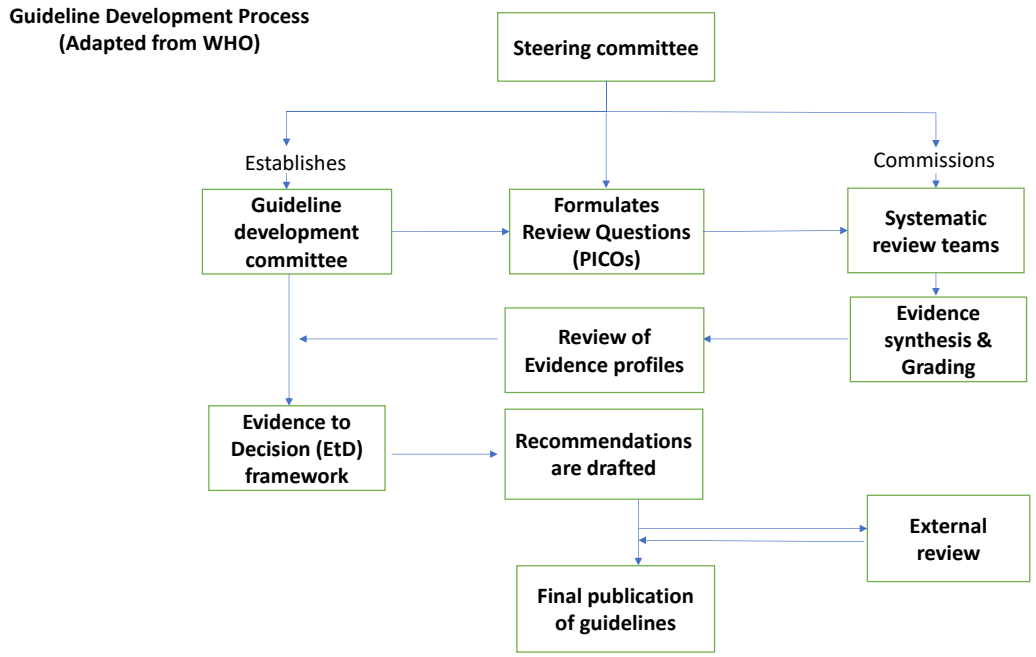


Figure 1: Guideline Development Process –adapted from WHO[1]

2. Rationale/ Scope:

The rapid advances in stem cell research have created high expectations in the field of cell-based therapies. Because of its regenerative potential, stem cell therapy has garnered significant interest among patients and practitioners. As a result, there has been rampant use of this experimental therapy despite limited knowledge of its safety and efficacy. Realizing that therapeutic applications need to be based on rational and ethical premises, these guidelines aim to summarize the evidence available on the efficacy and safety of stem cell therapy to guide 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 (Annexure-2):

Steering Group: This group was jointly chaired by the Secretary, DHR & DG, ICMR and DGHS and was involved 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 was 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: The review questions were commissioned to the systematic review teams to 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 had submitted the duly filled Declaration of Interests form adapted from the WHO.[1] These 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-3.

6. Defining the Scope and Key Questions:

The steering group held a meeting with the potential GDG members to identify the priority disease conditions on which the efficacy and safety of stem cell therapy need to be reviewed. A list of 10 broad disease groups was finalized including a total of 28 conditions. The group of 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 Expression of Interest 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. The criteria for evaluation were 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 (EtD) framework. They were as follows:

- No evidence of randomization
- 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 level of manipulation done to develop stem cell and stem cell derived products was interpreted by DHR secretariat into less than or more than minimal manipulation as defined by CDSCO (Annexure 1) and information provided in the trial itself. 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 discouraged, as it is easier to compare mean difference (MD) with the minimal clinically important difference (MCID).

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

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

The progress of the 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 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 prioritized 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. Subsequently, a countrywide expert consultation was also done. The draft document was then revised based on the inputs received and the guidelines was finalized, thereafter.

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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. Globally, stroke remained the second-leading cause of death (11·6% [UI: 10·8–12·2] of total deaths) and the third-leading cause of death and disability combined (5·7% [UI: 5·1–6·2] of total DALYs) 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.*

For RCTs using stem cells with less than minimal manipulation, approval from a registered Institutional Ethics Committee (IEC) is required before initiating the study and this therapy/procedure/product should demonstrate the type and number of stem cells administered. For RCTs involving stem cells that have undergone more than minimal manipulation, prior regulatory approval from the Central Drugs Standard Control Organization (CDSCO) is mandatory, in addition to IEC approval. The levels of manipulation for stem cell therapy have been defined by CDSCO (Annexure-1).

* 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. 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 cells[6] adipose-tissue derived mesenchymal stem cells[5], bone marrow-derived ALD-401 cells[17] 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], intra-arterially in two[4,14], and one in Lumber subarachnoid space.[11]In 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 years[7], 5 years[13] 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

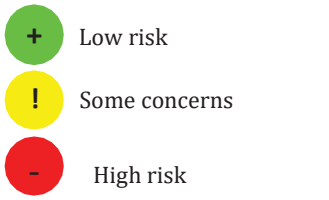
Critical outcomes reviewed and their MCID:

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	The Barthel Index for activities of daily living is an ordinal scale which 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**:**

	RoB2 Domains					
Study ID	D1	D2	D3	D4	D5	Overall
Bhatia 2018	!	+	+	+	!	!
Chen 2014	+	+	+	+	+	+
Fang 2018	+	!	+	+	-	-
Hess 2017	+	+	+	+	-	-
Houkin 2024	+	+	+	+	+	+
Jaillard 2020	+	!	+	+	-	-
Jin 2017	!	+	+	!	-	-
Law 2021	!	+	+	+	!	!
Moniche 2023	+	+	+	+	+	+
Niizuma 2023	+	!	+	+	+	!
Prasad 2014	+	+	+	+	+	+



D1 Randomization process

D2 Deviations from the intended interventions

D3 Missing outcome data

D4 Measurement of the outcome

D5 Selection of the reported result

2. Assessment for Barthel Index**:**

	ROB2 Domains					
Study ID	D1	D2	D3	D4	D5	Overall
Fang 2018	+	!	+	+	-	-
Jaillard 2020	+	!	+	+	-	-
Jin 2017	!	+	+	!	-	-
Law 2021	!	+	+	+	!	!
Prasad 2014	+	+	+	+	+	+

+ Low risk

! Some concerns

- High risk

D1 Randomization process

D2 Deviations from the intended interventions

D3 Missing outcome data

D4 Measurement of the outcome

D5 Selection of the reported result

3. Assessment for All-cause mortality:

	RoB2 Domains					
Study ID	D1	D2	D3	D4	D5	Overall
Bhatia 2018	!	+	+	+	!	!
Chen 2014	+	+	+	!	+	!
Fang 2018	+	!	+	+	+	!
Hess 2017	+	+	+	+	-	-
Houkin 2024	+	+	+	+	+	+
Jaillard 2020	+	!	+	+	+	!
Jin 2017	!	+	+	+	!	!
Law 2021	!	+	+	+	!	!
Moniche 2023	+	+	+	+	+	+
Niizuma 2023	+	!	+	+	+	!
Prasad 2014	+	+	+	+	+	+

+ Low risk

! Some concerns

- High risk

D1 Randomization process

D2 Deviations from the intended interventions

D3 Missing outcome data

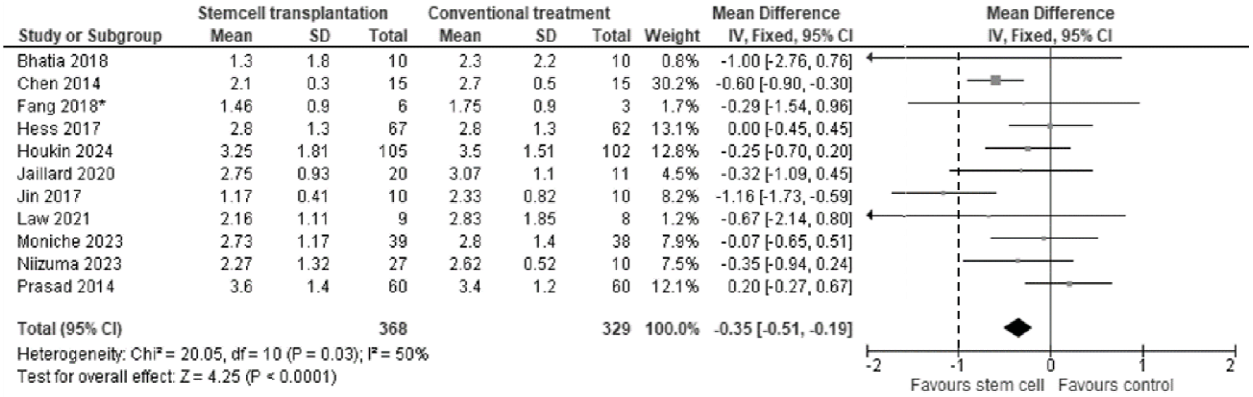
D4 Measurement of the outcome

D5 Selection of the reported result

Desirable Effects:

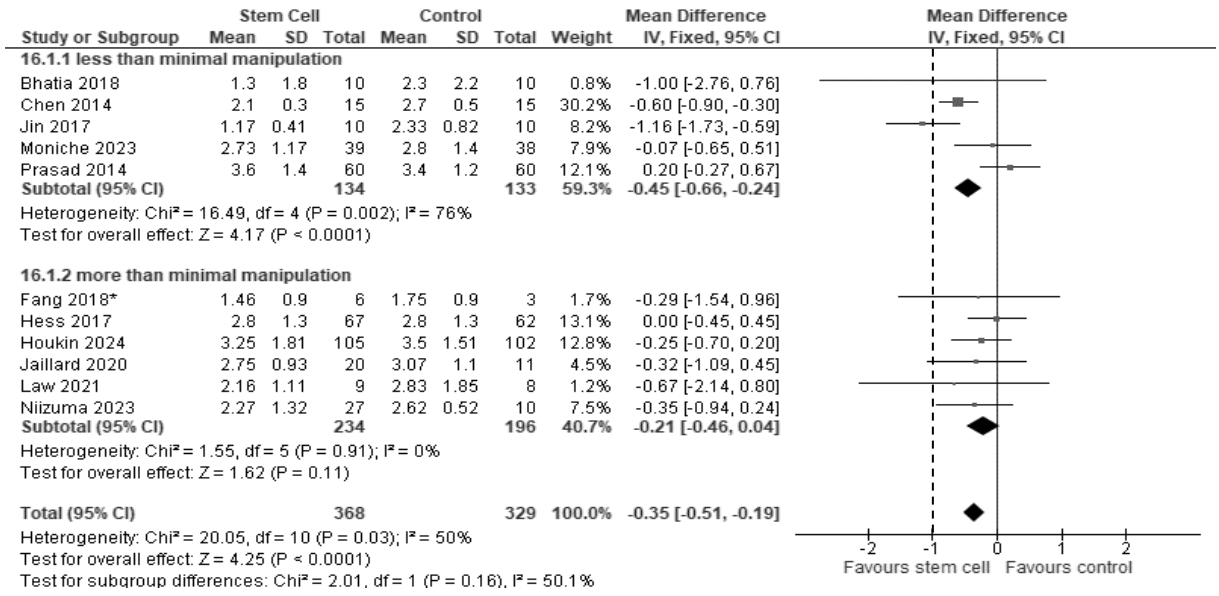
1. Disability: Eleven trials, with a total of 697 participants, reported the Modified Rankin Scale (mRS) at the end of follow up period (ranged from 6 months to 7 years). The mean difference in mRS was -0.35 (95% CI: -0.51 to -0.19) in the stem cell arm as compared to usual care. There seems to be a 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.

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

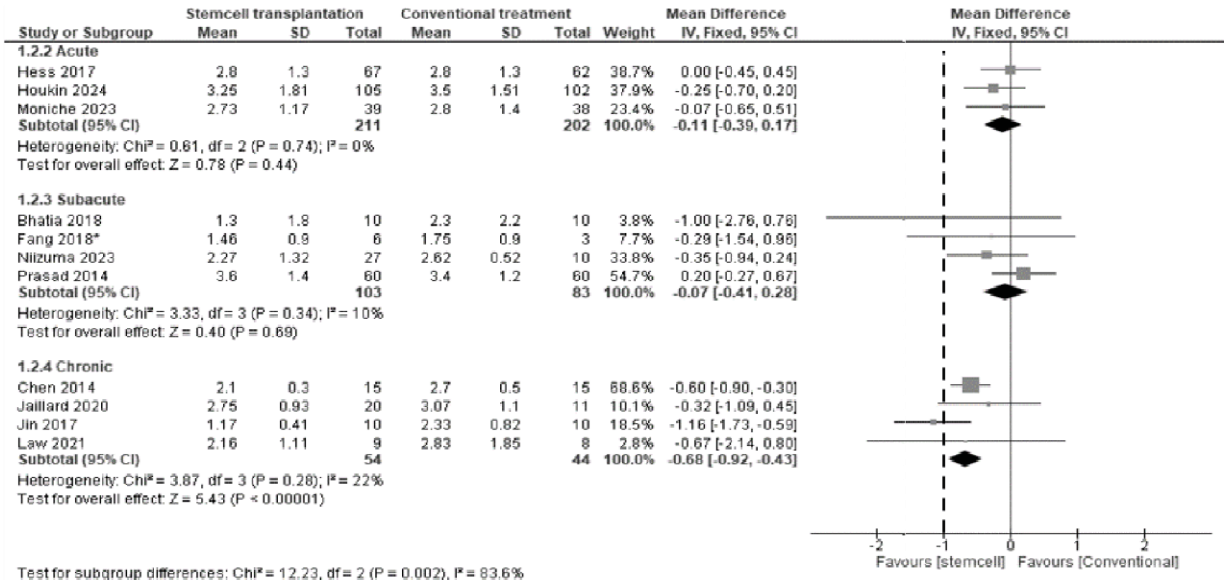


Subgroup analysis

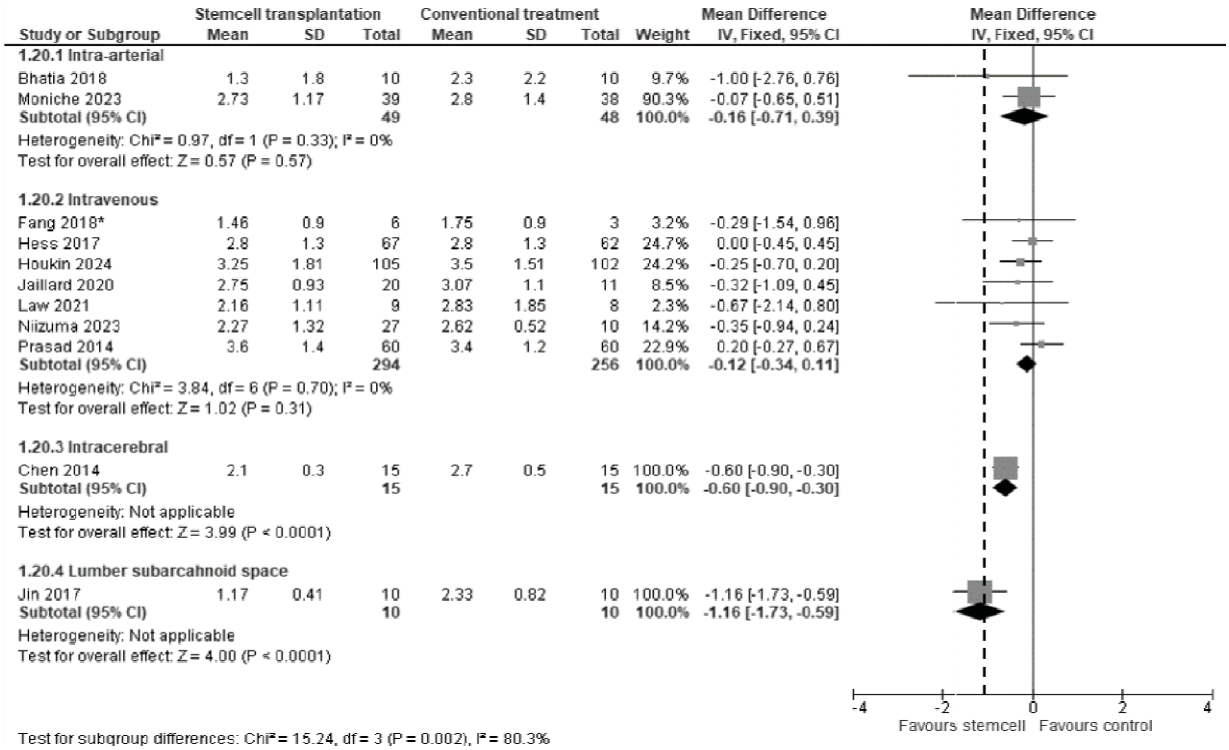
1.2. mRS at last follow up, **based on level of stem cell manipulation**:



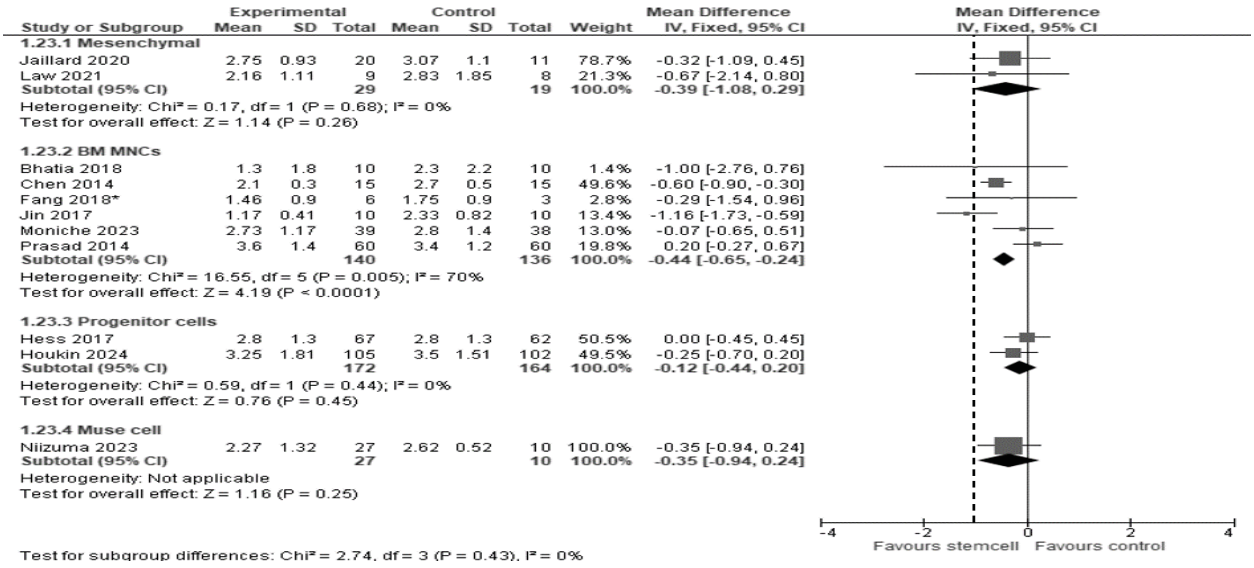
1.3. mRS at last follow-up, by phase of stroke:



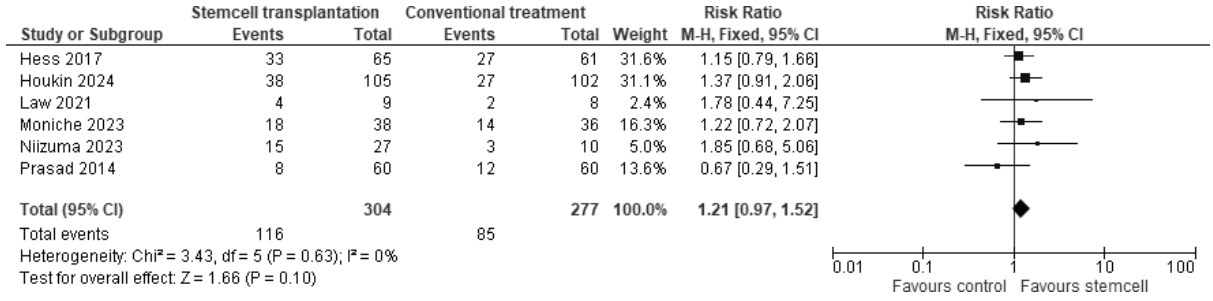
1.4. mRS at last follow-up, by route of administration of stem cell:



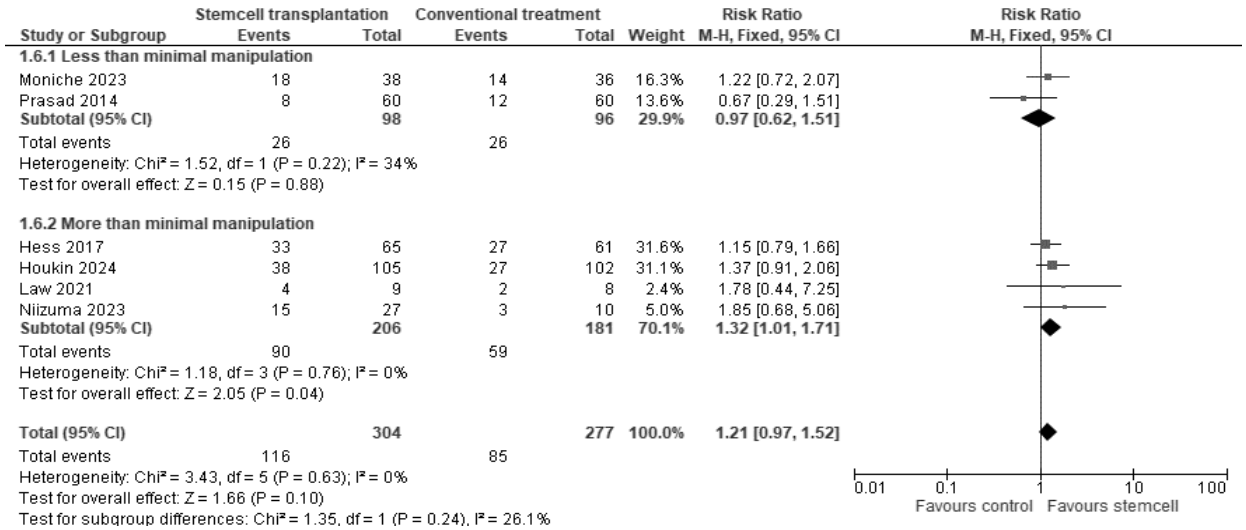
1.5. mRS at last follow-up, by type of stem cell:



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

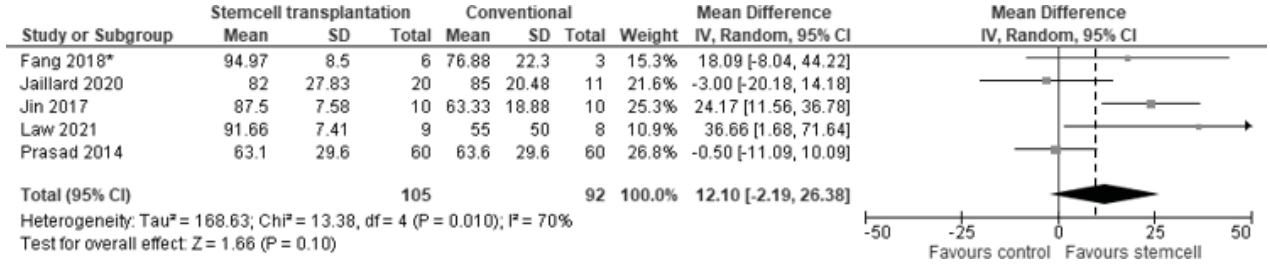


1.7. mRS 0-2 at last follow-up, **based on level of stem cell manipulation:**



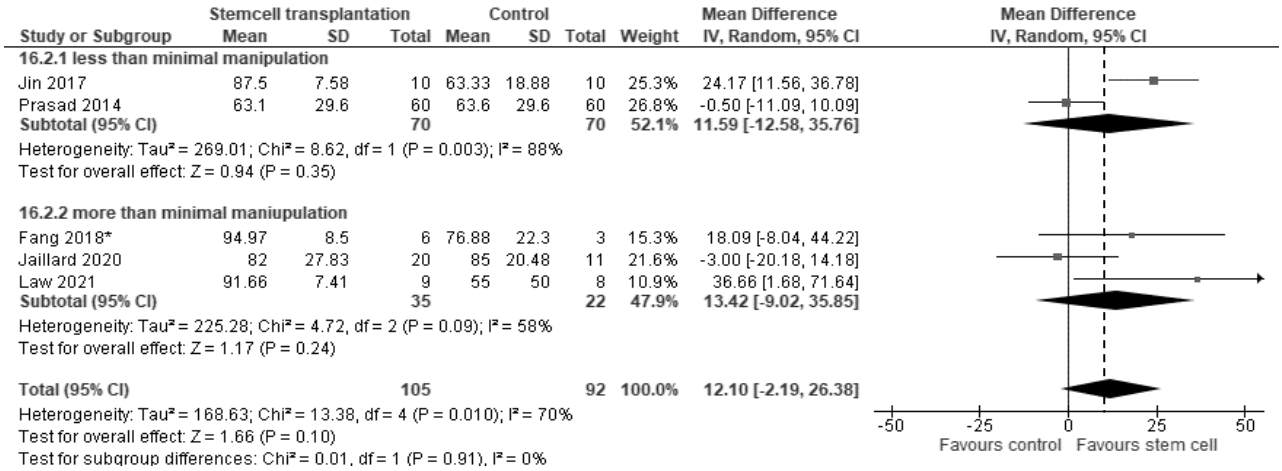
2. Dependency: Five trials, with a total of 197 participants, reported the Barthel Index (BI) score as a continuous variable at the end of follow up. (Follow-up period ranged from 1 year to 7 years). The mean difference in BI was 12.1 (95% CI: -2.19 to 26.38) in stem cell arm compared to usual care.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

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

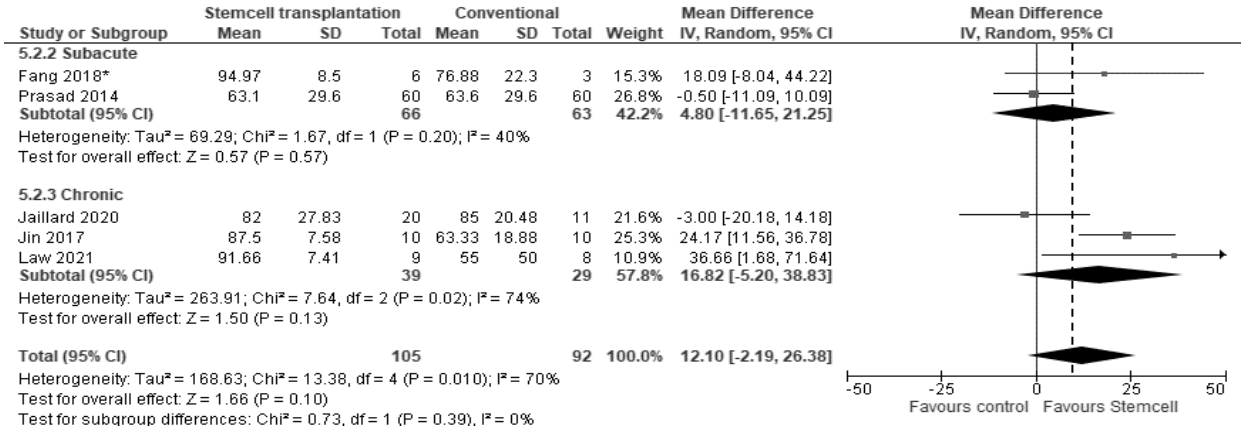


Subgroup analysis

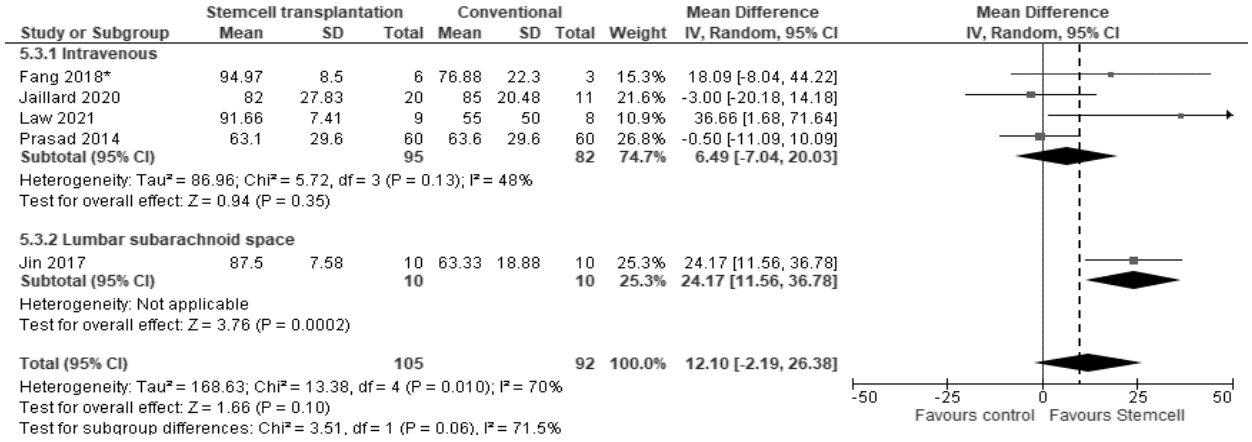
2.2. BI at last-follow up, **based on level of stem cell manipulation**:



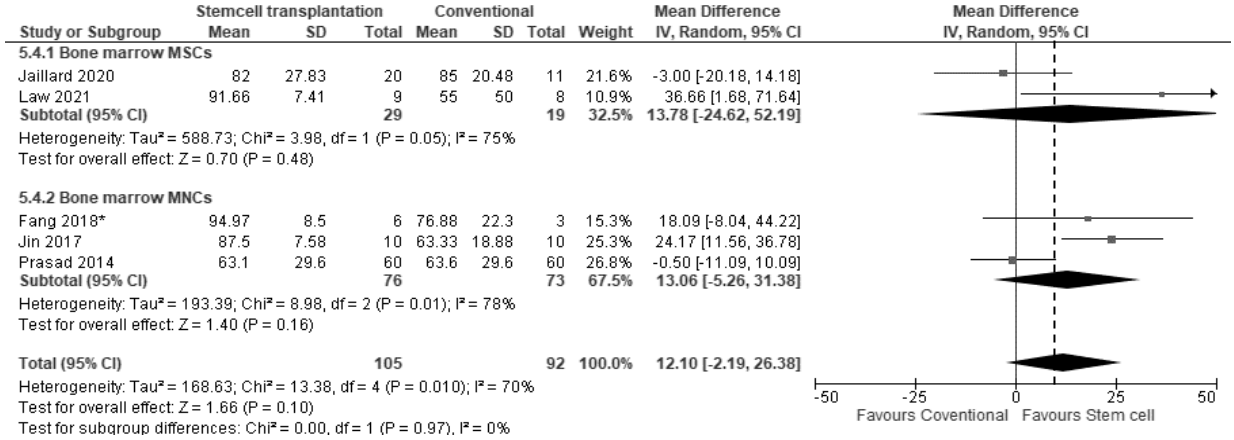
2.3. BI at last-follow up, by phase of disease:



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

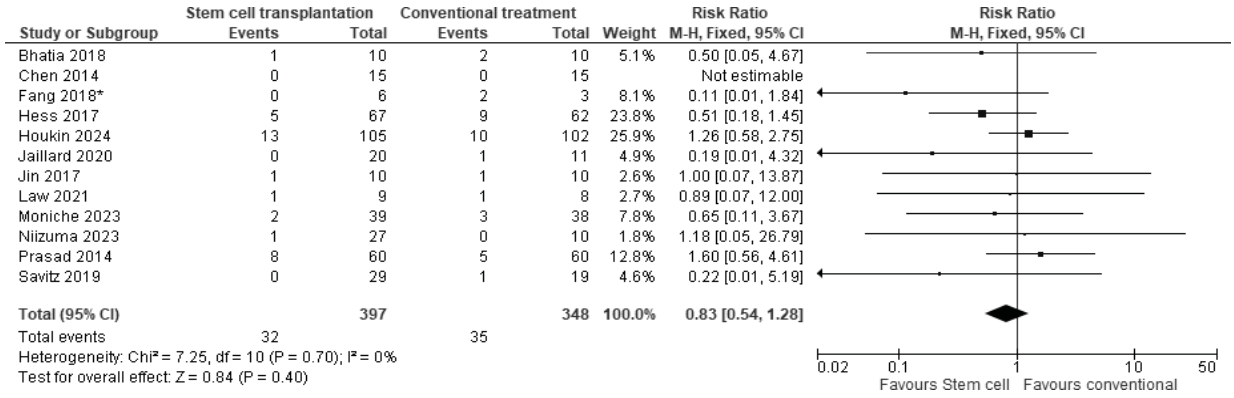


2.5. BI at last follow-up, by type of stem cell:



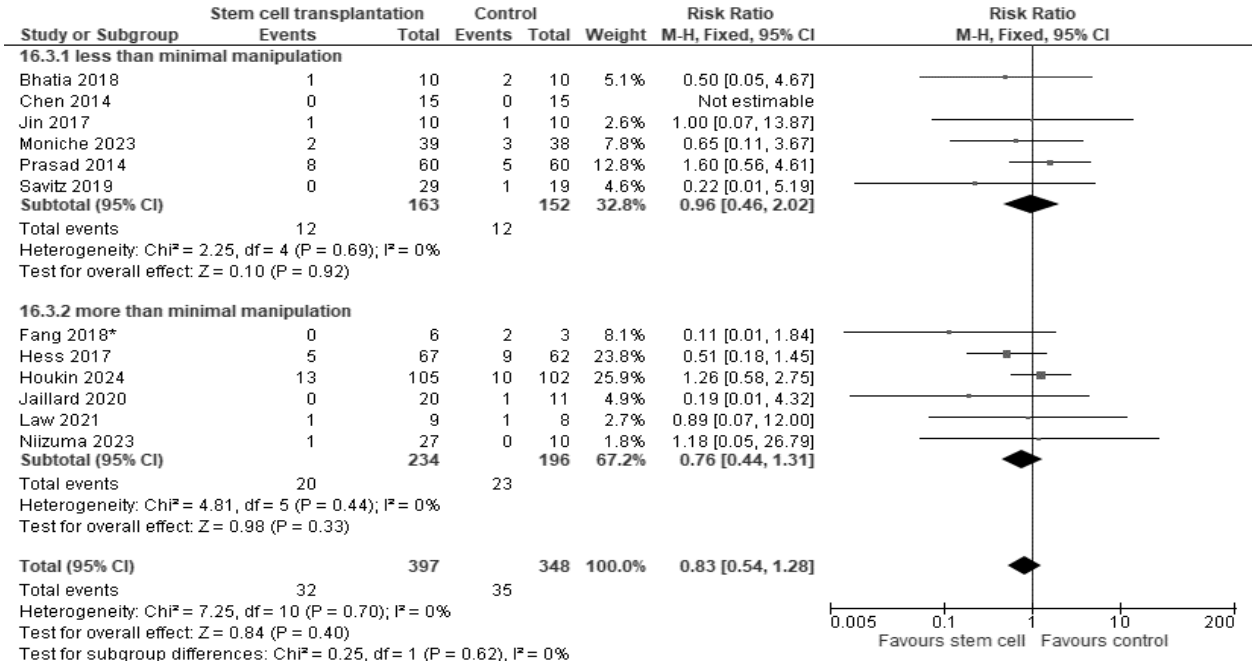
3. All-cause mortality: Twelve studies with a total of 745 participants and 67 events reported mortality. Pooled analysis yielded a risk ratio of 0.83 (95% CI: 0.54 to 1.28) in the stem cell arm as compared to usual care, which was statistically non-significant.

3.1. Forest plot showing the effect of stem cell therapy on all-cause mortality (1 year to 7 years):



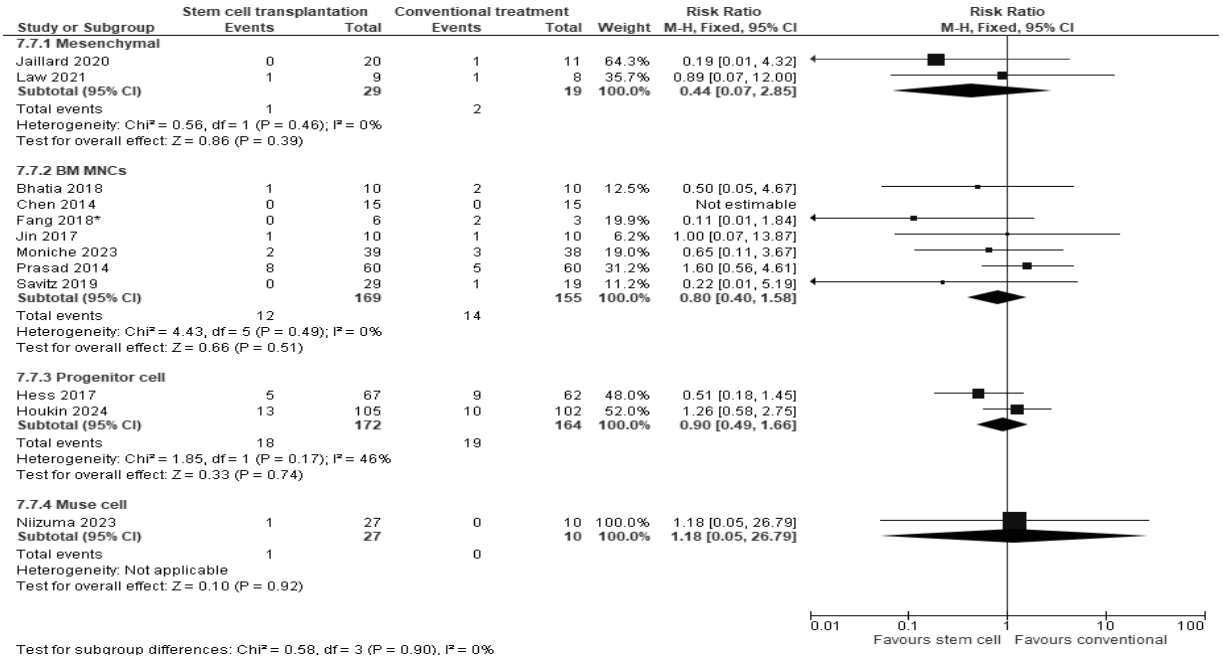
Subgroup analysis

3.2. Effect of stem cell therapy on all-cause mortality **based on level of stem cell manipulation**:



Study or Subgroup	Stem cell transplantation Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
16.3.1 less than minimal manipulation						
Bhatia 2018	1	10	2	10	5.1%	0.50 [0.05, 4.67]
Chen 2014	0	15	0	15		Not estimable
Jin 2017	1	10	1	10	2.6%	1.00 [0.07, 13.87]
Moniche 2023	2	39	3	38	7.8%	0.65 [0.11, 3.67]
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]
Subtotal (95% CI)		**163**		**152**	**32.8%**	**0.96 [0.46, 2.02]**
Total events	12		12			
Heterogeneity: Chi² = 2.25, df = 4 (P = 0.69); I² = 0%						
Test for overall effect: Z = 0.10 (P = 0.92)						
16.3.2 more than minimal manipulation						
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]
Law 2021	1	9	1	8	2.7%	0.89 [0.07, 12.00]
Niizuma 2023	1	27	0	10	1.8%	1.18 [0.05, 26.79]
Subtotal (95% CI)		**234**		**196**	**67.2%**	**0.76 [0.44, 1.31]**
Total events	20		23			
Heterogeneity: Chi² = 4.81, df = 5 (P = 0.44); I² = 0%						
Test for overall effect: Z = 0.98 (P = 0.33)						
Total (95% CI)		**397**		**348**	**100.0%**	**0.83 [0.54, 1.28]**
Total events	32		35			
Heterogeneity: Chi² = 7.25, df = 10 (P = 0.70); I² = 0%						
Test for overall effect: Z = 0.84 (P = 0.40)						
Test for subgroup differences: Chi² = 0.25, df = 1 (P = 0.62), I² = 0%						

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



Study or Subgroup	Stem cell transplantation Events	Total	Conventional treatment Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
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: Chi² = 0.56, df = 1 (P = 0.46); I² = 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: Chi² = 4.43, df = 5 (P = 0.49); I² = 0%						
Test for overall effect: Z = 0.66 (P = 0.51)						
7.7.3 Progenitor cell						
Hess 2017	5	67	9	62	48.0%	0.51 [0.18, 1.45]
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: Chi² = 1.85, df = 1 (P = 0.17); I² = 46%						
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**		**10**	**100.0%**	**1.18 [0.05, 26.79]**
Total events	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.10 (P = 0.92)						
Test for subgroup differences: Chi² = 0.58, df = 3 (P = 0.90), I² = 0%						

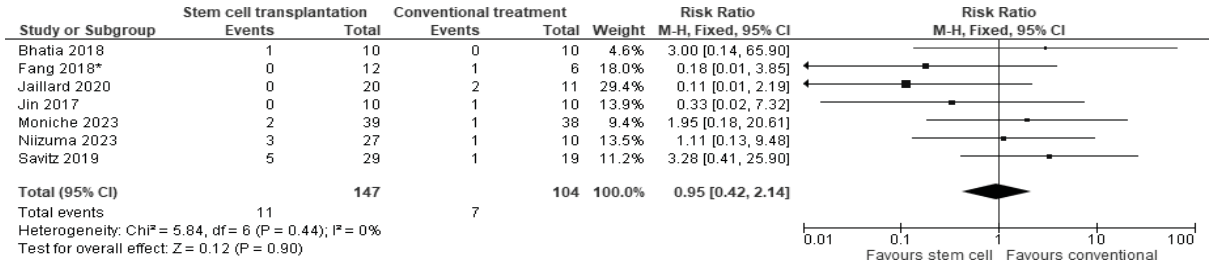
Undesirable effects:

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

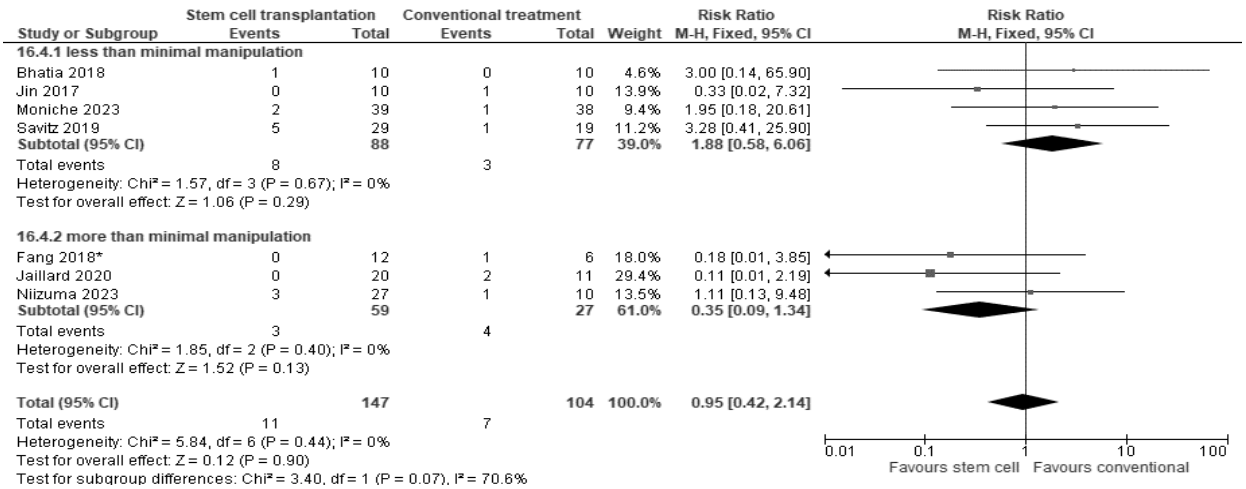
Outcomes	No of studies reporting SAE	Total events in stem cell arm	Total events in conventional arm	Risk ratio (95 % CI)
All-cause mortality	12	32	35	0.83 (0.54 to 1.28)
Recurrent stroke	7	11	7	0.95 (0.42 to 2.14)
Infection	7	52	43	0.89 (0.64 to 1.24)
Seizure	5	11	7	0.84 (0.39 to 1.81)
Worsening of neurological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

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:

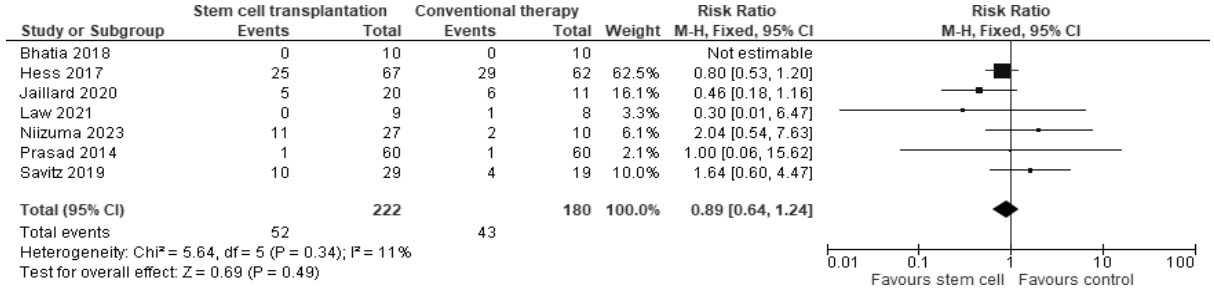


4.1.2. Recurrent stroke at last follow-up, **based on level of stem cell manipulation**:

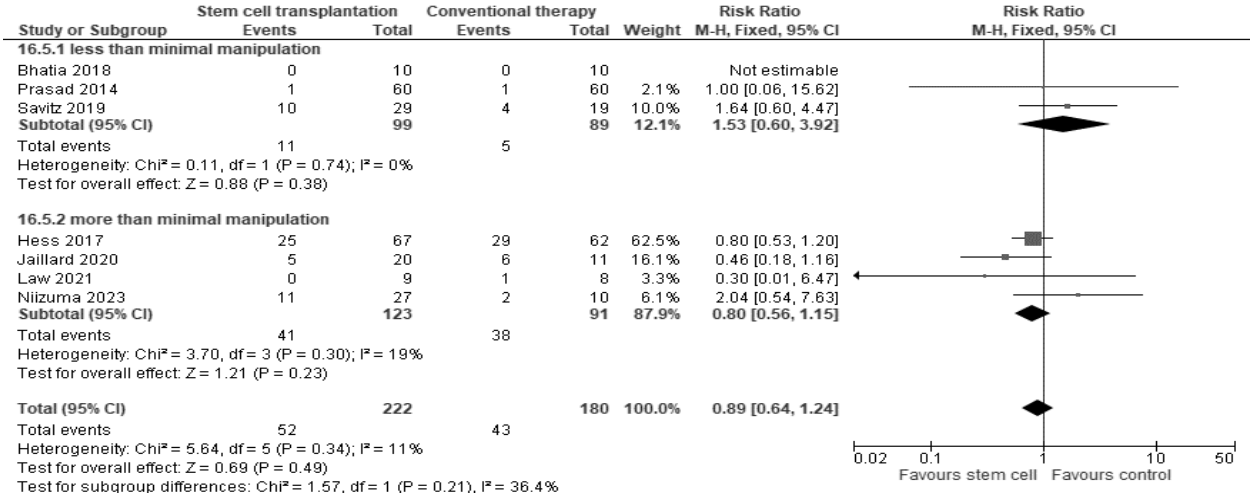


4.2. **Infection:** Seven studies with 402 participants reported infection. Pooled analysis yielded a risk ratio of RR=0.89 (95% CI: 0.64 to 1.24) in the stem cell arm as compared to usual care, which was statistically non-significant.

4.2.1. Infection at last follow-up:

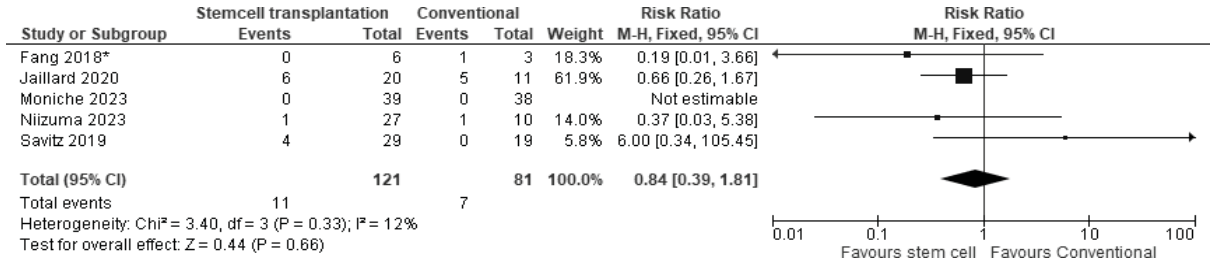


4.2.2. Infection at last follow-up, **based on level of stem cell manipulation**:

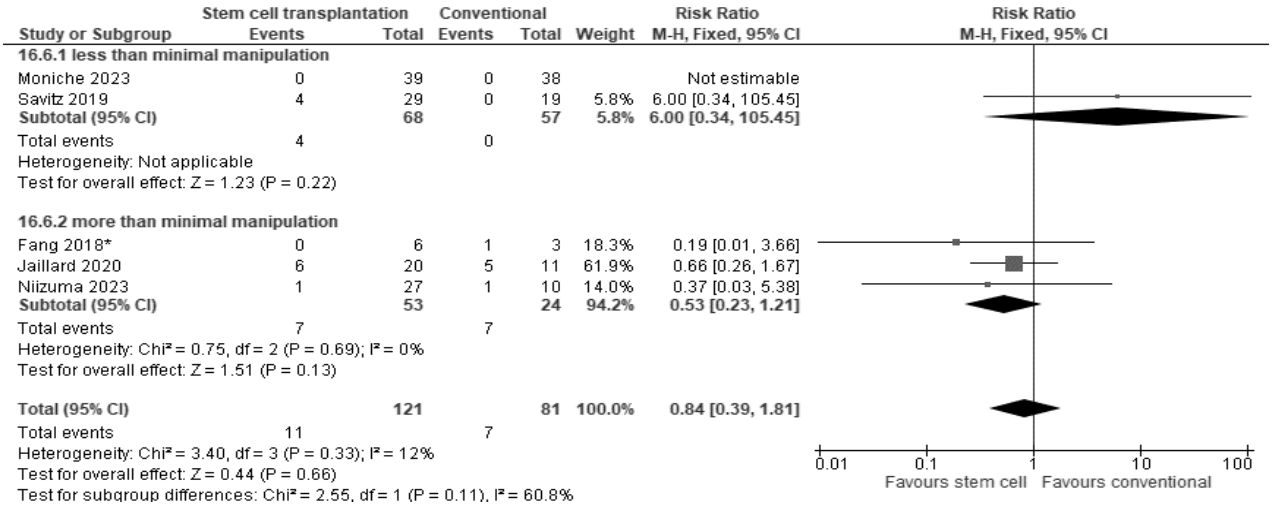


4.3. Seizure: Five studies with 202 participants reported seizure. Pooled analysis yielded a risk ratio of RR=0.84 (95% CI: 0.39 to 1.81) in the stem cell arm as compared to usual care, which was statistically non-significant.

4.3.1 Seizure at last follow-up:

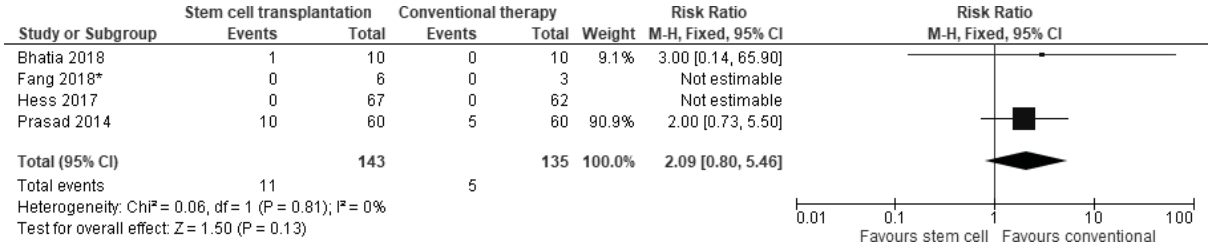


4.3.2. Seizure at last follow-up, **based on level of stem cell manipulation**:

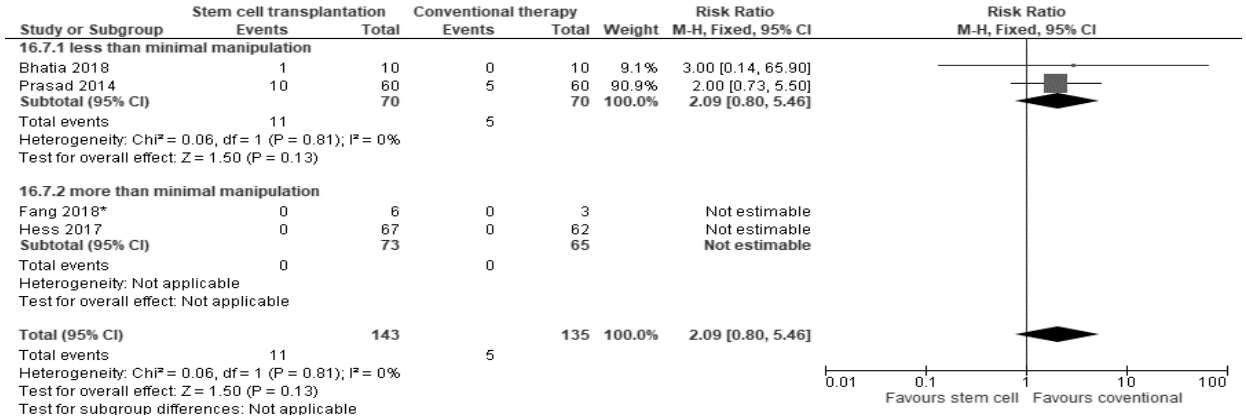


4.4. Worsening of neurological deficits: Four studies with 278 participants reported worsening of neurological deficits. Pooled analysis yielded a risk ratio of RR=2.09 (95% CI: 0.80 to 5.46) in the stem cell arm as compared to usual care, which was statistically non-significant.

4.4.1 Worsening of neurological deficits at last follow-up:

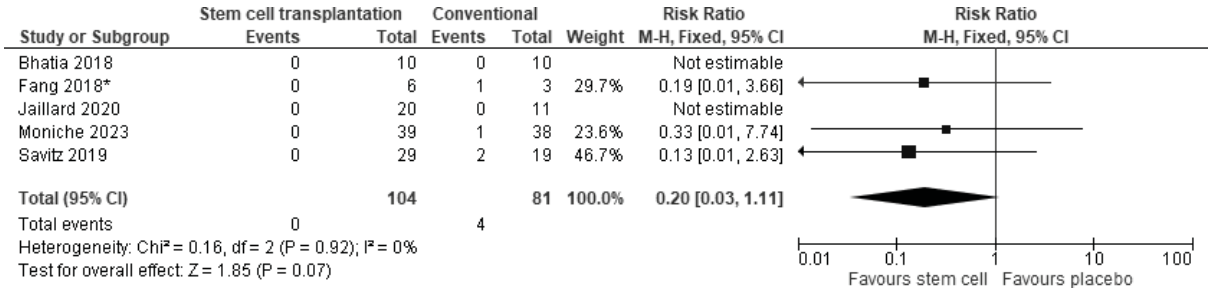


4.4.2. Worsening of neurological deficits at last follow-up, **based on level of stem cell manipulation**:

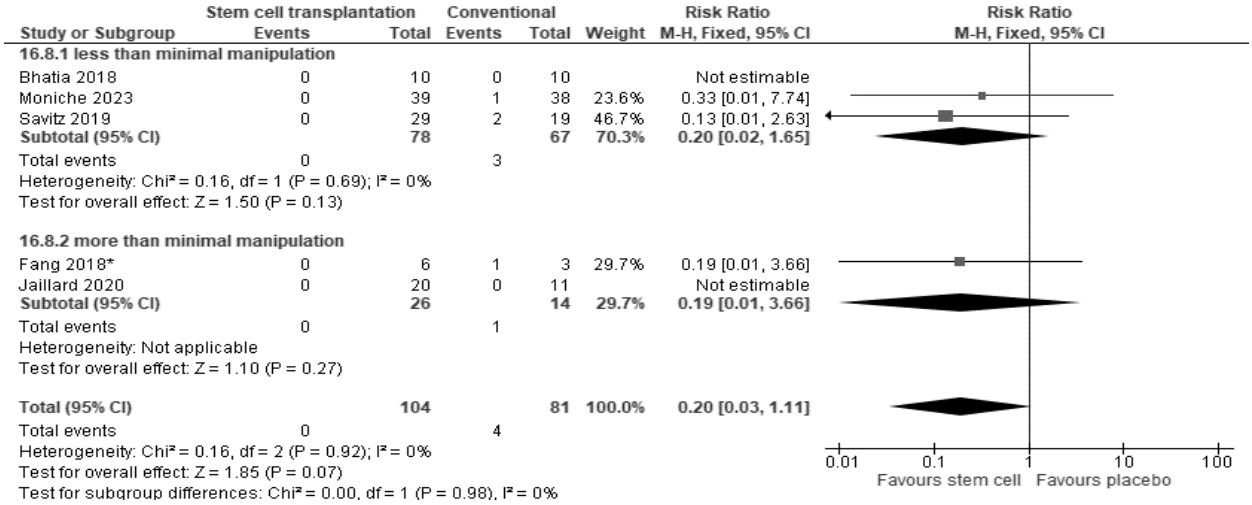


4.5. Development of any neoplasm: Four studies with 185 participants reported neoplasm development/ tumour formation. Pooled analysis yielded a risk ratio of RR=0.20 (95% CI: 0.03 to 1.11) in the stem cell arm as compared to usual care, which was statistically non-significant.

4.5.1 Development of any neoplasm at last follow-up:

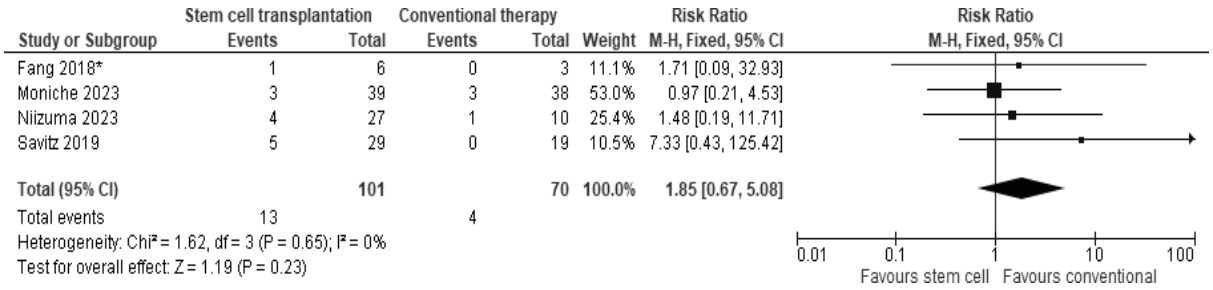


4.5.2. Development of any neoplasm at last follow-up, **based on level of stem cell manipulation**:

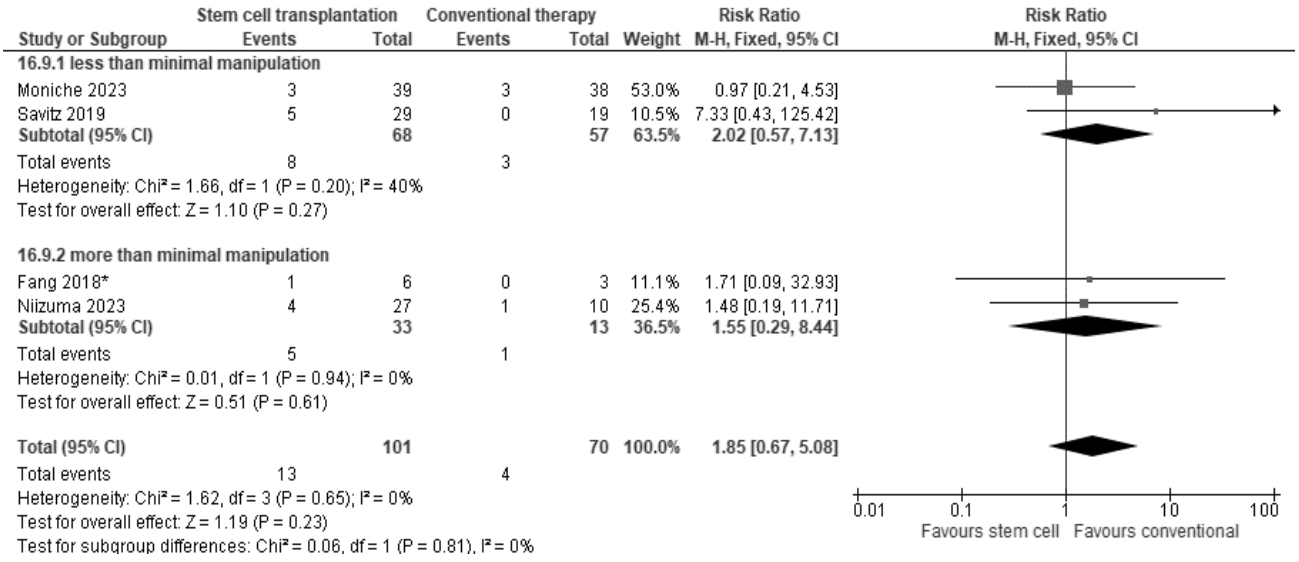


4.6. Recurrent vascular events: Four studies with 171 participants reported recurrent vascular events. Pooled analysis yielded a risk ratio of RR=1.85 (95% CI: 0.67 to 5.08) in the stem cell arm as compared to usual care, which was statistically non-significant.

4.6.1 Recurrent vascular events at last follow-up:



4.6.2. Recurrent vascular events at last follow-up, **based on level of stem cell manipulation**:



Summary of Findings: GRADE

Stem cell transplantation compared to Conventional treatment for Ischemic stroke

Patient or population: Ischemic stroke
Setting: Hospital
Intervention: Stem cell transplantation
Comparison: Conventional treatment

Outcomes	Anticipated absolute effects*(95% CI) Risk with Conventional treatment	Risk with Stem cell transplantation	Relative effect (95% CI)	No. of participants studies)	Certainty of the evidence (GRADE)	Comments
Disability assessed with: mRS at last follow up (6 months to 7 years) (higher =worse) Scale from: 0 to 6	The mean mRS score in the usual care arm was 2.73 (range: 1.75 to 3.5)	MD **0.35 lower** (0.51 lower to 0.19 lower)	-	697 (11 RCTs)	⊕⊕◯◯ Low[a,b]	An absolute change in mRS score by 1 was considered as MCID.
Dependency assessed with: BI at last follow up (range: 1 year to 7 years) (higher = better) Scale from: 0 to 100	The mean BI score in the usual care arm was 68.76 (range: 55 to 85)	MD **12.1 higher** (2.19 lower to 26.38 higher)	-	197 (5 RCTs)	⊕◯◯◯ Very low[c,d,e]	An absolute change in Barthel Index by 10 was considered as MCID.
All-cause mortality	101 per 1,000	**83 per 1,000** (54 to 129)	**RR 0.83** (0.54 to 1.28)	745 (12 RCTs)	⊕⊕◯◯ Low[a,e,f]	
Disability mRS 0-2 (mRS 0-2 at last follow up) assessed with: Modified rankin scale	307 per 1,000	**371 per 1,000** (298 to 466)	**RR 1.21** (0.97 to 1.52)	581 (6 RCTs)	⊕⊕◯◯ Low[a,e]	

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

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

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low certainty: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations

a. Downgraded one level for risk of bias as $1/3^{rd}$ – $2/3^{rd}$ of studies (by wt.) are at high 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 two level for risk of bias as less than $2/3^{rd}$ of studies (by wt.) were at low risk of bias.
d. Downgraded one level as the point estimates vary widely across the studies. There is substantial heterogeneity with I^2 of 70%.
e. Downgraded one level as the as CI of effect estimate crossed the line of null effect.
f. Although I^2 was 0%, Point estimates vary widely across the studies but the confidence interval overlap.

Evidence Profile:

Stem cell transplantation compared to Usual Care for Ischemic stroke

Certainty assessment							Summary of findings				
							Study event rates (%)			Anticipated absolute effects	
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	With Conventional treatment	With Stem cell trans-plantation	Relative effect (95% CI)	Risk with conventio nal treatment	Risk difference with Stem cell transplantation
Disability assessed with: mRS at last follow up (6 months to 7 years) (higher =worse); Scale from: 0 to 6											
697 (11 RCTs)	Serious[a]	Serious[b]	Not serious	Not serious	Not detected	⨁⨁◯◯ Low[a,b]		-	-	The mean mRS score in the usual care arm was 2.73 (range: 1.75 to 3.5)	MD **0.35 lower** (0.51 lower to 0.19 lower)
Dependency assessed with: BI at last follow up (range: 1 year to 7 years) (higher = better); Scale from: 0 to 100											
197 (5 RCTs)	Very serious[c]	Serious[d]	Not serious	Serious[e]	None	⨁◯◯◯ Very low[c,d,e]		-	-	The mean BI score in the usual care arm was 68.76 (range: 55 to 85)	MD **12.1 higher** (2.19 lower to 26.38 higher)
All-cause mortality											
745 (12 RCTs)	Serious[a]	Not serious[f]	Not serious	Serious[e]	Not detected	⨁⨁◯◯ Low[a,e,f]	35/348 (10.1%)	32/397 (8.1%)	**RR 0.83** (0.54 to 1.28)	35/348 (10.1%)	**17 fewer per 1,000** (from 46 fewer to 28 more)
Disability mRS 0-2 (mRS 0-2 at last follow up) assessed with: Modified rankin scale											
581 (6 RCTs)	Serious[a]	Not serious	Not serious	Serious[e]	None	⨁⨁◯◯ Low[a,e]	85/277 (30.7%)	116/304 (38.2%)	**RR 1.21** (0.9 to 1.52)	85/277 (30.7%)	**64 more per 1,000** (from 9 fewer to 160 more)

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

Explanations

a. Downgraded one level for risk of bias as 1/3rd – 2/3rd of studies (by wt.) are at high 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 two level for risk of bias as less than 2/3rd of studies (by wt.) were at low risk of bias.
d. Downgraded one level as the point estimates vary widely across the studies. There is substantial heterogeneity with I^2 of 70%.
e. Downgraded one level as the as CI of effect estimate crossed the line of null effect.
f. Although I^2 was 0%, Point estimates vary widely across the studies but the confidence interval overlap.

D. SUMMARY OF JUDGEMENTS:

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

Desirable effects	Trivial*
Undesirable effects	Varies**
Certainty of evidence	Very Low
Values	Probably no important uncertainty or variability
Balance of effects	Does not favor either the intervention or the comparison
Resources required	Large costs***
Certainty of evidence of required resources	Moderate
Cost effectiveness	Probably favors the comparison
Equity	Probably reduced
Acceptability	Probably yes
Feasibility	Probably yes
Recommendations: Stem cell therapy is **not recommended** in routine 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. Globally, stroke remained the second-leading cause of death (11·6% [UI: 10·8–12·2] of total deaths) and the third-leading cause of death and disability combined (5·7% [UI: 5·1–6·2] of total DALYs) 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 **not recommended** 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.*

For RCTs using stem cells with less than minimal manipulation, approval from a registered Institutional Ethics Committee (IEC) is required before initiating the study and this therapy/procedure/product should demonstrate the type and number of stem cells administered. For RCTs involving stem cells that have undergone more than minimal manipulation, prior regulatory approval from the Central Drugs Standard Control Organization (CDSCO) is mandatory, in addition to IEC approval. The levels of manipulation for stem cell therapy have been defined by CDSCO (Annexure-1).

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 mesenchymal stem cells	Intrathecal
Dai et al. 2013[5]	Chronic SCI	BM derived mesenchymal stem cells	Local (at site of injury)
El Kheir et al. 2014[6]	Chronic SCI	BM derived mesenchymal stem cells	Intrathecal
Levi et al. 2019[10]	Chronic SCI	Neural stem cells (allogenic)	Intramedullary
Saini et al. 2022[13]	Acute SCI (within 21 days)	CD34+ BM derived stem cells	Intramedullary

Critical outcomes reviewed and their MCID:

S. No.	Outcome reviewed	What does it measure?	MCID decided by the GDG
1.	Spinal Cord Independence Measure Scale (SCIM) Range: 0-100 Higher 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	-

Risk of Bias Assessment:



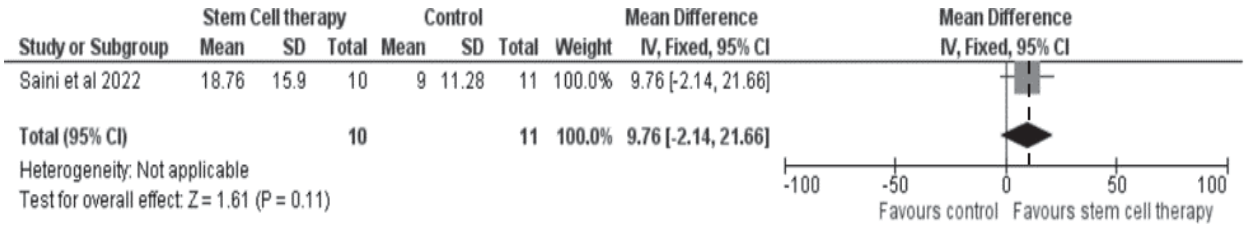
Desirable effects:

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

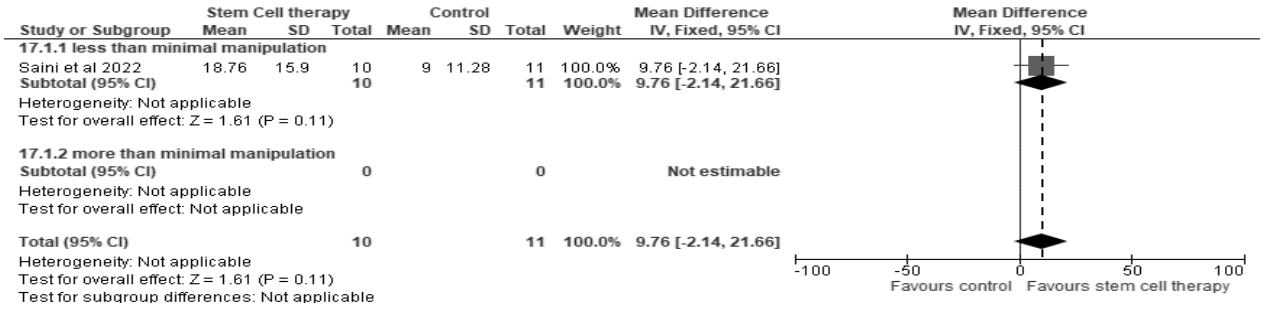
1. Dependency: Evidence from one RCT* with 21 participants of acute complete spinal cord injury reported a mean difference of 9.76 (95% CI: -2.14 to 21.66) in the SCIM Score in the stem cell therapy arm (intramedullary route) as compared to usual care at the end of six months. The difference was statistically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

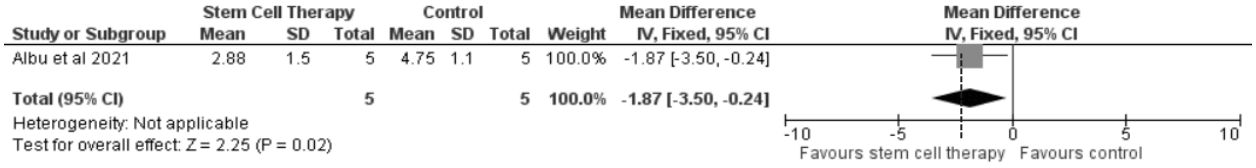


1.2 SCIM scale, **based on level of stem cell manipulation**:

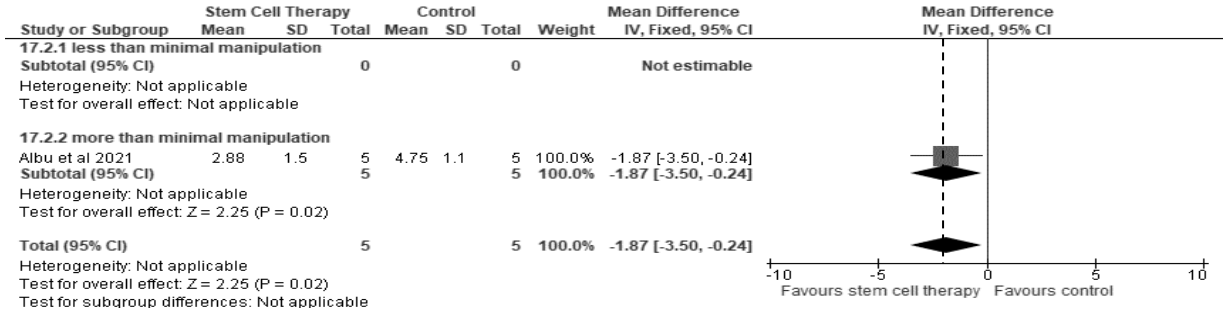


2. Bowel Function: Evidence from one RCT with 10 participants of chronic complete spinal cord injury reported a reduction in the Wexner Score with a mean difference of -1.87 (95% CI: -3.50 to -0.24) in the stem cell therapy arm (intrathecal route) as compared to usual care at the end of six months. The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

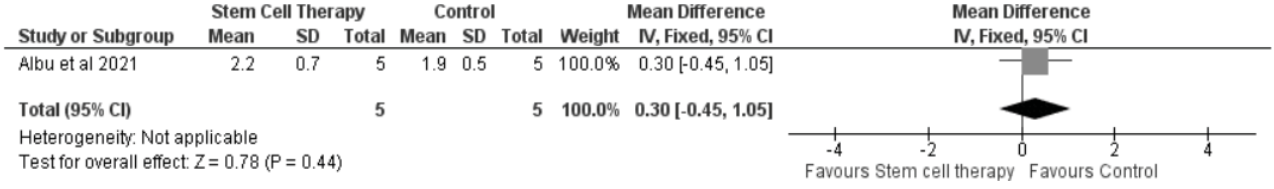


2.2 Wexner score**, based on level of stem cell manipulation**:

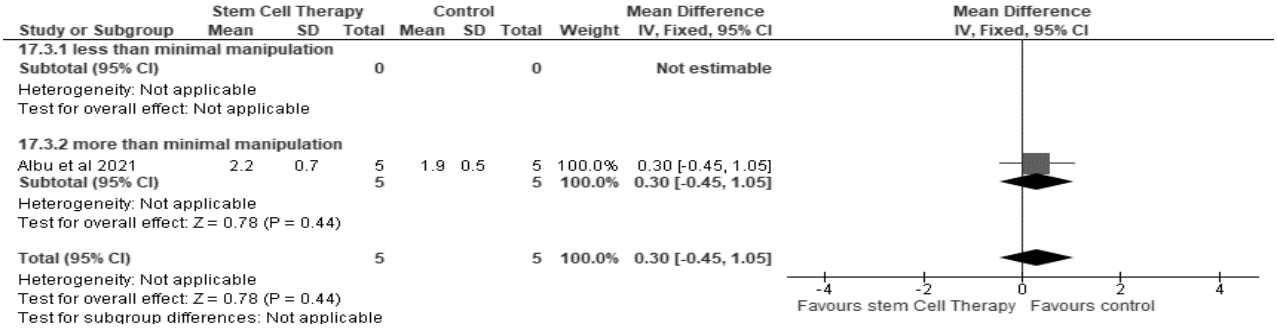


3. Bladder Function: Evidence from one RCT with 10 participants of chronic complete spinal cord injury reporting the Qualiven questionnaire (subscale- specific impact of urinary symptoms on quality of life) observed a mean difference of 0.30 (95% CI: -0.45 to 1.05) in the stem cell arm (intrathecal route) 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:

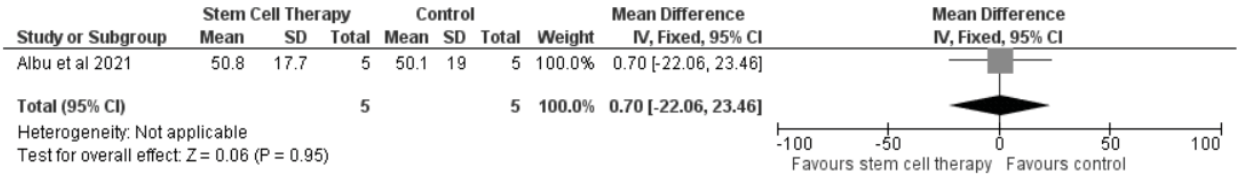


3.2 Bladder function, **based on level of stem cell manipulation**:

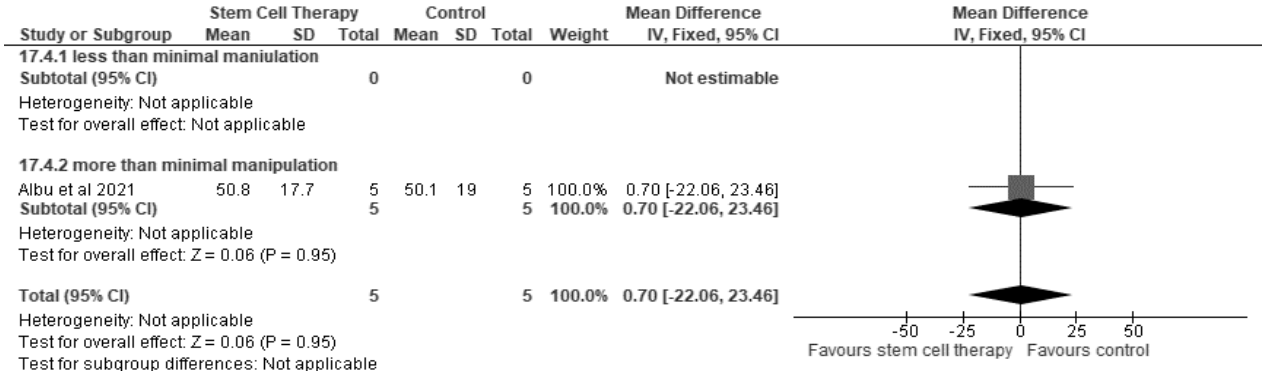


3. Quality of Life: Evidence from one RCT with 10 participants of chronic complete spinal cord injury reporting WHOQOL-BREF observed a mean difference of 0.70 (95% CI: -22.06 to 23.46) in the stem cell therapy arm (intrathecal route) as compared to usual care at the end of six months. The difference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

3.1 Quality of life at the end of six months:



3.2 Quality of life, **based on level of stem cell manipulation**:



4. Undesirable effects:

Serious Adverse Events: Albu et al[4], Dai et al[5] and El Kheir et al[6] did not report any SAEs in either of the arms. The SAEs reported by Levi et al[10] 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 al[13] 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).

Summary of findings:

Stem cell therapy compared to usual care in patients with Spinal Cord Injury

Patient or population: Patients with Spinal Cord Injury
Setting: Hospital/ Tertiary care
Intervention: Stem cell therapy
Comparison: Usual care

Outcomes	**Anticipated absolute effects***(95% CI) **Risk with standard of care**	**Risk with stem cell therapy**	Relative effect (95% CI)	Q of participants (studies)	Certainty of the evidence (GRADE)	Comments
Spinal Cord Independence Measure Scale (SCIM) at 6 months Scale: 0 to 100	The mean SCIM score in the usual care arm was 9	**MD 9.76 higher** (2.14 lower to 21.66 higher)	-	21 (1 RCT)	⊕◯◯◯ Very low[a,b,c]	An absolute change in SCIM scale by 10 was considered as MCID.
Wexner Score at 6 months Scale: 0 to 20	The mean Wexner score in the usual care arm was 4.75	**MD 1.87 lower** (3.50 lower to 0.24 lower)	-	10 (1 RCT)	⊕◯◯◯ Very low[a,b,d]	An absolute change in Wexner score by 2 points was considered as MCID.
Qualiven questionnaire (specific impact of urinary symptoms on QoL) at 6 months	The mean Qualiven Questionnaire in the usual care arm was 1.9	**MD 0.30 higher** (0.45 lower to 1.05 higher)	-	10 (1 RCT)	⊕◯◯◯ Very low[a,b,c]	
WHOQoL- BREF at 6 months Scale: 0 to 100	The mean QoL-BREF in the usual care arm was 50.1	**MD 0.70 higher** (22.06 lower to 23.46 higher)	-	10 (1 RCT)	⊕◯◯◯ Very low[a,b,c]	

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

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

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

Explanations
a. 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.

Evidence profile:

Stem cell therapy compared to usual care in patients with Spinal Cord Injury:

Certainty assessment							Summary of findings				
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With standard of care	With stem cell therapy		Risk with standard of care	Risk difference with stem cell therapy
SCIM at 6 months											
21 (1 RCT)	Very serious[a]	Inevaluable[b]	Not serious	Serious[c]	None	⊕◯◯◯ Very low[a,b,c]	-	-	-	The mean SCIM score in the usual care arm was 9	**MD 9.76 higher** (2.14 lower to 21.66 higher)
Wexner Score at 6 months											
10 (1 RCT)	Very serious[a]	Inevaluable[b]	Not serious	Serious[d]	None	⊕◯◯◯ Very low[a,b,d]	-	-	-	The mean Wexner score in the usual care arm was 4.75	**MD 1.87 lower** (3.50 lower to 0.24 lower)
Qualiven questionnaire (specific impact of urinary symptoms on QoL) at 6 months											
10 (1 RCT)	Very serious[a]	Inevaluable[b]	Not serious	Serious[c]	None	⊕◯◯◯ Very low[a,b,c]	-	-	-	The mean Qualiven Questionnaire in the usual care arm was 1.9	**MD 0.30 higher** (0.45 lower to 1.05 higher
WHOQoL- BREF at 6 months											
10 (1 RCT)	Very serious[a]	Inevaluable[b]	Not serious	Serious[c]	None	⊕◯◯◯ Very low[a,b,c]	-	-	-	The mean QoL-BREF in the usual care arm was 50.1	**MD 0.70 higher** (22.06 lower to 23.46 higher)

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

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.

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 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.*

For RCTs using stem cells with less than minimal manipulation, approval from a registered Institutional Ethics Committee (IEC) is required before initiating the study and this therapy/procedure/product should demonstrate the type and number of stem cells administered. For RCTs involving stem cells that have undergone more than minimal manipulation, prior regulatory approval from the Central Drugs Standard Control Organization (CDSCO) is mandatory, in addition to IEC approval. The levels of manipulation for stem cell therapy have been defined by CDSCO (Annexure-1).

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:

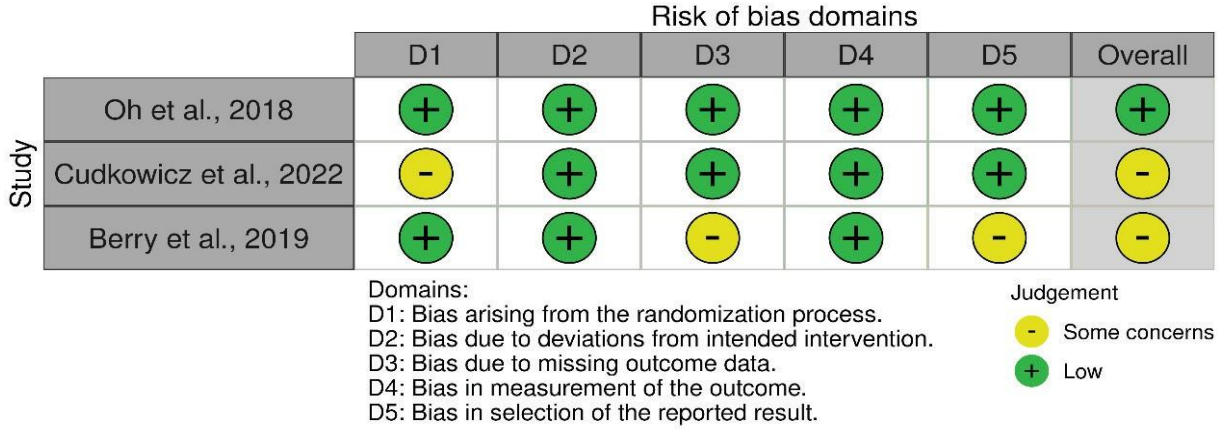
Key Question: In patients with Amyotrophic Lateral Sclerosis, what is the efficacy and safety of stem cell therapy as compared to usual care?

Included Studies: After conducting a thorough literature search upto 15th March 2024 using pre-specified 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. **All the included studies fall under the category of more than minimal manipulation.**

Critical outcomes reviewed and their MCID:

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

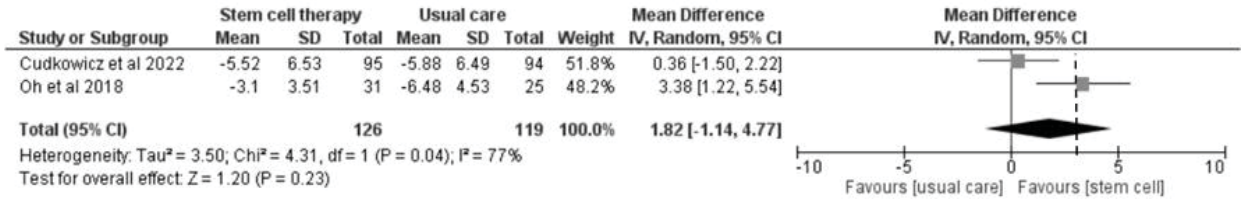
Risk of Bias Assessment:



Desirable effects:

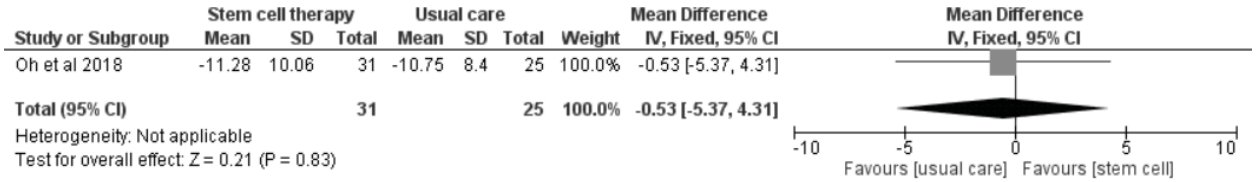
1. Revised Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS-R) score: Two trials with 248 participants reported the ALSFRS-R score. The mean difference for change from baseline in ALSFRS-R score between the stem cell therapy arm as compared to usual care at 6 months follow up was 1.82 (95%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

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

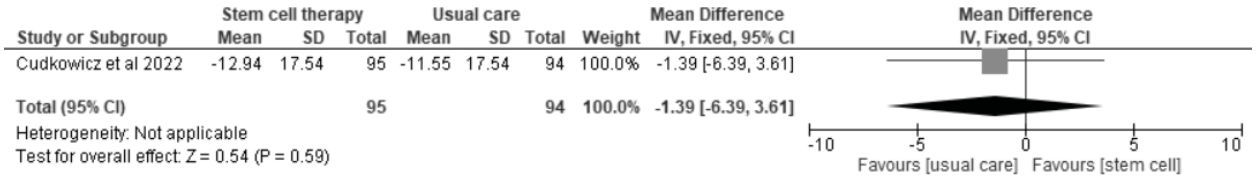


2. Vital Capacity: Oh et al[2] reported the mean difference of change from baseline in FVC between the stem cell arm and the usual care to be -0.53 (95 % CI: -5.37 to 4.31) at the end of four months, which was statistically not significant. Cudkowicz et al[3] reported the mean difference of change in 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:



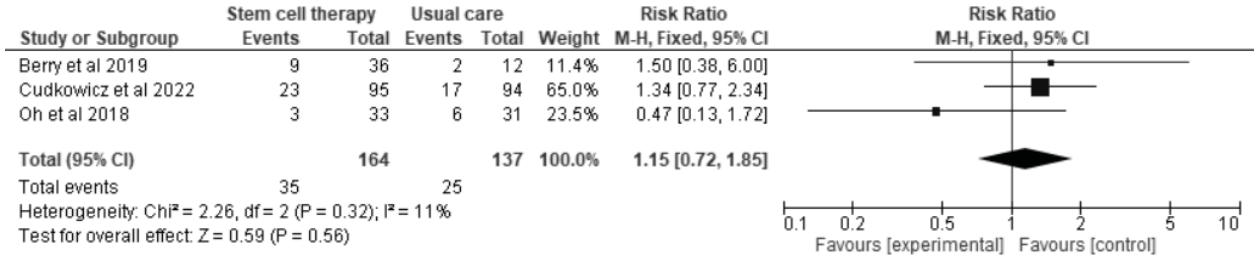
2.2 Change in SVC at the end of 6 months:



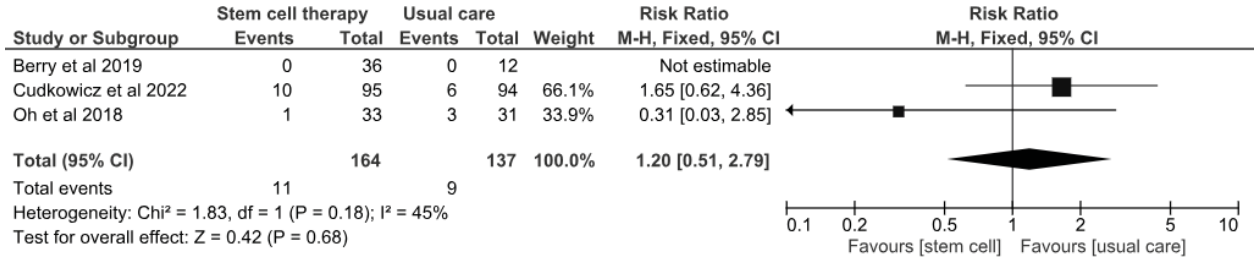
Undesirable effects:

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:



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



SUMMARY OF FINDINGS

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

Outcomes	Anticipated absolute effects*(95% CI) Risk with control	Risk with Stem cell therapy	Relative effect (95% CI)	Q of participants (studies)	Certainty of the evidence (GRADE)	Comments
Change in 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	**210 per 1,000** (131 to 338)	**RR 1.15** (0.72 to 1.85)	301 (3 RCTs)	⊕◯◯◯ Very low[c,d]	
All-cause mortality: at 6 months	66 per 1,000	**79 per 1,000** (34 to 183)	**RR 1.20** (0.51 to 2.79)	301 (3 RCTs)	⊕◯◯◯ Very low[a,b,c]	
Change in Forced Vital Capacity (FVC) at 4 months	-	**MD 0.53 lower** (5.37 lower to 4.31 higher)	-	56 (1 RCT)	⊕◯◯◯ Very Low[e,f]	
Change in Slow Vital Capacity (SVC) at 6 months	-	**MD 1.39 lower** (6.39 lower to 3.61 higher)	-	189 (1 RCT)	⊕◯◯◯ Very low[e,f,g]	

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

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

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

Explanations:
a. 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. Downgraded two level for risk of bias as less than 2/3rd of studies (by wt.) were at low risk of bias.
e. Single study was downgraded one level for inconsistency as it was inevaluable.
f. Downgraded two levels for imprecision as the 95% CI crossed the null effect line and was very wide; OIS not met.
g. The study had some concerns in the randomization process.

GRADE Evidence Profile

Certainty assessment							Summary of findings				
							Study event rates (%)			Anticipated absolute effects	
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	With control	With Stem cell therapy	Relative effect (95% CI)	Risk with control	Risk difference with Stem cell therapy
Change in ALS Function rating Scale-R (ALSFRS-R) at 6 months; Scale from: 0 to 48 (higher is better)											
248 (2 RCTs)	Serious[a]	Serious[b]	Not serious	Serious[c]	None	⨁◯◯◯ Very low[a,b,c]	-	-	-	-	**MD 1.82 ALSFRS-R higher** (1.14 lower to 4.77 higher)
Serious Adverse Events at 6 months											
301 (3 RCTs)	Very serious[d]	Not serious	Not serious	Serious[c]	None	⨁◯◯◯ Very low[c,d]	25/137 (18.2%)	35/164 (21.3%)	**RR 1.15** (0.72 to 1.85)	23/137 (16.8%)	**27 more per 1,000** (from 51 fewer to 155 more)
All-cause mortality: at 6 months											
301 (3 RCTs)	Serious[a]	Serious[b]	Not serious	Serious[c]	None	⨁◯◯◯ Very low[a,b,c]	9/137 (6.6 %)	11/164 (6.7%)	**RR 1.20** (0.51 to 2.79)	9/137(6.6%)	**13 more per 1,000** (from 32 fewer to 118 more)
Change in Forced Vital Capacity at 4 months											
56 (1 RCT)	Not serious	Inevaluable[e]	Not serious	Very serious[f]	None	⨁◯◯◯ Very low[e,f]	-	-	-	-	**MD 0.53 lower** (5.37 lower to 4.31 higher)
Change in Slow Vital Capacity at 6 months											
189 (1 RCT)	Serious[g]	Inevaluable[e]	Not serious	Very serious[f]	None	⨁◯◯◯ Very low[e,f,g]	-	-	-	-	**MD 1.39 lower** (6.39 lower to 3.61 higher)

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

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. Downgraded two level for risk of bias as less than 2/3rd of studies (by wt.) were at low risk of bias.

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

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

g. The study had some concerns in the randomization process.

D. SUMMARY OF JUDGEMENTS:

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

Desirable Effects	Don't Know*
Undesirable Effects	Don't Know*
Certainty of evidence	Very low
Values	Probably no important uncertainty or variability
Balance of effects	Does not favor either the intervention or the comparison
Resources required	Large costs**
Certainty of evidence of required resources	Moderate
Cost effectiveness	Probably favors the comparison
Equity	Probably reduced
Acceptability	Probably yes
Feasibility	Probably yes
Recommendations: Stem Cell Therapy is **not recommended** in routine clinical practice for 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 **<u>recommended</u>** 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 ≥ 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 ≥ 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 **<u>not recommended</u>** 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.*

For RCTs using stem cells with less than minimal manipulation, approval from a registered Institutional Ethics Committee (IEC) is required before initiating the study and this therapy/procedure/product should demonstrate the type and number of stem cells administered. For RCTs involving stem cells that have undergone more than minimal manipulation, prior regulatory approval from the Central Drugs Standard Control Organization (CDSCO) is mandatory, in addition to IEC approval. The levels of manipulation for stem cell therapy have been defined by CDSCO (Annexure-1).

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 al[2] included patients with relapsing remitting multiple sclerosis (RRMS) only and the study by Mancardi et al[3] 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 provided below. **All these studies fall under the category of less than minimal manipulation**:

Author	Type of MS –no. of participants	Dose of stem cell	Source & type of Stem Cell	Route
Mancardi et. al. 2015[3]	SPMS-13/ RRMS-7/RPMS-1	3 and 8 x 106 $CD34^+$/kg cells	AHSC	iv
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 provided below. **All these studies fall under the category of more than minimal manipulation**:

Author	Type of MS- no. of participants	Dose of stem cell	Source & type of Stem Cell	Route
Liufriu et al. 2014[6]	RRMS-9	1.87x106 MSCs/Kg bwt	BM-MSCs	iv
Li et al. 2014[5]	RRMS-16 SPMS-7	4x106 cells/kg	human umbilical cord-MSCs	iv
Lublin et al. 2014[7]	RRMs-10/ SPMS- 6	low dose 150 x 106 cells high dose 600 x 106 cells PDA	human placenta- MSCs	iv
Fernandez et al. 2018[9]	SPMS-30(all)	low dose 1 x 106 cells/kg high dose 4 x 106 cells/kg	AdMSCs	iv
Ucelli et al. 2021[8]	RRMS-94/SPMS-33/PPMS-17	1-2x106 cells/kg bwt	BM MSCs	iv
Nabavi et al. 2023[4]	RRMS-14/ SPMS-5/ PPMS-2	2x106 cells/kg cell	BM MSCs	iv

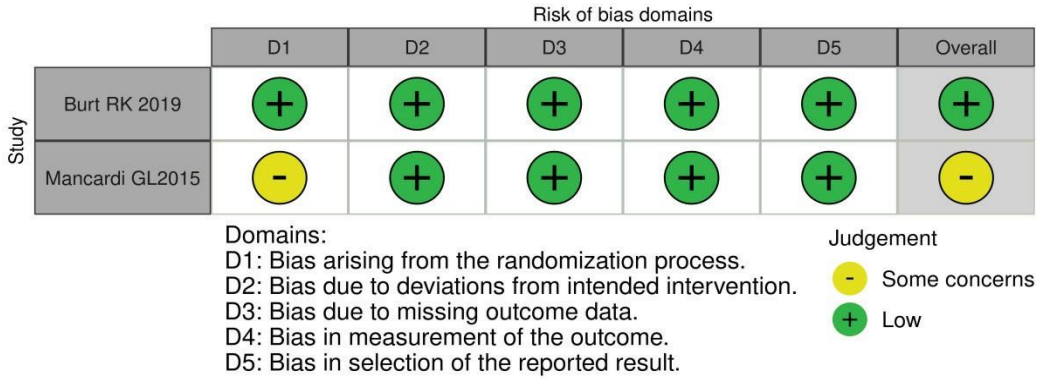
Critical outcomes reviewed and their MCID:

S. No.	Outcome reviewed	What does it measure?	MCID decided by the GDG
1.	The Expanded Disability Status Scale (EDSS) Range: 0-10 Higher score is worse	The Expanded Disability Status Scale (EDSS) is a method of quantifying disability in multiple sclerosis and monitoring changes in the level of disability over time. The EDSS scale ranges from 0 to 10 in 0.5 unit increments that represent higher levels of disability.	An absolute change in EDSS score by 0.5
2.	Annualized relapse rate (ARR)	ARR is computed as the total number of relapses in a given period divided by the total number of person-years in that period.	A difference of 0.6 for Annualized relapse rate (ARR)
3.	Proportion free of relapse	The proportion of patients who did not have a single relapse episode in a given period of time	A difference of 20/100 (20%)
4.	Serious adverse events	Mortality, non-hematopoietic grade 3 toxicities & grade 4 toxicities	-
5.	All-cause mortality	Total number of deaths in a population over a specific period of time	-
6.	Disease progression	Defined as an increase (worsening) in EDSS score of at least 1 point on 2 evaluations 6 months apart after at least 1 year of treatment, and not due to a non-MS disease process.	

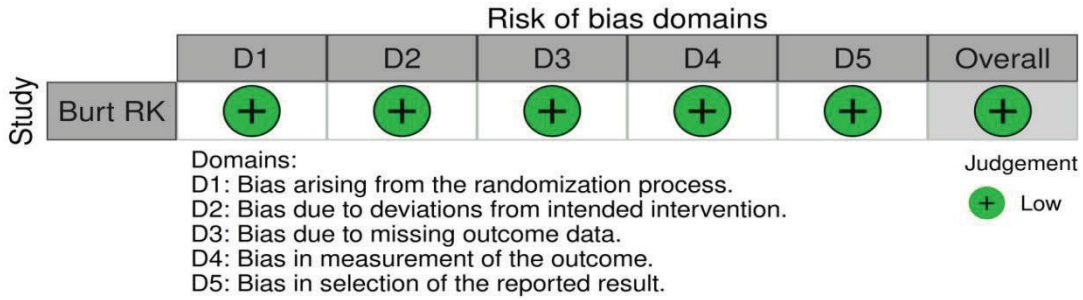
a. AUTOLOGOUS HEMATOPOIETIC STEM CELL TRANSPLANTATION (AHSCT)

Risk of Bias Assessment:

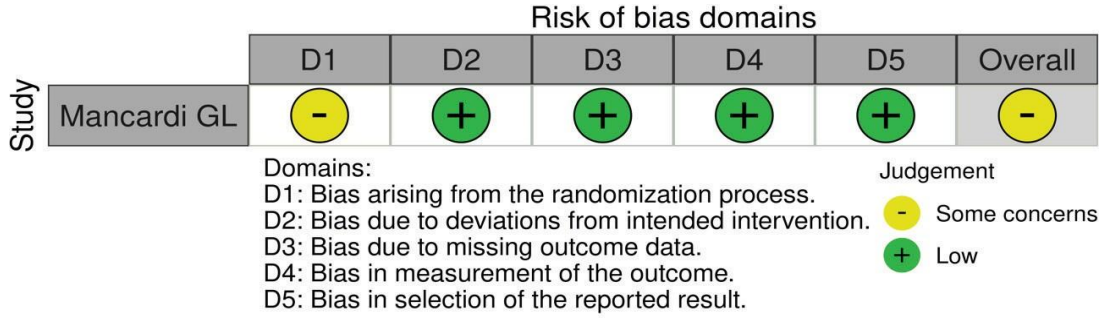
RoB -2 Disease progression and EDSS:



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



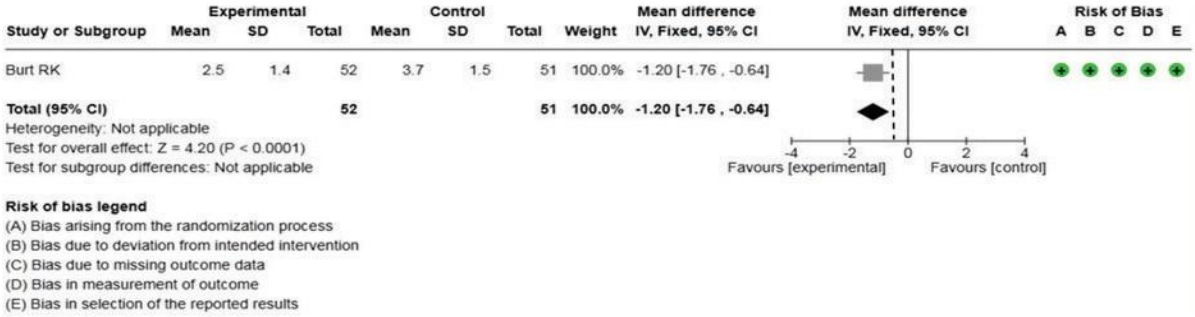
RoB -2 for outcome ARR between HSCT and usual care:



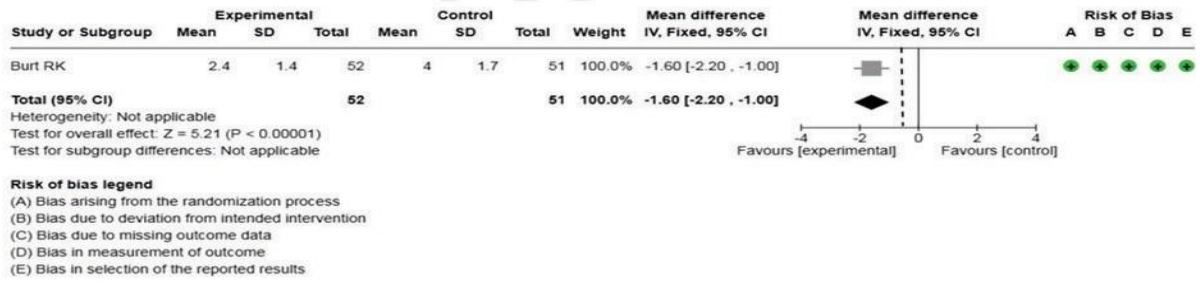
Desirable Effects (AHSCT):

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:

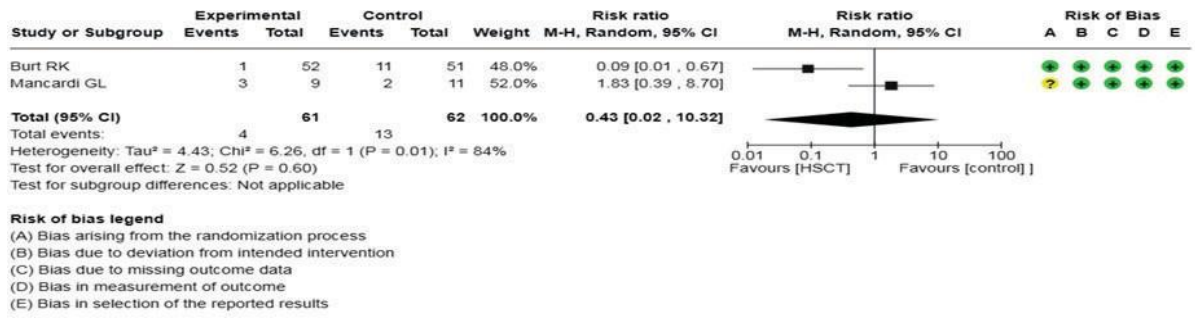


1.2 EDSS score at one year:



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.

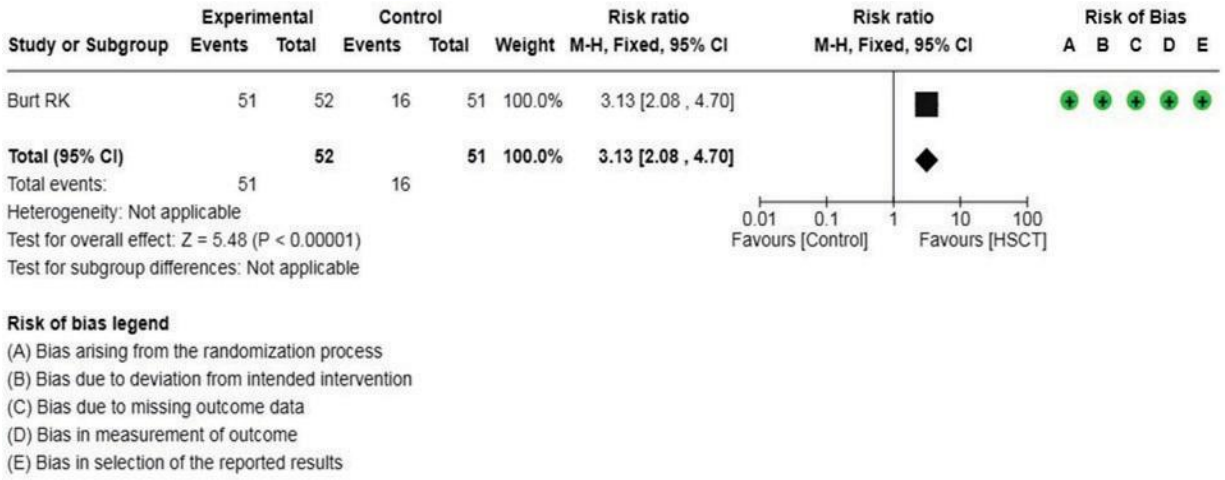
2.1 Disease progression measured by EDSS at one year:



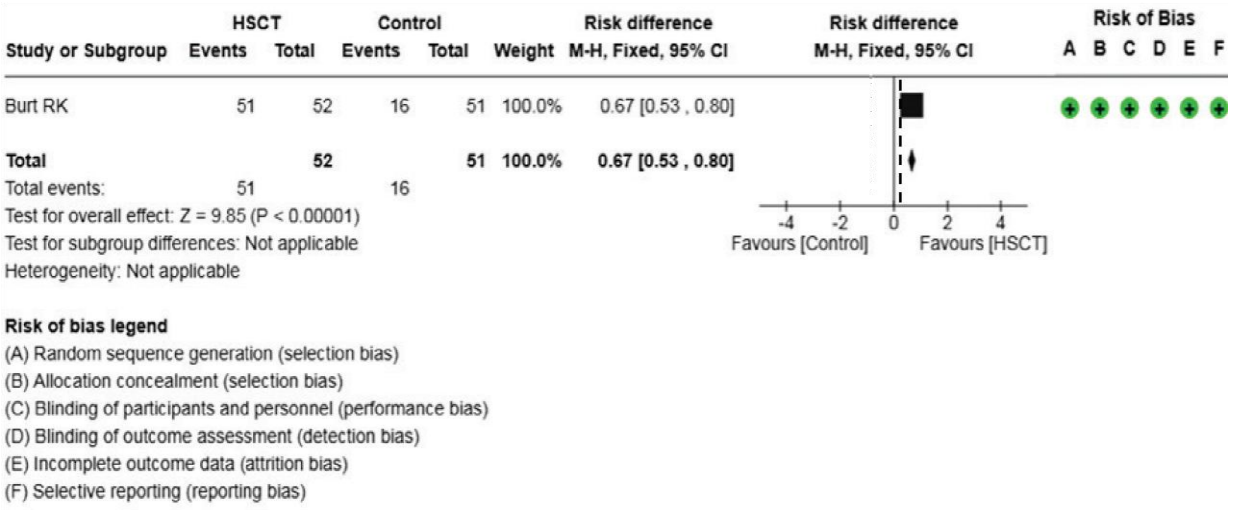
3. Proportion free from relapse: One trial with 103 participants reported that proportion of patients free of relapse at one year was higher in the HSCT group as compared to usual care with a risk ratio of 3.13 (95% CI: 2.08 to 4.70) and the results were statistically significant and important clinically.

3.1 Proportion free from relapse:

Risk Ratio

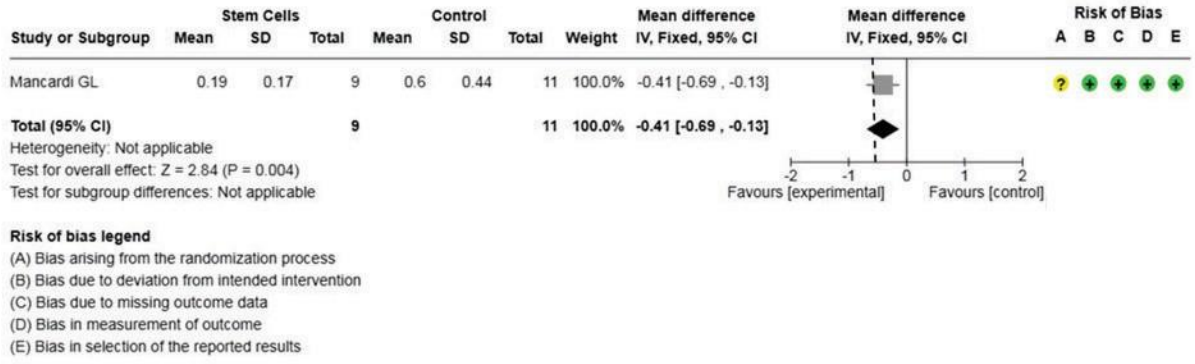


Risk Difference



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).

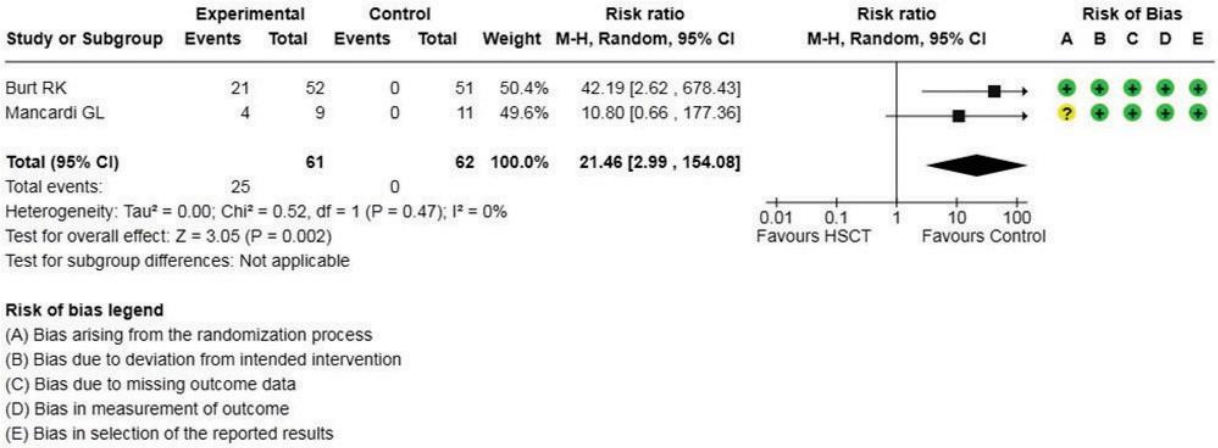
4.1 Annualized relapse rate:



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



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 al[2] 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
Comparison: Placebo/usual care

Outcomes	Anticipated absolute effects* (95% CI) Risk with placebo	Risk with HSCT	Relative effect (95% CI)	Q of participants (studies)	Certainty of the evidence (GRADE)	Comments
EDSS at six months	The mean EDSS in usual care arm was 3.7	**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	The mean EDSS in usual care arm was 4	**MD 1.6 lower** (2.2 lower to 1 lower)	-	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[c,d,e]	
Serious Adverse Event	0 per 1000	-	**RR 21.46** (2.99 to 154.08)	123 (2 RCTs)	⨁◯◯◯ Very low[c,e]	
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	The mean Annual relapse rate in usual care arm was 0.6	**MD 0.41 lower** (0.69 lower to 0.13 lower)	-	20 (1 RCT)	⨁◯◯◯ Very Low[a,b,f]	A change in Annual relapse rate by 0.6 was considered as MCID.

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

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

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
Comparison: Placebo/usual care

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Q of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with HSCT				

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

Explanations
a. Downgraded one level for inconsistency as it was inevaluable for single study.
b. Downgraded one level as OIS not met.
c. Downgraded one level for risk of bias as 1/3rd – 2/3rd of studies (by wt.) are at high risk of bias.
d. Highly inconsistent results on opposite side of line of no-effect.
e. The width of the confidence interval is too wide & OIS not met.
f. Downgraded one level for risk of bias as the study had some concerns in the randomization process.

GRADE EVIDENCE PROFILE:

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

Certainty assessment							Summary of findings				
							Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	With placebo	With HSCT		Risk with placebo	Risk difference with HSCT
EDSS at Six months											
103 (1 RCT)	Not serious	Inevaluable[a]	Not serious	Serious[b]	None	⨁⨁◯◯ Low[a,b]	-	-	-	The mean EDSS in usual care arm was 3.7	**MD 1.2 lower** (1.76 lower to 0.64 lower)
EDSS at One year											
103 (1 RCT)	Not serious	Inevaluable[a]	Not serious	Serious[b]	None	⨁⨁◯◯ Low[a,b]	-	-	-	The mean EDSS in usual care arm was 4	**MD 1.6 lower** (2.2 lower to 1 lower)
Disease Progression at one year											
123 (2 RCTs)	Serious[c]	Very serious[d]	Not serious	Very serious[e]	None	⨁◯◯◯ Very low[c,d,e]	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											
123 (2 RCTs)	Serious[c]	Not serious	Not serious	Very serious[e]	None	⨁◯◯◯ Very low[c,e]	0/62 (0.0%)	25/61 (41.0%)	**RR 21.46** (2.99 to 154.08)	0/62 (0.0%)	-
Proportion free from relapse at one year											
103 (1 RCT)	Not serious	Inevaluable[a]	Not serious	Serious[b]	None	⨁⨁◯◯ Low[a,b]	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)

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

Certainty assessment							Summary of findings				
Annual Relapse rate											
20 (1 RCT)	Serious[f]	Inevaluable[a]	Not serious	Serious[b]	None	⊕◯◯◯ Very Low[a,b,f]	-	-	-	The mean Annual relapse rate in usual care arm was 0.6	**MD 0.41 lower** (0.69 lower to 0.13 lower)

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

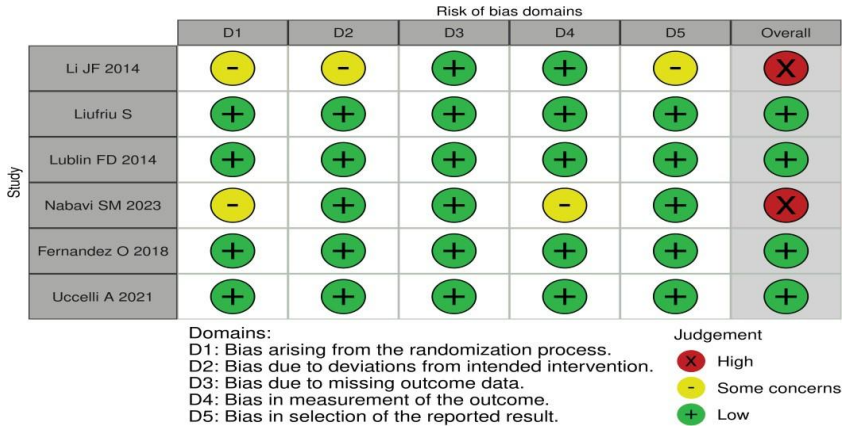
Explanations

a. Downgraded one level for inconsistency as it was inevaluable for single study.
b. Downgraded one level as OIS not met.
c. Downgraded one level for risk of bias as 1/3rd – 2/3rd of studies (by wt.) are at high risk of bias.
d. Highly inconsistent results on opposite side of line of no-effect.
e. The width of the confidence interval is too wide & OIS not met.
f. Downgraded one level for risk of bias as the study had some concerns in the randomization process.

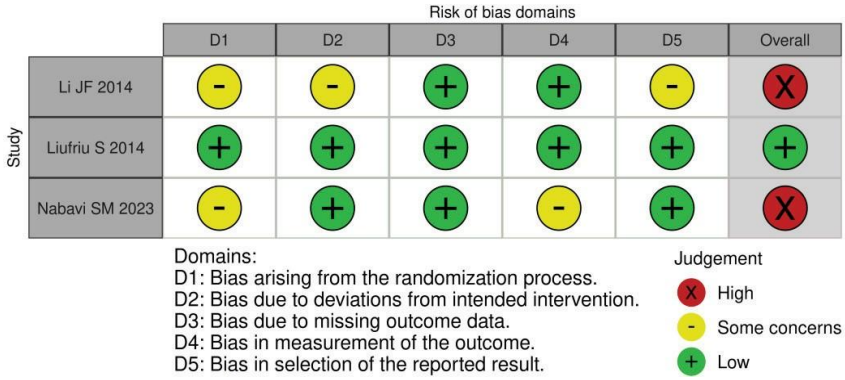
b. MESENCHYMAL STEM CELL THERAPY:

Risk of Bias assessment:

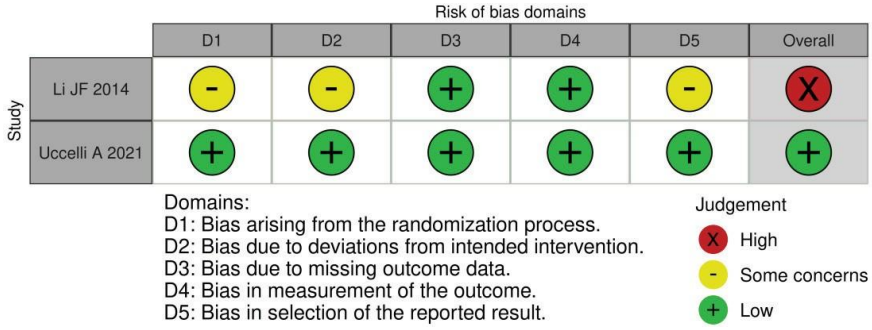
Risk of bias using RoB-2 tool for outcome EDSS of studies using Mesenchymal stem cells:



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



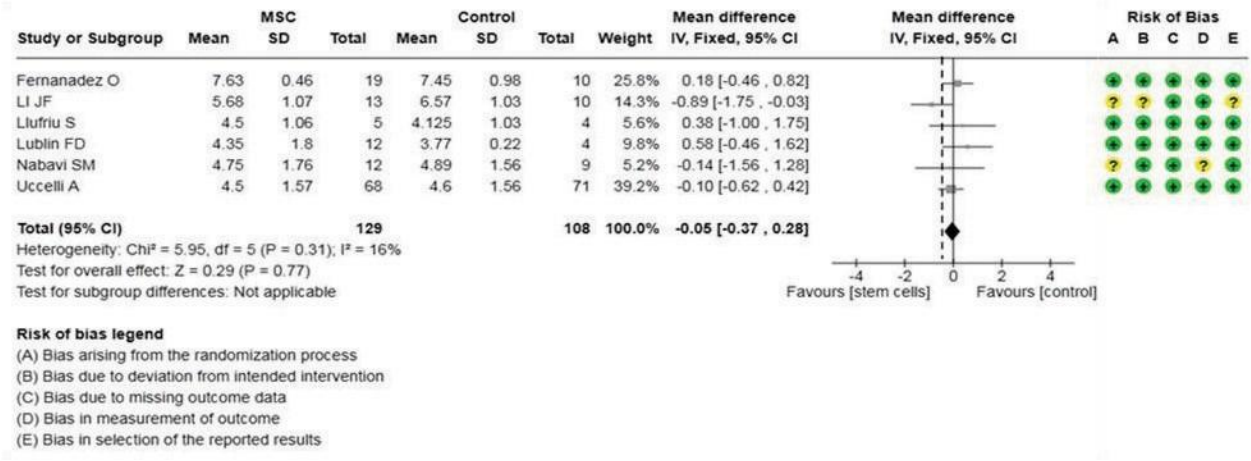
RoB-2 for annual relapse rate of studies using mesenchymal stem cells:



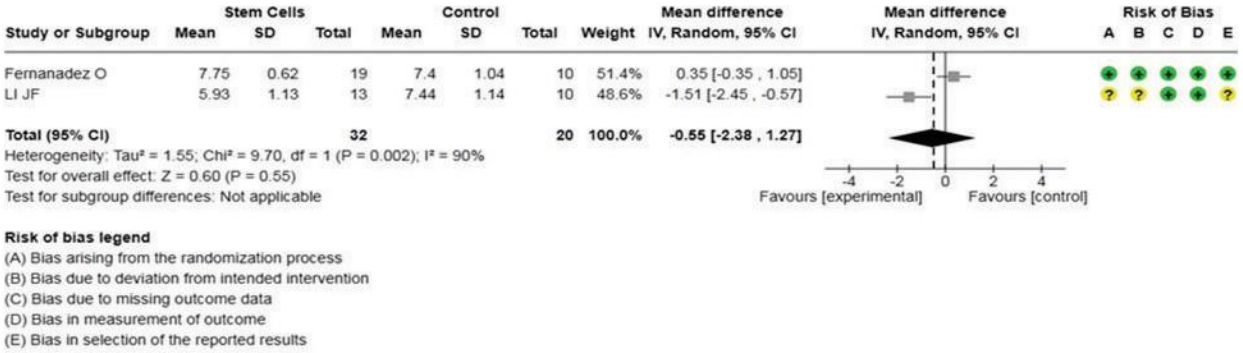
Desirable Effects (MSCs):

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:

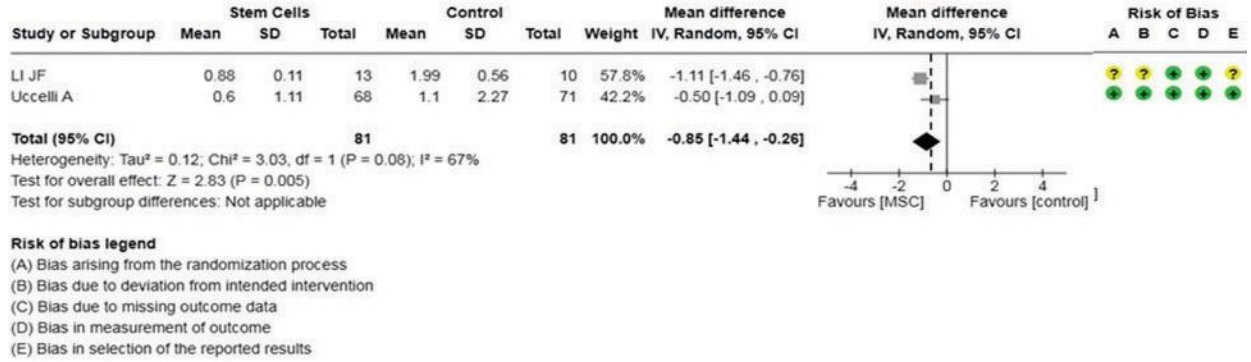


1.2 EDSS score at one year:



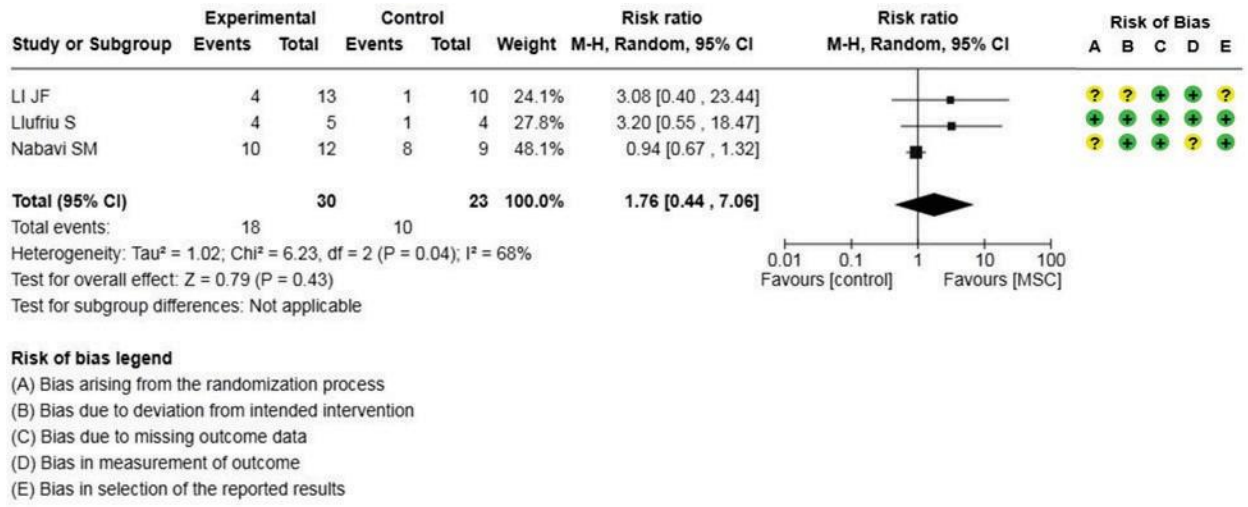
2. Annual relapse rate: Two trials with 162 participants reported annual relapse rate. The mean difference for annual relapse rate was -0.85 (95% CI: -1.44 to -0.26) in the MSC therapy arm as compared to the usual care. There seems to be a small clinically important reduction in average or annual relapse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

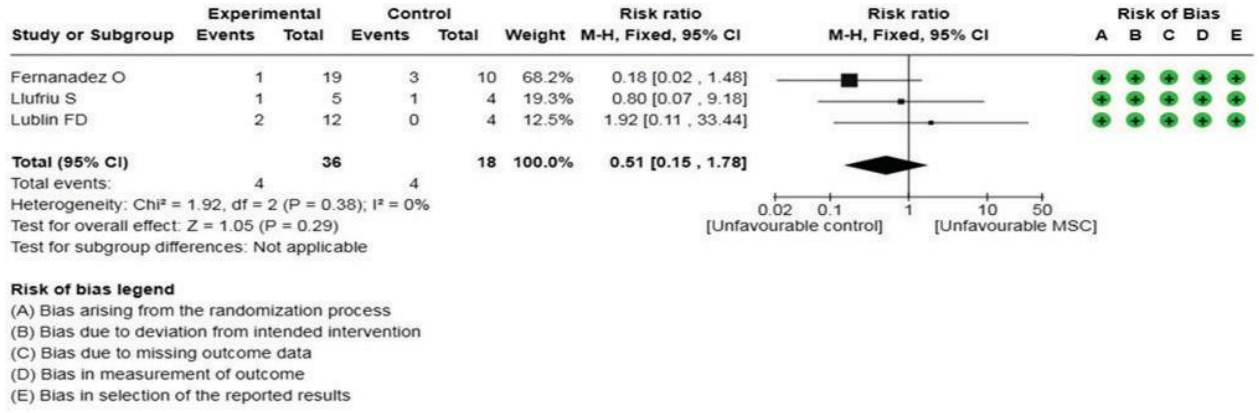
3.1 Proportion free from relapse at last follow-up:



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):



The type of serious adverse events reported by Lublin et al[7] in the above analysis were choking, respiratory infection, urinary infection, Grade I Anaphylactoid reaction and Grade 2 superficial thrombophelebitis.

Summary of Findings: GRADE

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

Outcomes	Anticipated absolute effects*(95% CI) 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)	The mean EDSS in usual care arm was 5.23 (range: 3.77 to 7.45)	**MD 0.05 lower** (0.37 lower to 0.28 higher)	-	(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)	The mean EDSS in usual care arm was 7.42 (range: 7.4 to 7.44)	**MD 0.55 lower** (2.38 lower to 1.27 higher)	-	52 (2 RCTs)	⊕◯◯◯ Very low[c,d,e]	
Annual relapse rate	The Annual relapse rate in usual care arm was 1.54 (range: 1.1 to 1.99)	**MD 0.85 lower** (1.44 lower to 0.26 lower)	-	162 (2 RCTs)	⊕◯◯◯ Very low[c,e,f]	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 1.76** (0.44 to 7.06)	53 (3 RCTs)	⊕◯◯◯ Very low[b,c,g]	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 0.51** (0.15 to 1.78)	54 (3 RCTs)	⊕⊕⊕◯ Moderate[b]	

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

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

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

Outcomes	Anticipated absolute effects*(95% CI)		Relative effect (95% CI)	Q of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	**Risk with Stem cell (MSC)**				

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low certainty: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations

a. Less than 1/3rd of studies by weight are at risk of bias
b. CI crossing the line of null effect, OIS not met
c. Downgraded one level for risk of bias as 1/3rd – 2/3rd of studies (by wt.) are at high risk of bias.
d. Downgraded one level for inconsistency as CI not overlapping
e. CI crossing the line of MCID, OIS not met
f. Downgraded one level for inconsistency as I^2- 67%
g. Overlapping confidence intervals, therefore no serious inconsistency

GRADE EVIDENCE PROFILE:

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

Certainty assessment							Summary of findings				
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With placebo	With Stem cell (MSC)		Risk with placebo	Risk difference with Stem cell (MSC)
EDSS at Six Months (EDSS 0-10, 0 good 10 worse)											
237 (6 RCTs)	Not serious[a]	Not serious	Not serious	Serious[b]	None	⊕⊕⊕◯ Moderate[a,b]	-	-	-	The mean EDSS usual care arm was 5.23 (range: 3.77 to 7.45)	**MD 0.05 lower** (0.37 lower to 0.28 higher)
EDSS at one year (EDSS 0-10, 0 good 10 worse)											
52 (2 RCTs)	Serious[c]	Serious[d]	Not serious	Serious[e]	None	⊕◯◯◯ Very low[c,d,e]	-	-	-	The mean EDSS in usual care arm was 7.42 (range: 7.4 to 7.44)	**MD 0.55 lower** (2.38 lower to 1.27 higher)
Annual relapse rate											
162 (2 RCTs)	Serious[c]	Serious[f]	Not serious	Serious[e]	None	⊕◯◯◯ Very low[c,e,f]	-	-	-	The annual relapse rate in usual care arm was 1.54 (range: 1.1 to 1.99)	**MD 0.85 lower** (1.44 lower to 0.26 lower)
Proportion free from relapse at last follow up											
53 (3 RCTs)	Very serious[c]	Not serious[g]	Not serious	Serious[b]	None	⊕◯◯◯ Very low[b,c,g]	10/23 (43.5%)	18/30 (60.0%)	**RR 1.76** (0.44 to 7.06)	10/23 (43.5%)	330 more per 1,000 (from 243 fewer to 1,000 more)
Serious Adverse Events											
54 (3 RCTs)	Not serious	Not serious	Not serious	Serious[b]	None	⊕⊕⊕◯ Moderate[b]	4/18 (22.2%)	4/36 (11.1%)	**RR 0.51** (0.15 to 1.78)	4/18 (22.2%)	109 fewer per 1,000 (from 189 fewer to 173 more)

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

Explanations

a. Less than 1/3rd of studies by weight are at risk of bias
b. CI crossing the line of null effect, OIS not met
c. Downgraded one level for risk of bias as 1/3rd – 2/3rd of studies (by wt.) are at high risk of bias.
d. Downgraded one level for inconsistency as CI not overlapping
e. CI crossing the line of MCID, OIS not met
f. Downgraded one level for inconsistency as I^2- 67%
g. Overlapping confidence intervals, therefore no serious inconsistency

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:

1. 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 Therapy 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 proof of concept studies and large multicenter RCTs with adequate long-term follow up to determine safety and efficacy. 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: Clarification on the 'stem cell derived products' as per directives under section 33P of the Drugs & Cosmetics Act, 1940 as defined under New Drugs and Clinical Trials Rules, 2019

It is clarified that "Stem cell derived product" means a drug which has been derived from processed stem cells and which has been processed by means of substantial or more than minimal manipulation with the objective of propagation and / or differentiation of a cell or tissue,' cell activation, and production of a cell-line, which includes pharmaceutical or chemical or enzymatic treatment, altering a biological characteristic, combining with a non-cellular component, manipulation by genetic engineering including gene editing & gene modification.

For the purpose of this clause:

I. Substantial or more than minimal manipulation means ex-vivo alteration in the cell population (T-Cell depletion, cancer cell depletion), expansion, which is expected to result in alteration of function.

II. The isolation of tissue, washing, centrifugation, suspension in acceptable medium, cutting, grinding, shaping, disintegration of tissue, separation of cells, isolation of a specific cell, treatment with antibiotics, sterilization by washing or gamma irradiation, freezing, thawing and such similar procedures, regarded as minimal manipulations and are not considered as processing by means of substantial or more than minimal manipulation.

III. Stem cells removed from an individual for implantation of such cells only into the same individual for use during the same surgical procedure should not undergo processing steps beyond rinsing, cleaning or sizing and these steps shall not be considered as processing.

Further, the cell-based products and tissue-based products which have been processed by means of substantial or more than minimal manipulation as per criteria mentioned above are also covered under the New Drugs and Clinical trials Rules, 2019.

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Annexure 3: 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

Dr. Anurag Aggarwal, Trivedi School of Biosciences, Ashoka University, Sonipat, Haryana	None declared	Not applicable
Dr. Alok Srivastava, Christian Medical College, Vellore	None declared	Not applicable
Dr. Sujata Mohanty, All India Institute of Medical Sciences, New Delhi	She declared that she is a member of the Subject Expert Committees of CDSCO & NMC.	The Steering Group did not see it as a potential CoI.
Dr. Maneesha Inamdar, Institute for Stem Cell Science and Regenerative Medicine, Bengaluru	None declared	Not applicable
Dr. Anupam Kumar, Institute of Liver and Biliary Sciences, New Delhi	None declared	Not applicable
Dr. Naresh K, Sree Chitra Tirunal Institute for Medical Sciences and Technology (SCTIMST), Kerala	None declared	Not applicable
Dr. M V Padma Srivastava, All India Institute of Medical Sciences, New Delhi	The member declared that she has received research support from DST with an interest related to the subject matter and is a member of the Committee of DGHS related to the subject matter.	The Steering Group did not see it as a potential CoI.
Dr. Jeyaraj D Pandian, Christian Medical College, Ludhiana	The member declared that he has received research support from ICMR within the past 4 years.	The Steering Group did not see it as a potential CoI.
Dr. Ajay Asrana, National Institute of Mental Health and Neurosciences, Bangalore	None declared	Not applicable
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Dr. Dhaval Shukla, Professor, Department of Neurosurgery, NIMHANS, Bangalore	None declared	Not applicable

CENTRE FOR EVIDENCE-BASED GUIDELINES

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