Evidence-based Guidelines for the use of Stem Cell Therapy

Pediatric Conditions

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DISCLAIMER

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

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

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ABBREVIATIONS

ABC	:	Adaptive Behaviour Composite
ASD	:	Autism Spectrum Disorder
AUCB	:	Autologous Umbilical Cord Blood
BMMSCs	:	Bone Marrow Mesenchymal Stem Cells
BPD	:	Bronchopulmonary Dysplasia
BSID- II	:	Bayley Scales of Infant and Toddler Development- II
CARS	:	Childhood Autism Rating Scale
CB	:	Cord Blood
CDCs	:	Cardio Sphere-Derived Cells
CFA	:	Comprehensive Functional Assessment
CGI	:	Clinical Global Impression
CI	:	Confidence Interval
CP	:	Cerebral Palsy
DMD	:	Duchenne Muscular Dystrophy
DoIs	:	Declaration of Interests
ECMO	:	Extra Corporeal Membrane Oxygenation
EMG	:	Electromyography
EtD	:	Evidence to Decision
FIM	:	Functional Independence Measure
GARS-II	:	Gilliam Autism Rating Scale-Second Edition
GDG	:	Guideline Development Group
GDT	:	Guideline Development Tool
GMFM	:	Gross Motor Function Measure
GMPM	:	Gross Motor Performance Measure
GRADE	:	Grading of Recommendations Assessment, Development and Evaluation system
GW	:	Gestational Weeks
HIE	:	Hypoxic-Ischaemic Encephalopathy
HINE	:	Hammersmith Infant Neurological Examination
HOPE	:	Halt Cardiomyopathy Progression
MA	:	Meta-Analysis
MAS	:	Modified Ashworth Scale
MCID	:	Minimal Clinically Important Difference
MD	:	Mean Difference
MeSH	:	Medical Subject Headings
MRI	:	Magnetic Resonance Imaging
MSCs	:	Mesenchymal Stem/Stromal Cells
NICE	:	National Institute for Care and Health Excellence
NIV	:	Non-Invasive Ventilation
OI	:	Osteogenesis Imperfecta
PANDA	:	Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal infection
PDD-NOS	:	Pervasive Developmental Disorder - Not Otherwise Specified
PEDI	:	Paediatric Evaluation of Disability Inventory
PICO	:	Population Intervention, Comparator and Outcome
PMA	:	Post Menstrual Age
PODCI	:	Paediatric Outcomes Data Collection Instrument
PRISMA	:	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PUL	:	Performance of Upper Limb

QoL	:	Quality of Life
RCT	:	Randomized Controlled Trial
ROB 2	:	Cochrane Risk-Of-Bias Tool For Randomized Trials Version 2
RRs	:	Risk Ratios
SAEs	:	Serious Adverse Events
SCT	:	Stem Cell Transplantation
SD	:	Standard Deviation
SEM	:	Standard Error of Mean
SMA	:	Spinal Muscular Atrophy
SMD	:	Standardized Mean Difference
SPADMSCs	:	Side Population Adipose-Derived Mesenchymal Stem Cells
SR	:	Systematic Review
TRC	:	Technical Resource Centre
VABS	:	Vineland Adaptive Behaviour and Socialization Subscales
VABS-3	:	Vineland Adaptive Behaviour Scale Third Edition
WHO	:	World Health Organization

EXECUTIVE SUMMARY

1. Background & Rationale:

Diseases of the newborn such as bronchopulmonary dysplasia, cerebral palsy, and hypoxic-ischemic encephalopathy continue to be major causes of infant mortality and long-term morbidity. In addition, neuromuscular disorders like autism spectrum disorder, spinal muscular atrophy and muscular dystrophy also constitute a significant disease burden in the pediatric population. Effective therapies for the prevention or treatment of these conditions are still lacking as recent clinical trials have shown modest or no benefit. Stem cell therapy is rapidly emerging as a novel therapeutic tool for several neonatal diseases that utilizes the unique properties of self-renewal and differentiation of stem cells, to regenerate or replace damaged cells and tissues. 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 & efficacy of such approaches. The overall goal of these guidelines is to provide evidence-based recommendations for the use of stem cell therapy in seven pediatric conditions namely autism spectrum disorder, cerebral palsy, muscular dystrophy, spinal muscular atrophy, bronchopulmonary dysplasia, hypoxic ischemic encephalopathy and osteogenesis imperfecta.

2. Target audience:

The recommendations in this guideline are intended to inform the policy makers, patients and health care professionals especially pediatricians 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 pediatric conditions.

3. Guideline Development Methods:

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

4. Summary of Recommendations:

S. No.	Key Question	Recommendation	Rationale/Justification
1.	In patients with autism spectrum disorder (ASD), 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 autism spectrum disorder. Strength: Conditional# Certainty of Evidence: Low *#It may be used only in the context of rigorously conducted randomized controlled trials.*	There is low certainty evidence of trivial improvement in the behavior and functional ability. There may be a small increase in undesirable effects with stem cell therapy.
2.	In patients with cerebral palsy (CP), 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 cerebral palsy. 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 improvement in functional ability. The undesirable effects are variable and heterogenous.
3.	In patients with muscular dystrophy (MD), 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 muscular dystrophy**. Strength: Conditional# Certainty of Evidence: Very Low *#It may be used only in the context of rigorously conducted clinical trials.*	There is very low certainty evidence of trivial improvement in muscle strength and functional ability of patients with muscular dystrophy. There is a small increase in undesirable effects with stem cell therapy.
4.	a) In preterm neonates at high risk of Bronchopulmonary Dysplasia (BPD), what is the safety and efficacy of stem cell therapy in prevention of BPD, as compared to usual care?	a) Stem Cell Therapy is **not recommended** in routine clinical practice for the prevention of BPD in high-risk preterm neonates. Strength: Conditional# Certainty of Evidence: Low *#It may be used only in the context rigorously conducted randomized controlled trials.*	a) The evidence is inadequate in quality and quantity to determine the safety and efficacy of stem cell therapy for the prevention of BPD in high-risk preterm neonates.
	b) In infants with moderate and severe Bronchopulmonary Dysplasia, what is the efficacy and safety of	b) Stem Cell Therapy is **not recommended** in routine clinical practice for the treatment of moderate and severe BPD. Strength: Conditional#	b) There is lack of evidence to determine the safety and efficacy of stem cell therapy in treatment of

	stem cell therapy as compared to usual care?	Certainty of Evidence: No included studies *#It may be used only in the context of rigorously conducted randomized controlled trials.*	infants with moderate and severe BPD.
5.	In patients with spinal muscular atrophy (SMA), 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 muscular atrophy. Strength: Conditional# Certainty of Evidence: Very low *#It may be used only in the context of rigorously conducted clinical trials.*	The evidence is inadequate in quantity and quality to determine the safety and efficacy of stem cell therapy in spinal muscular atrophy.
6.	In patients with hypoxic ischemic encephalopathy (HIE), 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 hypoxic ischemic encephalopathy. Strength: Conditional# Certainty of Evidence: No included studies *#It may be used only in the context of rigorously conducted randomized controlled trials.*	There is lack of evidence to determine the safety and efficacy of stem cell therapy for treatment of HIE.
7.	In patients with osteogenesis imperfect (OI), 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 osteogenesis imperfecta. Strength: Conditional# Certainty of Evidence: No included studies *#It may be used only in the context of rigorously conducted clinical trials.*	There is lack of evidence to determine the safety and efficacy of stem cell therapy in treatment of OI.

*This recommendation is not applicable to gene therapy.

** The evidence for this recommendation is derived from RCTs that included participants with Duchenne Muscular dystrophy only.

I. GUIDELINE DEVELOPMENT PROCESS

1. Introduction:

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

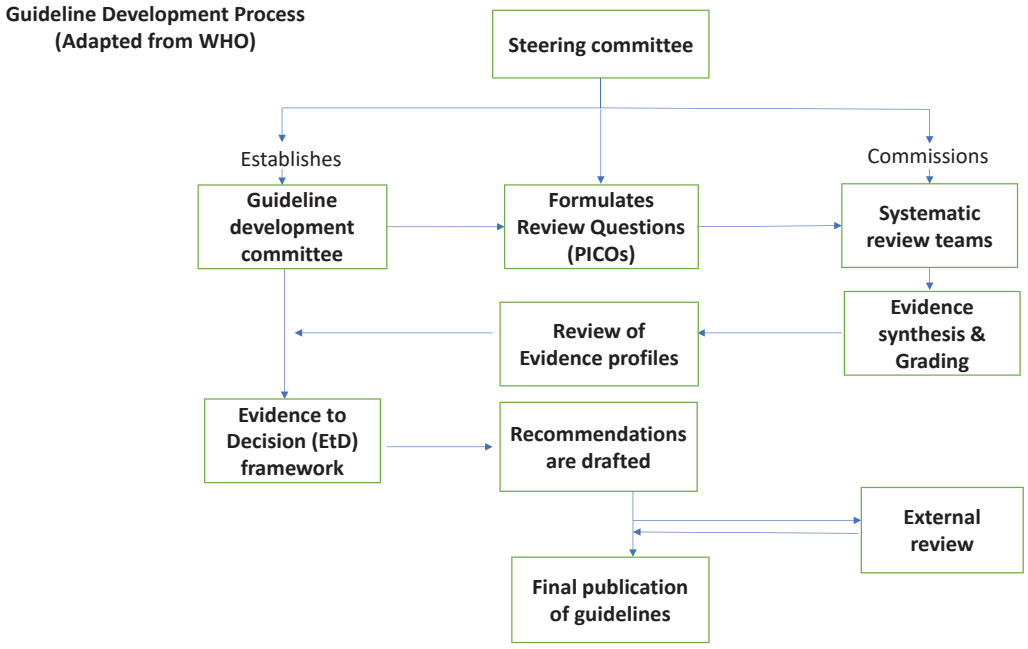

Figure 1: Guideline Development Process –adapted from WHO[1]

2. Rationale/ Scope:

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

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

The disease conditions included for review in the present guidelines are autism spectrum disorder, cerebral palsy, muscular dystrophy, spinal muscular atrophy, bronchopulmonary dysplasia, hypoxic ischemic encephalopathy and osteogenesis imperfecta. These were selected based on the directives from the MoHFW and a review of literature on the therapeutic use of stem cell therapy in pediatric 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 pediatricians 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 pediatric conditions.

4. Contributors:

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

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

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

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

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

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

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

5. Management of Conflict of interests:

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

All the potential GDG members were asked to fill up the Declaration of Interests (DoIs) form that was adapted from the WHO.[2] These declarations were then reviewed by the steering group and managed appropriately. A summary of the DOIs and how they were managed is provided in Annexure-2.

6. Defining the Scope and Key Questions:

The steering group held a meeting with the potential GDG members to identify the priority disease conditions on which the efficacy and safety of stem cell therapy need to be reviewed. A list of 10 broad disease groups was finalized including a total of 28 conditions. The group of pediatric conditions included seven diseases- autism spectrum disorder, cerebral palsy, muscular dystrophy, spinal muscular atrophy, bronchopulmonary dysplasia, hypoxic ischemic encephalopathy and osteogenesis imperfecta.

Thereafter, a meeting was held by the GDG to decide on the key review questions relevant for the selected diseases in the PICO format i.e. Population, Intervention, Comparator and Outcome. The outcomes that matter most to the concerned population were carefully selected and specified as critical outcomes for the guideline development. *These questions were formulated without keeping the*

literature in mind in order to obviate bias. Considering the scarcity of evidence for this experimental intervention, it was decided to keep the PICO question as broad as possible and do a subsequent subgroup analysis for relevant subgroups as needed. These PICO questions are available in the respective disease section.

7. Systematic Reviews 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. Out of a total of 130 applications received, 28 teams were selected to conduct SRs and MA. The criteria for evaluation included methodological expertise, subject expertise, quality of systematic reviews published, database access, strength of team and conflict of interests, if any. The systematic reviews were thus commissioned andall 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 to find relevant review articles was carried out. Non-English articles were excluded only if translation was not possible. Regarding 'Population', for any disease condition, all the grades of severity were included, and subgroup analyses (if mentioned apriori in the protocol) was done wherever needed. All interventions with well characterized stem cells or stem cell-derived products were included.

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

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

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

Data extraction methods: Data extraction was conducted by the systematic review teams and reviewed by the ICMR-DHR secretariat and the methodologists. The teams were advised to use plot digitizer wherever feasible, if values were not available in text. Imputations and assumptions were best to be avoided. All methodological queries were resolved with the help of guideline methodologists and the teams were also advised to refer to the *Cochrane Handbook for Systematic*

Reviews of Interventions to resolve any methodological queries.[3] While doing meta-analysis, the use of standardized mean difference (SMD) was to be minimized, as it is easier to compare mean difference (MD) with the minimal clinically important difference (MCID).

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

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

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

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

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

9. GRADing of the certainty of the evidence:

The GRADE approach was used to access the certainty of evidence using the GRADEpro GDT software (https://www.gradepro.org/). At baseline RCTs start with high certainty of evidence and this certainty can be downgraded based on pre-defined criteria like the risk of bias, inconsistency,

imprecision, indirectness, and publication bias. Publication bias was evaluated only if the number of studies for a particular meta-analysis were more than 10. If the studies were less than 10, it was considered inevaluable. The systematic review teams completed the reviews and shared the evidence profiles with the guideline secretariat. The secretariat then reviewed the evidence profiles with the help of guideline methodologists and any discrepancies in the review were resolved through discussion with the systematic review teams. The table below highlights the significance of the certainty of evidence as per GRADE.[4]

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

10. Drafting of Evidence to Decision frameworks:

The Guideline secretariat prepared the draft EtD 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 discussion 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 an agreement by 75% or more of the GDG members. Consensus was reached for all recommendations in this guideline and there were no strong disagreements. The GDG also identified caveats in the existing evidence and highlighted areas for future research.

12. Strength of Recommendations:

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

13. Document preparation and peer review:

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

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II. RECOMMENDATIONS

1. AUTISM SPECTRUM DISORDER

A. BACKGROUND:

Autism spectrum disorder (ASD) constitutes a diverse group of conditions manifesting with neurological disabilities impacting the communication abilities, and social behavior in children. The spectrum includes Childhood Autism or Autistic Disorder, Pervasive Developmental Disorder - Not Otherwise Specified (PDD-NOS), Atypical Autism and Asperger Syndrome. The exact etiology is not known and the disease is believed to be caused by an interplay of genetic, environmental, and epigenetic factors. Globally, the estimated prevalence is about 0.01%.[1] India also reports a high burden of this disorder with a slightly higher prevalence in rural areas (0.11%) compared to urban areas (0.09%).[2] Treatment and management remain a challenge due to the scarcity of approved pharmaceutical medications. Diverse treatments have been tried to improve the core symptoms such as bumetanide, buspirone, intranasal oxytocin, intranasal vasopressin, and prednisolone. Alternate treatment strategies are continually being explored.

B. RECOMMENDATIONS:

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

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

Rationale/Justification:
There is low certainty evidence of trivial improvement in the behavior and functional ability. There may be a small increase in undesirable effects with stem cell therapy. Results should be interpreted with caution, in view of various study limitations like high risk of bias, small number of participants and/or events in the included studies, different sources of stem cell as well as non-specific outcome measures and limited period of follow-up.

C. SUMMARY OF EVIDENCE:

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

Included Studies: A total of 5224 citations were identified (PubMed=1722, Embase=2337, Web of Science=1135, Cochrane Library=30). 1246 duplicate records were removed before the screening. A

total of 3978 articles were screened by their titles, followed by abstracts. 3946 articles were excluded based on the inclusion criteria of the review. On full text screening, 29 did not meet the eligibility criteria and were excluded. Thus, three studies were eligible for inclusion in this review. These three RCTs, one from Iran (Sharifzadeh et al. 2020)[3], and two from USA (Dawson et al. 2020 and Chez et al. 2018)[4,5], evaluated autologous bone marrow derived stem cells and Umbilical Cord Blood total nucleated cells as mentioned below:

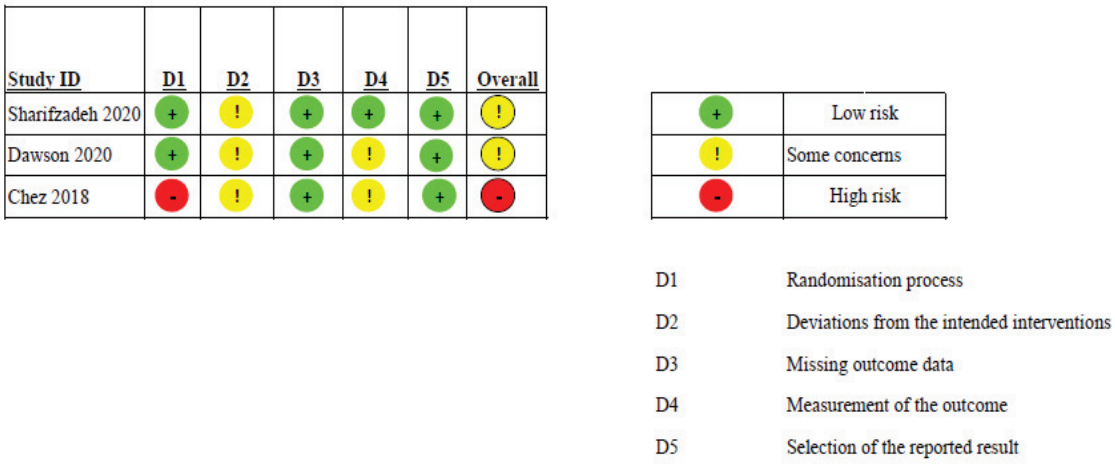
RCT	Intervention Group	Control group	Type of stem cell, Dose	Route of Administration
Sharifzadeh et al. (2020)[3]	Intrathecal bone marrow mesenchymal stem cells (BMMSCs)	Control group	BMMSC, first, 0.5-1 × 10^8 cells per 2 ml.	Intrathecal
Dawson et al. (2020)[4]	Autologous/allogenic umbilical cord blood (CB)	Placebo	CB, the number of therapeutic cells ≥2.5 × 10^7 cells/kg.	Intravenous
Chez et al. (2018)[5]	Autologous umbilical cord blood (AUCB)	Placebo	AUCB, exact dosage not mentioned.	Intravenous

Critical outcomes reviewed:

S. No.	Outcomes	What does it measure?
1.	Childhood Autism Rating Scale (CARS): Range: 15-60 Higher is worse	CARS is a 15-item scale where each item is scored on a scale ranging from one to four. Thus, the total score can range from 15 to 60. The scale evaluates various components of children's behavior in terms of communication, socialization, sensory sensitivities, and emotional responses. Scores of 30–36.5 suggest mild to moderate autism and 37–60 suggest severe autism.
2.	Gilliam Autism Rating Scale-Second Edition (GARS-II): Higher is worse	The GARS-2 is a 42-item scale with three subscales of stereotyped behaviors, communication, and social interaction, each including 14 items. Each component of the subscale is rated from 0 to 3, where lower score indicates less severity and a score of 3 represents greater behavioral changes and higher severity. The final score in GARS-II autism index determines the probability of autism in patients as follows: very likely (score of 85 or higher), possible (score of 70-84), and unlikely (score of 69 or lower).

3.	Clinical Global Impression (CGI): Higher is worse	CGI is a test that measures performance and behavior of patients over the past 7 days in various areas of life (work, home, school) and interpersonal relationships. It has two components of global improvement and severity of illness. • CGI-Severity is rated on seven-point scale (1-7) where 1 denotes no illness and increasing scores denote greater severity of illness. • CGI-Improvement score is assessed after initiation of the treatment and it is conducted to evaluate and compare the condition with the baseline condition. This scale is also rated on a seven-point scale where a lower score indicates marked improvement and higher score indicates worsening since the initiation of treatment.
4.	The Vineland Adaptive Behavior Scales, Third Edition (VABS-3): Higher is better	VABS is a caregiver interview measuring domains of adaptive functioning, socialization, communication, daily living skills and motor skills. The scores can be as low as 20 and as high as 130-140. Scores above 80 are classified using approximately the same ranges as IQ tests. Scores below 80 are categorized as borderline adaptive functioning (70–80); mildly deficient adaptive functioning (51–69); moderately deficient adaptive behavior (36–50); severely deficient adaptive behavior; (20– 35); and markedly or profoundly deficient adaptive behavior (<20).
5.	SAEs	Serious adverse events

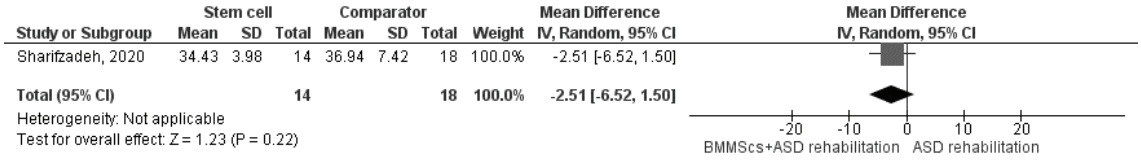
Risk of Bias Assessment:



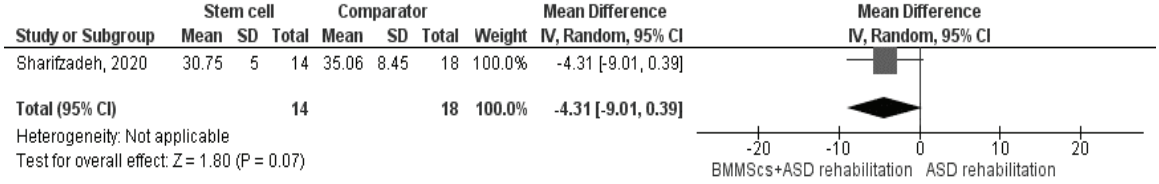
Desirable Effects:

1. **CARS Total scores:** Evidence from one trial, with a total of 32 participants reporting the CARS total score showed a mean difference of -2.51 (95% CI: -6.52 to 1.50) in the stem cell transplantation arm as compared to usual care at the end of 6 months and -4.31 (95% CI: -9.01 to 0.39) at the end of 12 months. The differences were statistically non-significant at both time points.

CARS Total scores at 6 months:

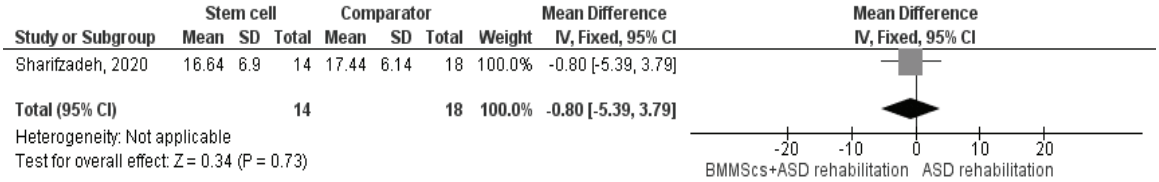


CARS Total scores at 12 months:

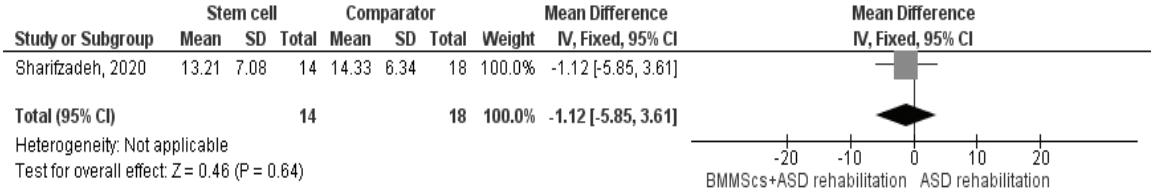


2. **GARS-II Total scores:** Evidence from one trial, with a total of 32 participants reporting the GARS-II total score showed a mean difference of -0.80 (95% CI: -5.39 to 3.79) in the stem cell transplantation arm as compared to usual care at the end of 6 months and -1.12 (95% CI: -5.85 to 3.61) at the end of 12 months. The differences were statistically non-significant at both time points.

GARS-II Total scores at 6 months:



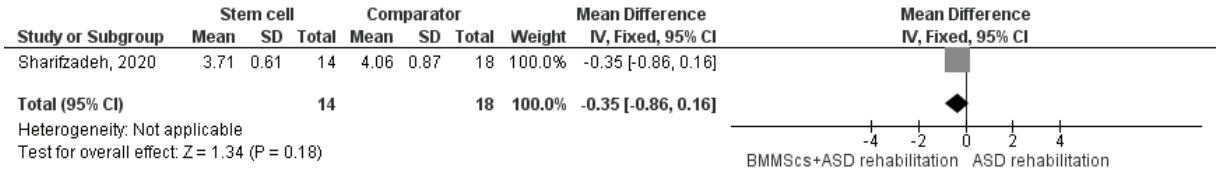
GARS-II Total scores at12 months:



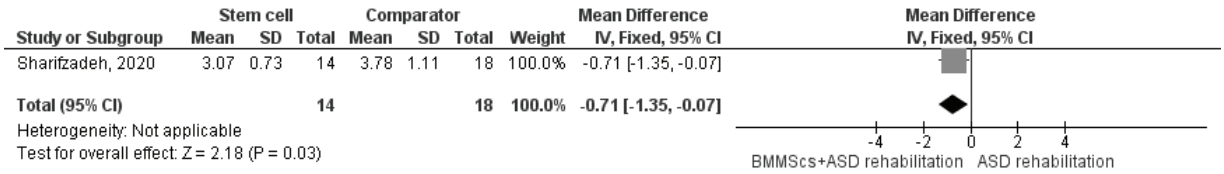
3. Clinical Global Impression:

3.1 CGI Severity of illness scores: Evidence from one trial, with a total of 32 participants reporting the CGI-severity of illness showed a mean difference of -0.35 (95% CI: -0.86 to 0.16) in the stem cell transplantation arm as compared to usual care at the end of 6 months. The difference was statistically non-significant at 6 months. The mean difference was -0.71 (95% CI: -1.35 to -0.07) at the end of 12 months. The difference was statistically significant at 12 months.

CGI Severity of illness scores at 6 months:

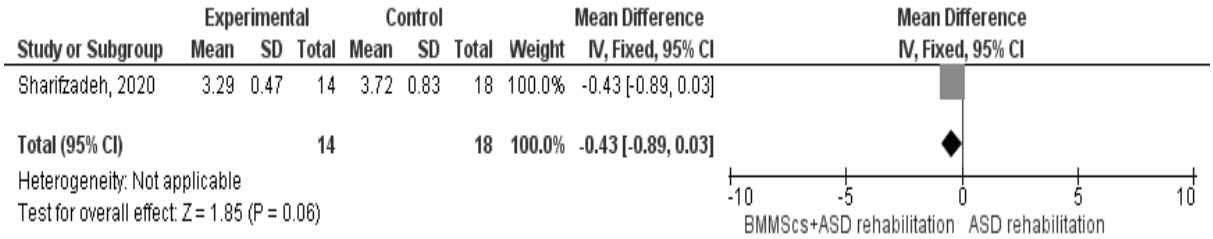


CGI Severity of illness scores at 12 months:

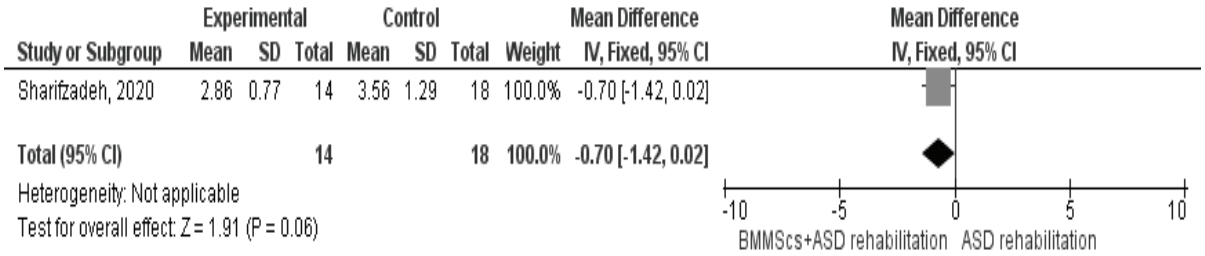


3.2 CGI Global improvement scores: Evidence from one trial, with a total of 32 participants reporting the CGI-global improvement scores showed a mean difference of -0.43 (95% CI: -0.89 to 0.03) in the stem cell transplantation arm as compared to usual care at the end of 6 months and -0.70 (95% CI: -1.42 to0.02) at the end of 12 months. The differences were statistically non-significant at both time points.

CGI Global improvement scores at 6 months:

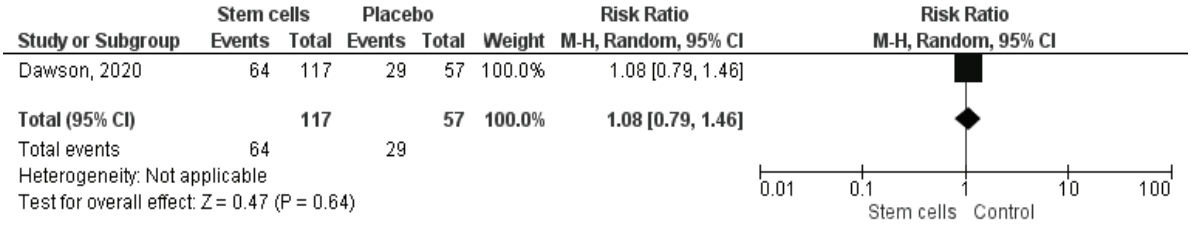


CGI Global improvement scores at 12 months:



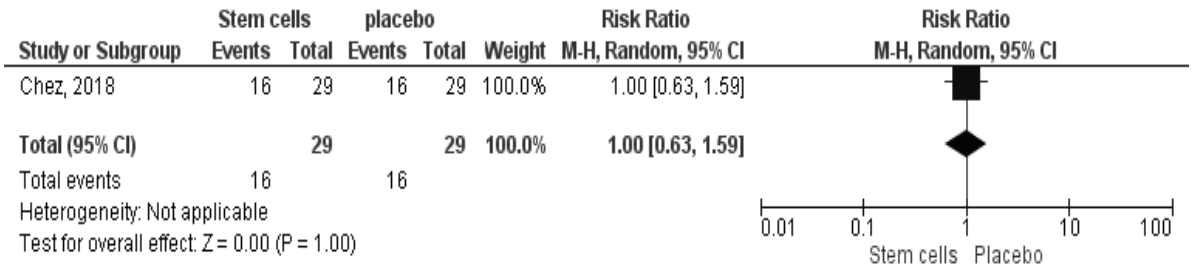
3.3 Number with improvement in CGI scores at 6 months: Evidence from one trial, with a total of 174 participants reporting the number of participants with improvement in CGI scores showed a risk ratio of 1.08 (95% CI: 0.79 to 1.46) in the stem cell transplantation arm in comparison to usual care at the end of 6 months. The ratio is statistically non-significant.

Number with improvement in CGI scores at 6 months:

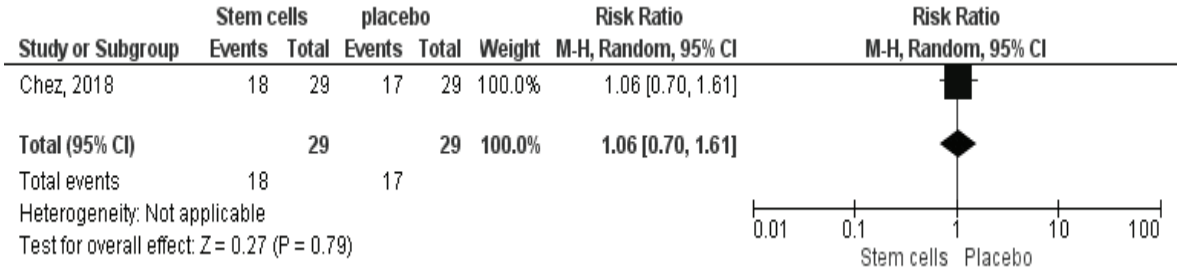


3.4 Number with improvement in CGI scores (Sub scales) at 6 months: Evidence from one trial, with a total of 58 participants reporting the number of participants with improvement in CGI scores in the expressive domain showed a risk ratio of 1.00 (95% CI: 0.63 to 1.59) in the stem cell transplantation arm in comparison to usual care at the end of 6 months. The risk ratio was 1.06 (95% CI: 0.70 to 1.61) for improvement in CGI scores in the receptive domain and 1.13 (95% CI: 0.73 to 1.74) in the social domain. All the ratios are statistically non-significant.

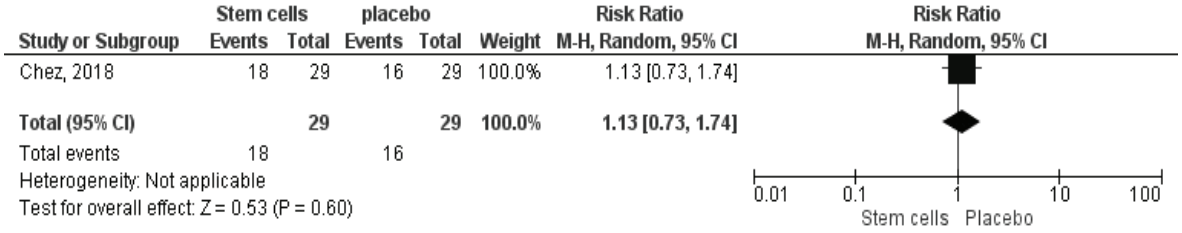
3.4.1 Expressive:



3.4.2 Receptive:



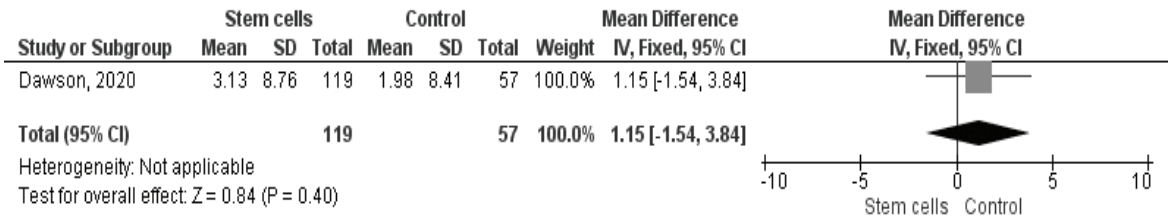
3.4.3 Social:



4. Vineland scores:

4.1 Mean change in Vineland scores VABS-3 (subscale) at 6-months: Evidence from one trial, with a total of 176 participants reporting the mean change in Vineland scores showed a mean difference of 1.15 (95% CI: -1.54 to 3.84) in the stem cell transplantation arm as compared to usual care at the end of 6 months. The differences were statistically non-significant.

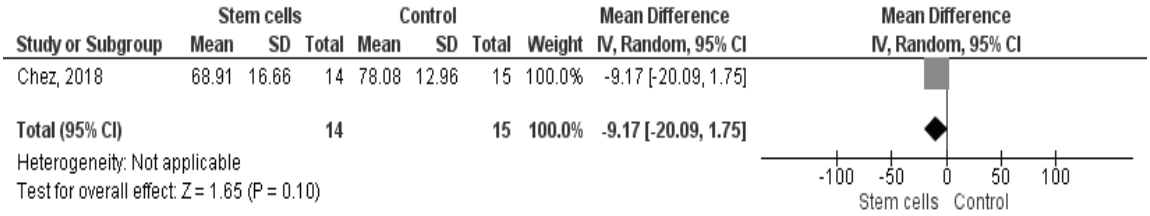
Vineland scores VABS-3 (subscale) at 6-months:



4.2 Vineland Adaptive Behavior Scale for Socialization: Evidence from one trial, with a total of 29 participants reporting the score of Vineland Adaptive Behavior Scale for Socialization showed a mean difference of -9.17 (95% CI: -20.09 to 1.75) in the stem cell transplantation

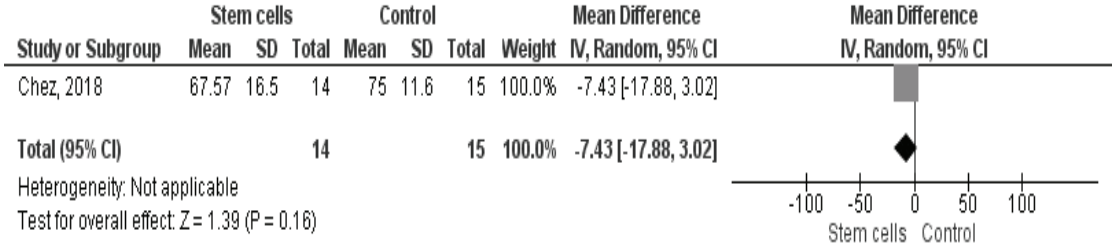
arm as compared to usual care at the end of 6 months. The differences were statistically non-significant.

Vineland Adaptive Behavior Scale for Socialization at 6 months:

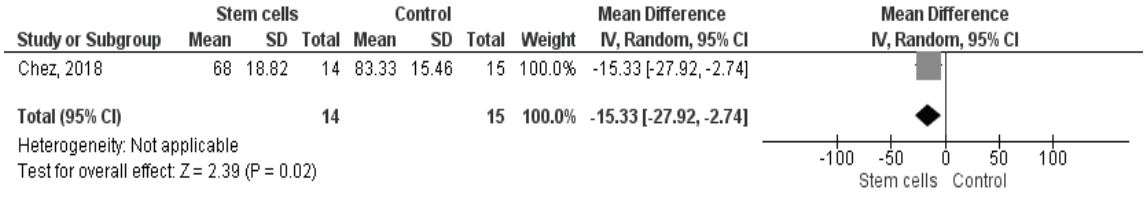


4.3 Vineland subscales:

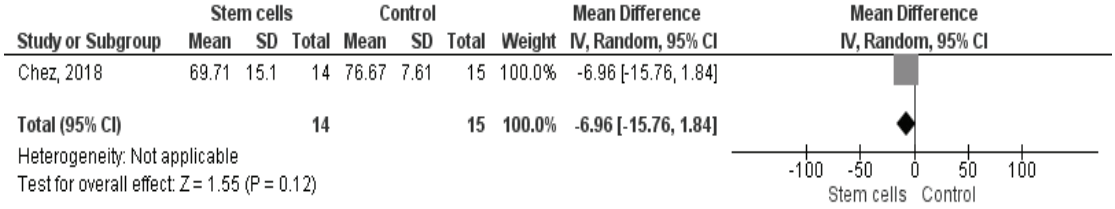
4.3.1 Adaptive Behavior Composite (ABC): Evidence from one trial, with a total of 29 participants reporting the ABC score showed a mean difference of -7.43 (95% CI: -17.88 to 3.02) in the stem cell transplantation arm as compared to usual care at the end of 6 months. The difference was statistically non-significant.



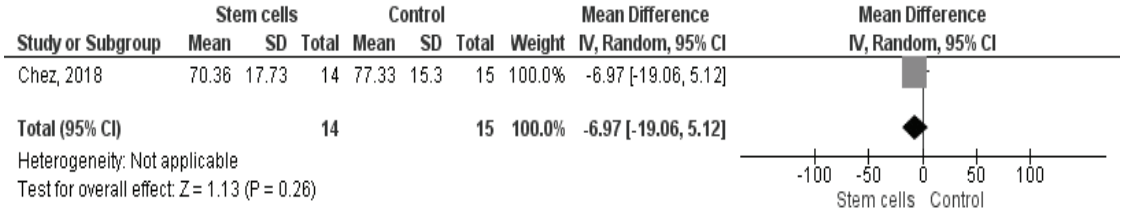
4.3.2 Communication score: Evidence from one trial, with a total of 29 participants reporting the communication score showed a mean difference of -15.33 (95% CI: -27.92 to -2.74) in the stem cell transplantation arm as compared to usual care at the end of 6 months. The difference was statistically significant.



4.3.3 Motor score: Evidence from one trial, with a total of 29 participants reporting the motor score showed a mean difference of -6.96 (95% CI: -15.76 to 1.84) in the stem cell transplantation arm as compared to usual care at the end of 6 months. The difference was statistically non-significant.



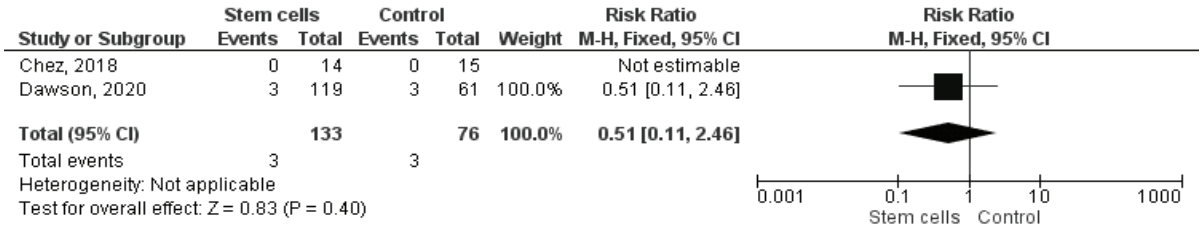
4.3.4 Daily activities score: Evidence from one trial, with a total of 29 participants reporting the daily activities score showed a mean difference of -6.97 (95% CI: -19.06 to 5.12) in the stem cell transplantation arm as compared to usual care at the end of 6 months. The difference was statistically non-significant.



Undesirable effects:

5. **Serious Adverse Events (SAEs):** Sharifzadeh et al[3] 2020 reported that none of the participants in their trial had any of the side effects they looked for viz. injection related effects, hospital complications, short-term or long-term complications within 12 months of stem cell therapy. Dawson et al[4] 2020 reported the frequency of SAEs in both the groups; 3/119 (2.5%) participants in the cord blood group experienced moderate SAEs while 3/61 (4.9%) in the control group experienced SAEs. There were 6 SAEs reported in 6 unique participants, including 3 in the placebo arm (viral gastroenteritis, dehydration, and aggression), 1 in the autologous CB cohort (concussion), and 2 in the allogenic CB cohort (pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection [PANDAS] and dehydration). Chez et al[5] 2018 reported no serious adverse events in either group. The pooled risk ratio (RR) was 0.51 (95% CI: 0.11 to 2.46), which was statistically non-significant.

Serious adverse events at 12 months:



Summary of findings: GRADE

Stem cell therapy as compared to usual care for autism spectrum disorder (ASD)

Patient or population: Children with ASD
Setting: Tertiary care/Hospital
Intervention: Stem cell therapy
Comparison: Usual care

Outcomes	Anticipated absolute effects*(95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with standard therapy	**Risk with Stem cell therapy**				
Efficacy: CARS total scores at 12 months	-	MD **4.31 lower** (9.01 lower to 0.39 higher)	-	32 (1 RCT)	⊕⊕◯◯ Low[a,b]	
Safety: Serious adverse events at 12 months	39 per 1,000	**20 per 1,000** (4 to 95)	RR 0.51 (95% CI: 0.11 to 2.46)	209 (2 RCTs)	⊕◯◯◯ Very low[b,c,d]	
GARS-II total score at 12 months	-	MD **1.12 lower** (5.85 lower to 3.61 higher)	-	32 (1 RCT)	⊕⊕◯◯ Low[a,b]	
CGI severity at 12 months	-	MD **0.71 lower** (1.35 lower to 0.07 lower)	-	32 (1 RCT)	⊕⊕◯◯ Low[a,b]	
CGI Global Improvement at 12 months	-	MD **0.7 lower** (1.42 lower to 0.02 higher)	-	32 (1 RCT)	⊕⊕◯◯ Low[a,b]	

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

CI: confidence interval; **MD:** mean difference; R**R:** 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 due to single study
b. Downgraded due to wide confidence intervals of the effect estimates.
c. Downgraded due to high risk of bias in one study due to inadequate randomization and lack of blinding of staff personnel, outcome assessors. Other two studies had some concerns due to lack of blinding of participants in one study while no information on blinding of staff personnel and outcome assessors.
d. Downgraded due to variation in the effect estimates.

Evidence Profile:
Stem cell therapy as compared to usual care

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 standard therapy	With Stem cell therapy	Relative effect (95% CI)	Risk with standard therapy	Risk difference with Stem cell therapy
Efficacy: CARS total scores at 12 months											
32 (1 RCT)	not serious	inevaluable[a]	not serious	serious[b]	None	⊕⊕◯◯ Low[a,b]	-	-	-	-	MD **4.31 lower** (9.01 lower to 0.39 higher)
Safety: Serious adverse events at 12 months											
209 (2 RCTs)	serious[c]	serious[d]	not serious	serious[b]	None	⊕◯◯◯ Very low[b,c,d]	3/76 (3.9%)	3/133 (2.3%)	**RR 0.51** 95% CI: 0.11 to 2.46	3/76 (3.9%)	**19 fewer per 1,000** (from 35 fewer to 55 more)
GARS-II total score at 12 months											
32 (1 RCT)	not serious	inevaluable[a]	not serious	serious[b]	None	⊕⊕◯◯ Low[a,b]	-	-	-	-	MD **1.12 lower** (5.85 lower to 3.61 higher)
CGI severity at 12 months											
32 (1 RCT)	not serious	inevaluable[a]	not serious	serious[b]	None	⊕⊕◯◯ Low[a,b]	-	-	-	-	MD **0.71 lower** (1.35 lower to 0.07 lower)
CGI Global Improvement at 12 months											
32 (1 RCT)	not serious	inevaluable[a]	not serious	serious[b]	None	⊕⊕◯◯ Low[a,b]	-	-	-	-	MD **0.7 lower** (1.42 lower to 0.02 higher)

CI: confidence interval; **MD:** mean difference; **RR: Risk Ratio**

Explanations
a. Downgraded due to single study
b. Downgraded due to wide confidence intervals of the effect estimates.
c. Downgraded due to high risk of bias in one study due to inadequate randomization and lack of blinding of staff personnel, outcome assessors. Other two studies had some concerns due to lack of blinding of participants in one study while no information on blinding of staff personnel and outcome assessors.
d. Downgraded due to variation in the effect estimates.

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

***** This judgment was made as there is low certainty evidence of trivial improvement in the behavior and functional ability.

** This judgment was made as there may be a small increase in undesirable effects with stem cell therapy.

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

E. CAVEATS IN EXISTING EVIDENCE:

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

- Lack of sufficient number of RCTs with low risk of bias
- Small number of participants and events in the included trials
- Heterogeneity across trials in patient population and type of stem cell therapy, cell dosage, route of administration and time of administration
- Use of different diagnostic and evaluation tools by studies
- Lack of long term follow up of participants thus providing insufficient evidence on the safety of this experimental therapy
- Lack of cost effectiveness data

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1. Zeidan J, Fombonne E, Scorah J, Ibrahim A, Durkin MS, Saxena S, et al. Global prevalence of autism: A systematic review update. 2022;15(5):778-90.
2. Chauhan A, Sahu JK, Jaiswal N, Kumar K, Agarwal A, Kaur J, et al. Prevalence of autism spectrum disorder in Indian children: A systematic review and meta-analysis. Neurology India. 2019;67(1):100-4.
3. Sharifzadeh N, Ghasemi A, Tavakol Afshari J, Moharari F, Soltanifar A, Talaei A, et al. Intrathecal autologous bone marrow stem cell therapy in children with autism: A randomized controlled trial. 2021;13(2):e12445.
4. Dawson G, Sun JM, Baker J, Carpenter K, Compton S, Deaver M, et al. A Phase II Randomized Clinical Trial of the Safety and Efficacy of Intravenous Umbilical Cord Blood Infusion for Treatment of Children with Autism Spectrum Disorder. The Journal of pediatrics. 2020;222:164-73.e5.
5. Chez M, Lepage C, Parise C. Safety and Observations from a Placebo-Controlled, Crossover Study to Assess Use of Autologous Umbilical Cord Blood Stem Cells to Improve Symptoms in Children with Autism. 2018;7(4):333-41.

2. CEREBRAL PALSY

A. BACKGROUND:

Cerebral palsy (CP) is defined as a group of permanent disorders that affect movement and posture; causes limitation in activity, and are attributed to non-progressive insults to the developing fetal or infant brain. The motor impairment of cerebral palsy is often accompanied by disturbances of sensation, perception, intellectual disability, communication, behavior, by epilepsy and by secondary musculoskeletal problems. Globally, cerebral palsy is one of the most common causes of motor disability in childhood. The study by Chauhan et al (2019) derived an overall pooled prevalence of cerebral palsy per 1000 children to be 2.95 (95%CI 2.03–3.88).[1]

B. RECOMMENDATIONS:

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

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

Rationale/Justification:
There is very low certainty evidence of trivial improvement in functional ability. The undesirable effects are variable and heterogenous. 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 cerebral palsy, what is the efficacy and safety of stem cell therapy as compared to usual care?

Included Studies: During the identification phase, a comprehensive search across multiple databases yielded a total of 3,822 records. These included 1,609 records from PubMed, 1,030 from Embase, 384 from Web of Science, and 799 from the Cochrane Central database. After duplicates were removed, 1,257 unique records were retained for screening. During the screening phase, titles and abstracts of these records were reviewed, resulting in the exclusion of 1,235 studies that were irrelevant to the PICO. This left 22 full-text articles to be assessed for eligibility. In the eligibility phase, 9 of these articles were excluded due to issues such as being uncontrolled trials or having incomplete data. Out of the remaining 13 RCTs[2-14], 9 trials met the 'reliable body of evidence' criteria, as specified by the GDG and were used for synthesizing evidence.

Research studies were conducted in Iran, USA, China, and South Korea. Specifically, four studies were from Iran and USA, five were from China, and four were from South Korea. The sample sizes of the studies varied from 36 to 105 participants, with publication year ranging from 2012 to 2023. The primary routes of stem cell administration were intravenous infusion and intrathecal injection, with doses ranging from 4×10^6 to 5.2×10^8/kg. Most studies involved children ≤5 years of age. The type of stem cells included were umbilical cord derived stem cells, bone marrow or peripheral blood stem cells and neural progenitor cells. The trials published by Amanat et al[6] and Zarrabi et al[13] were probably part of a single three arm trial as both these trials have the same clinical trial registration number (ClinicalTrials.gov; NCT03795974) and control data raising suspicion about salami slicing.

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

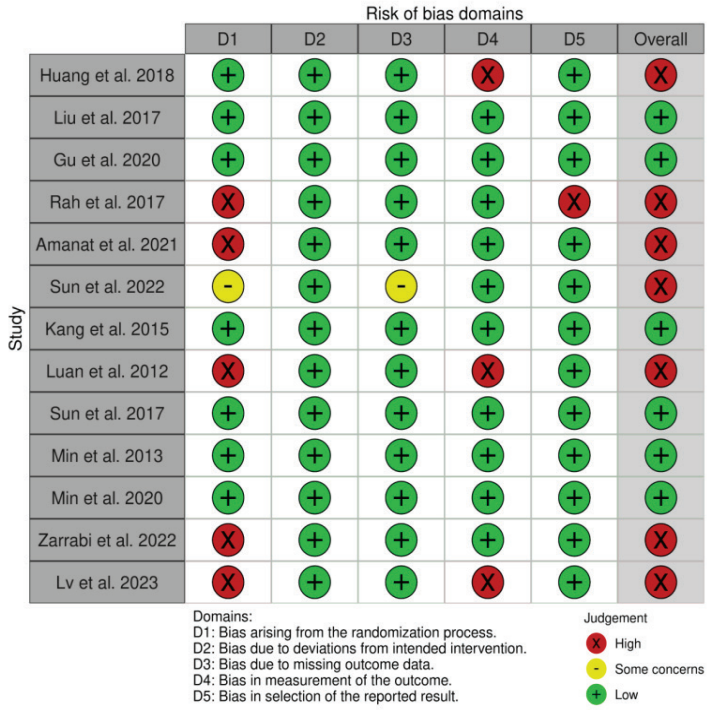
S. No.	Author	Issue
1.	Liu et al. (2017)[8]	The data appears unrealistic. The score ranges from 0-100 while the trial provides values of more than 100, which is biologically not plausible.
2.	Gu et al. (2020)[4]	Data for efficacy outcome differs in the text and table, hence not included in the analysis.
3.	Rah et al. (2017)[5]	This was a crossover study. Outcome measures were not assessed separately before crossover. Baseline characteristics were not given
4.	Luan et al. (2012)[3]	Data not available

Critical Outcomes reviewed:

S. No.	Outcomes	What does it measure
1.	Gross Motor Function Measure (GMFM): 0-100 Higher is better	Tool to assess motor function in children with CP. There are two versions of the GMFM commonly used: GMFM-66 and GMFM-88. The GMFM-66 is the original version of the measure and assesses 66 motor skills across five dimensions: lying and rolling, sitting, crawling and kneeling, standing and walking, running, and jumping. Each skill is scored on a four-point scale, ranging from 0 (does not initiate) to 3 (performs fully). The GMFM-88 is an expanded version of the GMFM-66 and includes an additional 22 motor skills tasks, resulting in a total of 88 items. This version provides a more comprehensive assessment of gross motor function and allows for a finer-grained analysis of a child's abilities across a broader range of motor skills.

2.	Gross Motor Performance Measure (GMPM) 0-100 Higher is better	Observational tool used to assess the quality of movement in children with cerebral palsy. It is used to evaluate changes in the quality of a child's gross motor behavior over time.
3.	Comprehensive Functional assessment (CFA) Higher is better	Functional assessment in 5 functional areas including cognizance, language competence, self-care, motor function, and social adaptability. Raw scores are collected in each functional area and the total scores are calculated as their sum.
4.	Pediatric Evaluation of Disability Inventory (PEDI) 0-56 Higher is better	Comprehensive tool for evaluating function in children with disabilities. It assesses three domains: self-care, mobility, and social function. The self-care domain includes tasks such as dressing, eating, and personal hygiene. The mobility domain focuses on activities related to mobility, such as walking, climbing stairs, and using transportation. The social function domain evaluates a child's interactions with others, play skills, and participation in social activities.
5.	Functional Independence Measure (WeeFIM) 18-126 Higher is better	Assessment tool that measures a child's consistent performance in essential daily functional skills. The instrument consists of an 18-item, 7-level ordinal scale over three main domains (self-care, mobility, and cognition).
6.	Bayley Scales of Infant and Toddler Development- II (BSID) 0 to 112 for Motor scale raw score 0 to 178 for Mental scale raw score Higher is better	Widely used assessment tool designed to evaluate the developmental functioning of infants and young children. It plays a significant role in assessing children with cerebral palsy and provides valuable insights into their cognitive, language, motor, and socio-emotional development.
7.	Modified Ashworth scale (MAS) Higher is better	Clinical tool used to assess muscle tone and spasticity in patients with cerebral palsy. The 6-point scale assigns a grade of spasticity from a score of 0-4.

Risk of Bias Assessment:

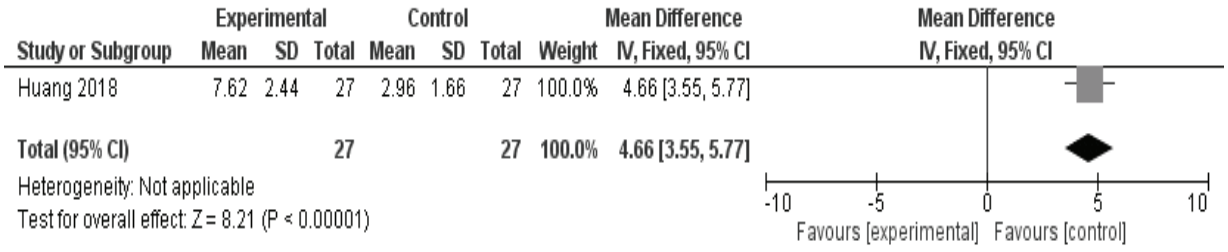


Desirable effects:

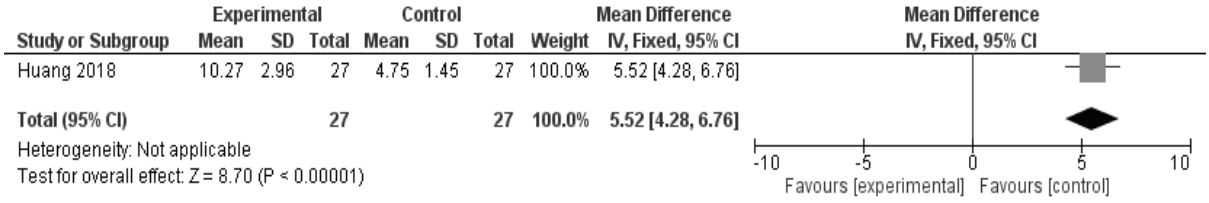
1. GMFM:

1.1. GMFM-88: Evidence from 1 trial involving 54 participants reported the change in GMFM-88 scale and yielded a mean difference of 4.66 (95% CI: 3.55 to 5.77) at the end of six months and 5.52 (95% CI: 4.28 to 6.76) at the end of 12 months between the stem cell arm and usual care arm. 1 trial reported the post score of GMFM-88 and showed a mean difference of 33 (95% CI: 13.35 to 52.65) between the stem cell arm and usual care arm at the end of 24 months. The data is statistically significant at all three time points.

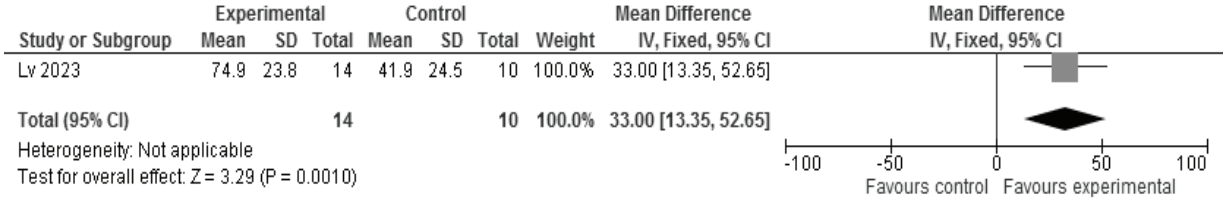
GMFM-88 at the end of 6 months:



GMFM-88 at the end of 12 months:

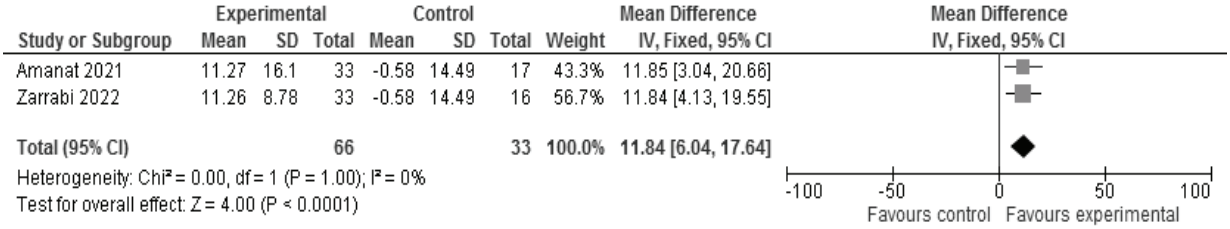


GMFM-88- post score at the end of 24 months:

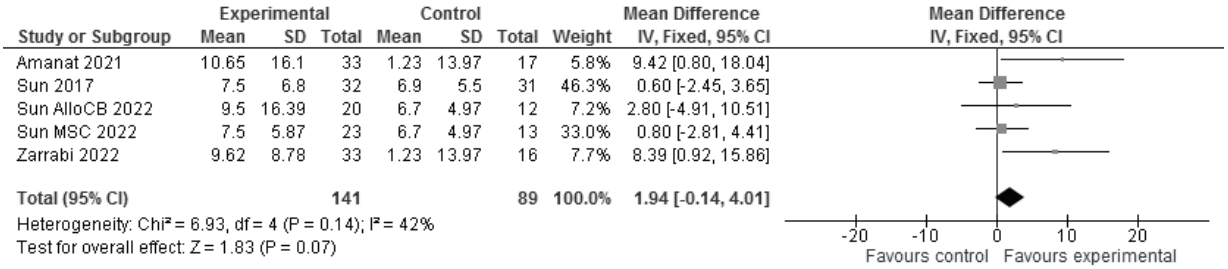


1.2. GMFM-66: Evidence from 2 trials involving 99 participants reported the GMFM-66 scale and yielded a mean difference of 11.84 (95% CI: 6.04 to 17.64) at the end of 6 months between the stem cell arm and usual care arm. Evidence from 4 trials with 230 participants reported a mean difference of 1.94 (95% CI: -0.14 to 4.01) at the end of 12 months. The difference was statistically significant at 6 months but non-significant at 12 months.

GMFM-66 score at the end of 6 months:

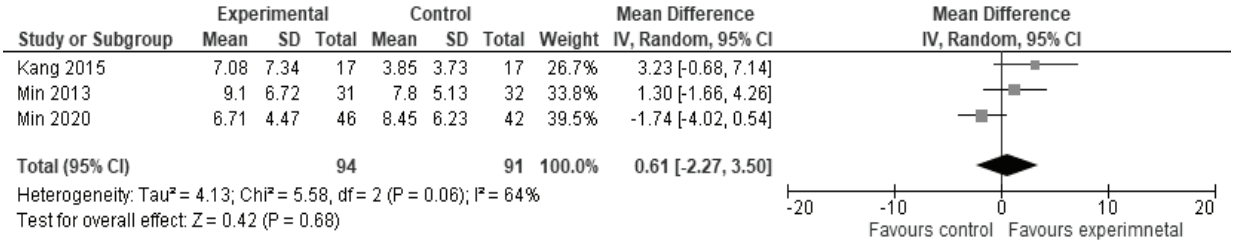


GMFM-66 score at the end of 12 months:

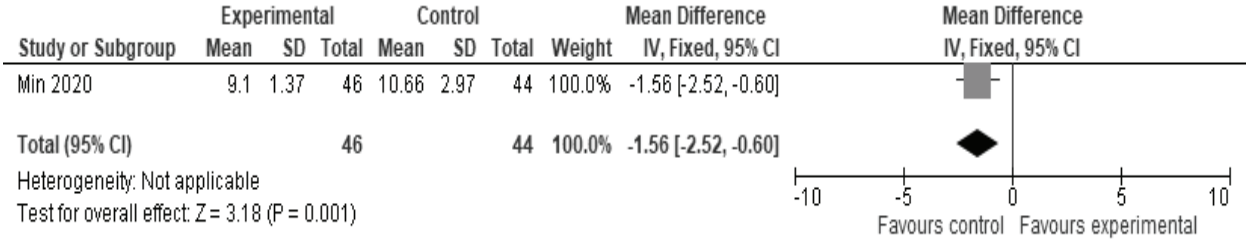


1.3. GMFM (type not mentioned) change score: Evidence from 3 trials involving 185 participants reported the change in GMFM scale and yielded a mean difference of 0.61 (95% CI: -2.27 to 3.50) at the end of 6 months between the stem cell arm and usual care arm, which was statistically non-significant.1 trial with 90 participants reported a mean difference of -1.56 (95% CI: -2.52 to -0.60) at the end of 12 months, which was statistically significant.

GMFM (type not mentioned) change score at the end of 6 months:

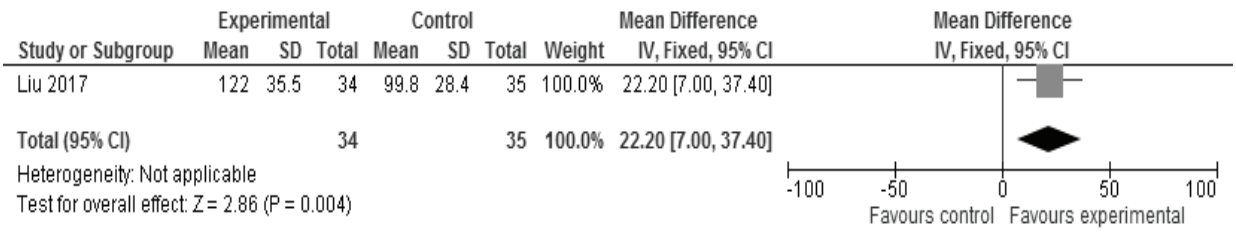


GMFM (type not mentioned) change score at the end of 12 months:

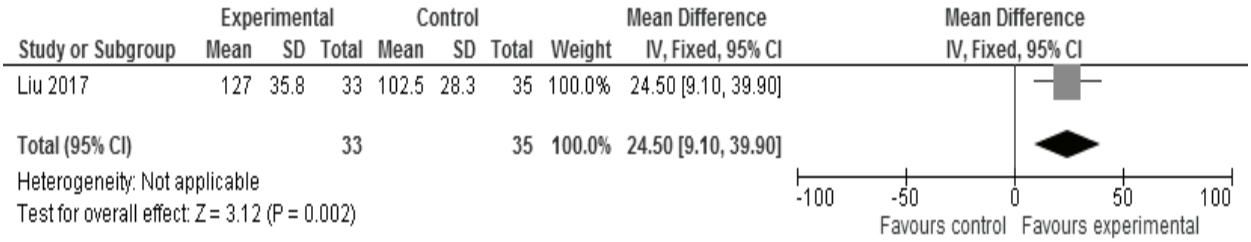


1.4. GMFM (type not mentioned) post score: Evidence from 1 trial with 69 participants reported the post score of GMFM scale and showed a mean difference of 22.20 (95% CI: 7.00 to 37.40) at the end of 6 months. Another trial with 68 participants reported a mean difference of 24.50 (95% CI: 9.10 to 39.90) at the end of 12 months between the stem cell arm and usual care arm. The differences were statistically significant at both time points.

GMFM (type not mentioned) post score at 6 months:

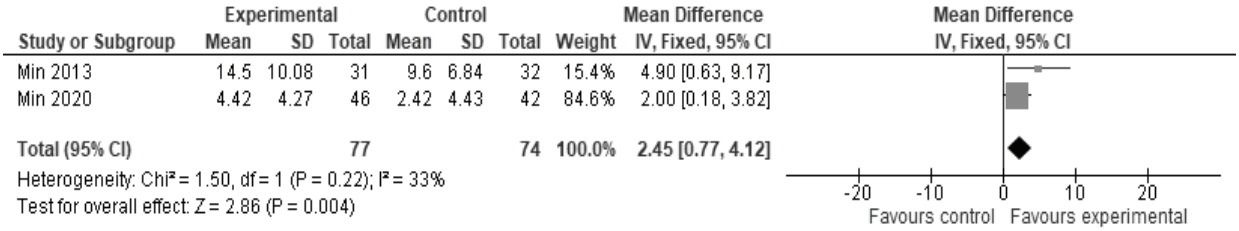


GMFM (type not mentioned) post score at 12 months:

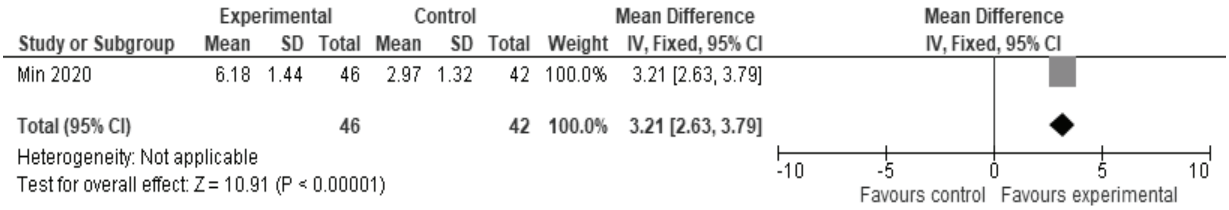


2. GMPM: Evidence from 2 trials involving 151 participants reporting the GMPM scale yielded a mean difference of 2.45 (95% CI: 0.77 to 4.12) at the end of 6 months and from 1 trial with 88 participants yielded a mean difference of 3.21 (95% CI: 2.63 to 3.79) at the end of 12 months between the stem cell arm and usual care arm. The differences were statistically significant at both time points.

GMPM at the end of 6 months:

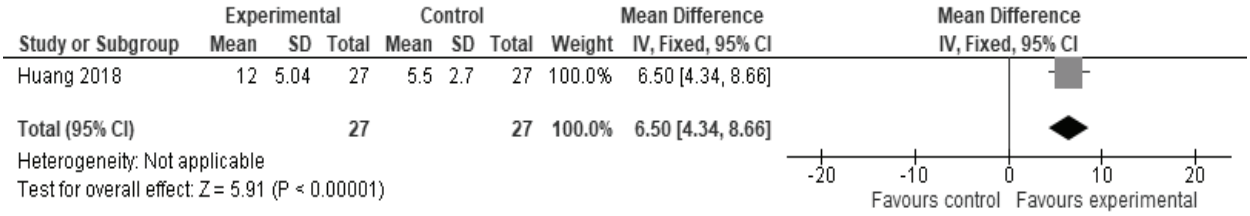


GMPM at the end of 12 months:

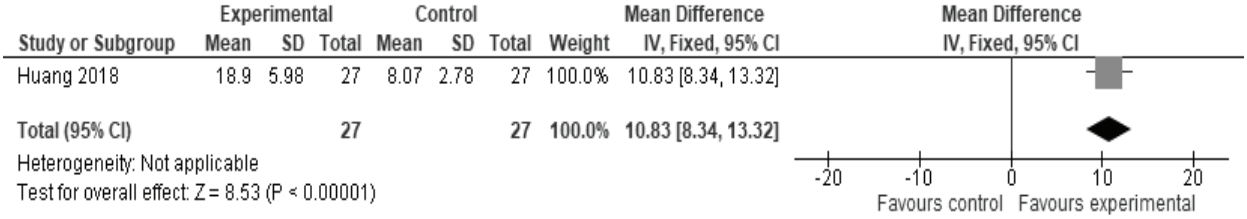


3. CFA: Evidence from 1 trial with 54 participants reporting the change in CFA yielded a mean difference of 6.50 (95% CI: 4.34 to 8.66) at the end of 6 months and 10.83 (95% CI: 8.34 to 13.32) at the end of 12 months between the stem cell arm and usual care arm. The differences were statistically significant at both time points.

CFA at 6 months:

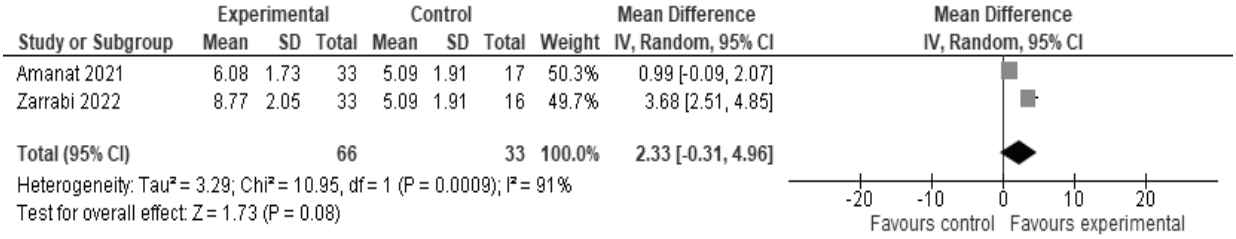


CFA at 12 months:

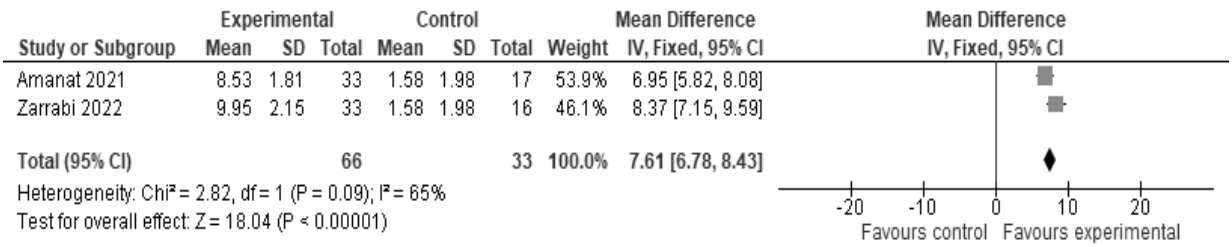


4. PEDI: Evidence from 2 trials involving 99 participants reported the change in PEDI and yielded a mean difference of 2.33 (95% CI: -0.31 to 4.96) at the end of 6 months and 7.61 (95% CI: 6.78 to 8.43) at the end of 12 months between the stem cell arm and usual care arm. The difference was statistically non-significant at 6 months but significant at 12 months.

PEDI at 6 months:

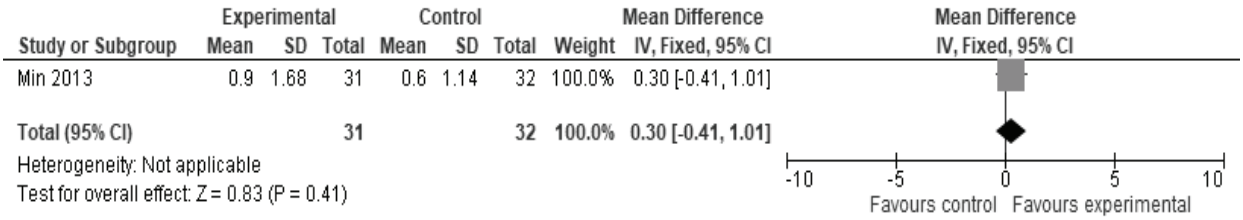


PEDI at 12 months:



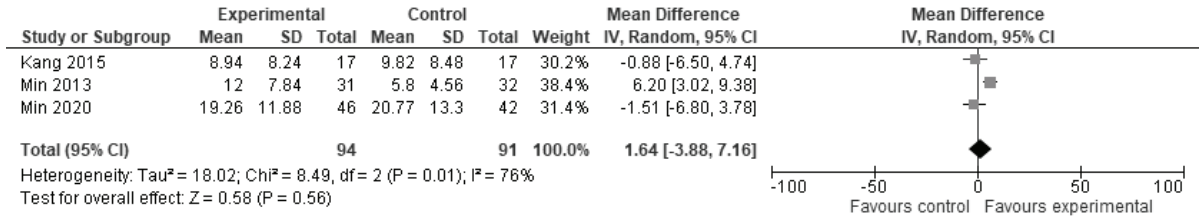
5. WeeFIM: Evidence from 1 trial involving 63 participants reported the change in WeeFIM and yielded a mean difference of 0.30 (95% CI: -0.41 to 1.01) at the end of 6 months between the stem cell arm and usual care arm. The difference was statistically non-significant.

WeeFIM at 6 months:

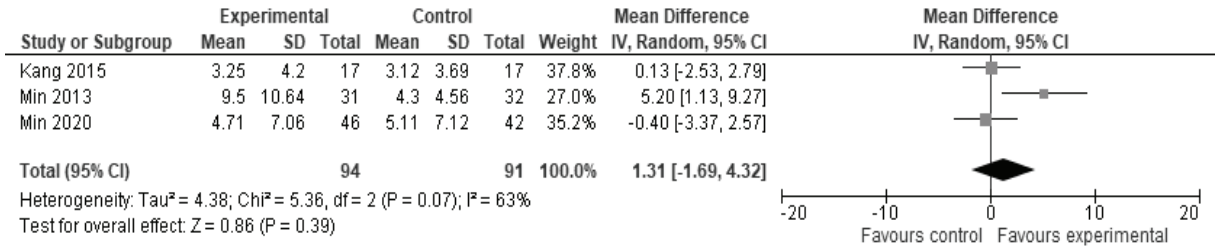


6. BSID:

6.1. BSID Mental scale: Evidence from 3trialsinvolving 185 participants reported the BSID mental scale with a mean difference of 1.64 (95% CI: -3.88 to 7.16) at the end of 6 months between the stem cell arm and usual care arm. The difference was statistically non-significant.

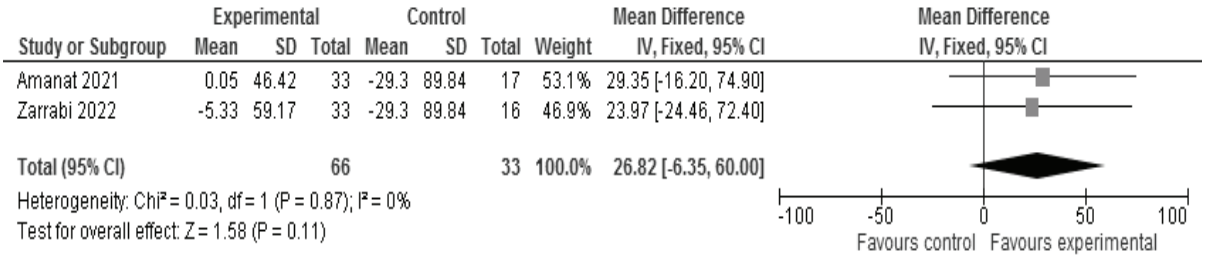


6.2. BSID Motor scale: Evidence from 3 trials involving 185 participants reported the BSID motor scale with a mean difference of 1.31 (95% CI: -1.69 to 4.32) at the end of 6 months between the stem cell arm and usual care arm. The difference was statistically non-significant.



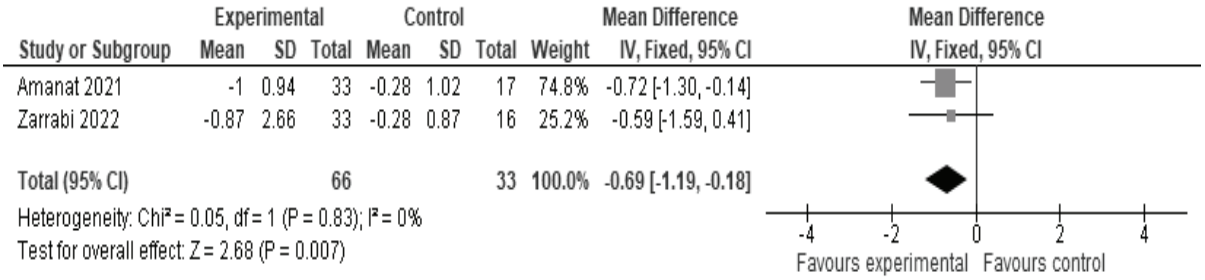
7. CP Quality of Life (QoL): Evidence from 2 trials involving 99 participants reported the CPQoL with a mean difference of 26.82 (95% CI: -6.35 to 60.00) at the end of 12 months between the stem cell arm and usual care arm. The difference was statistically non-significant.

QoL at 12 months:



8. MAS: Evidence from 2 trials involving 99 participants reported the MAS with a mean difference of -0.69 (95% CI: -1.19 to -0.18) at the end of 12 months between the stem cell arm and usual care arm. The difference was statistically significant.

MAS at 12 months:



Undesirable effects:

1. **Serious Adverse Events:** 2 trials reported serious adverse events as tabulated below.

Study	Intervention	Control
Min et al. (2013)[9]		
Pneumonia	1	1
Influenza	1	1
Death	1	0
UTI	0	1
Min et al. (2020)[12]		
Pneumonia	1	1
Seizure	1	2
Otitis media	1	0
Pyrexia	1	0
Entropion	0	1
Hepatitis viral	0	1
Nasopahryngitis	0	1
Labial frenectomy	0	1

Summary of findings: GRADE

Stem cell therapy as compared to usual care for cerebral palsy

Patient or population: In children with cerebral palsy
Setting: Hospitals/ Tertiary care
Intervention: Stem cell
Comparison: Control/ Usual care

Outcomes	Anticipated absolute effects*(95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with control	Risk with Stem cell				
GMFM-88 at 6 months	-	MD **4.66 higher** (3.55 higher to 5.77 higher)	-	54 (1 RCT)	⊕◯◯◯ very low[a,b,c]	
GMFM change score at 6 months	-	MD **0.61 higher** (2.27 lower to 3.5 higher)	-	185 (3 RCTs)	⊕⊕◯◯ Low[c,d]	
GMPM at 6 months	-	MD **2.45 higher** (0.77 higher to 4.12 higher)	-	151 (2 RCTs)	⊕⊕⊕◯ Moderate[c]	
GMPM at 12 months	-	MD **3.21 higher** (2.63 higher to 3.79 higher)	-	88 (1 RCT)	⊕⊕◯◯ Low[b,c]	
PEDI at 6 months	-	MD **2.33 higher** (0.31 lower to 4.96 higher)	-	99 (2 RCTs)	⊕◯◯◯ very low[a,c]	
PEDI at 12 months	-	MD **7.61 higher** (6.78 higher to 8.43 higher)	-	99 (2 RCTs)	⊕◯◯◯ very low[a,c]	
GMFM-66 at 12 months	-	MD **1.94 SD higher** (0.14 lower to 4.01 higher)	-	230 (4 RCTs)	⊕⊕◯◯ Low[c,e]	
CFA at 12 months	-	MD **10.83 higher** (8.34 higher to 13.32 higher)	-	54 (1 RCT)	⊕◯◯◯ very low[a,b,c]	
WeeFIM at 6 months	-	MD **0.3 higher** (0.41 lower to 1.01 higher)	-	63 (1 RCT)	⊕⊕◯◯ Low[b,c]	
BSID – Mental Scale at 6 months	-	MD **1.64 higher** (3.88 lower to 7.16 higher)	-	185 (3 RCTs)	⊕⊕⊕◯ Moderate[c]	
BSID- Motor Scale at 6 months	-	MD **1.31 higher** (1.69 lower to 4.32 higher)	-	185 (3 RCTs)	⊕⊕⊕◯ Moderate[c]	

Summary of findings: GRADE

Stem cell therapy as compared to usual care for cerebral palsy

Patient or population: In children with cerebral palsy
Setting: Hospitals/ Tertiary care
Intervention: Stem cell
Comparison: Control/ Usual care

Outcomes	Anticipated absolute effects*(95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with control	**Risk with Stem cell**				
CPQoL at 12 months	-	MD **26.82 higher** (6.35 lower to 60 higher)	-	99 (2 RCTs)	⊕◯◯◯ very low[a,c]	
MAS at 12 months	-	MD **0.69 lower** (1.19 lower to 0.18 lower)	-	99 (2 RCTs)	⊕◯◯◯ very low[a,c]	

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

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

Explanations

a. downgraded two levels for risk of bias as more than 2/3rd of studies (by wt.) are at high risk of bias
b. downgraded one level for inconsistency as single study is inevaluable for inconsistency
c. downgraded one level for imprecision due to small sample size
d. downgraded one level for inconsistency due to inconsistent results across studies
e. downgraded one level for risk of bias as 1/3rd – 2/3rd of studies are at high risk of bias

Evidence profile:

Stem cell therapy as compared to usual care for cerebral palsy

Certainty assessment							Summary of findings				
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With control	With SCT		Risk with control	Risk difference with Stem cell
GMFM-88 at 6 months											
54 (1 RCT)	very serious[a]	Inevaluable[b]	not serious	serious[c]	None	⊕◯◯◯ very low[a,b,c]	-	-	-	-	MD **4.66 higher** (3.55 higher to 5.77 higher)
GMFM change score at 6 months											
185 (3 RCTs)	not serious	serious[d]	not serious	serious[c]	None	⊕⊕◯◯ Low[c,d]	-	-	-	-	MD **0.61 higher** (2.27 lower to 3.5 higher)
GMPM at 6 months											
151 (2 RCTs)	not serious	not serious	not serious	serious[c]	None	⊕⊕⊕◯ Moderate[c]	-	-	-	-	MD **2.45 higher** (0.77 higher to 4.12 higher)
GMPM at 12 months											
88 (1 RCT)	not serious	Inevaluable[b]	not serious	serious[c]	None	⊕⊕◯◯ Low[b,c]	-	-	-	-	MD **3.21 higher** (2.63 higher to 3.79 higher)
PEDI at 6 months											
99 (2 RCTs)	very serious[a]	not serious	not serious	serious[c]	None	⊕◯◯◯ very low[a,c]	-	-	-	-	MD **2.33 higher** (0.31 lower to 4.96 higher)
PEDI at 12 months											
99 (2 RCTs)	very serious[a]	not serious	not serious	serious[c]	None	⊕◯◯◯ very low[a,c]	-	-	-	-	MD **7.61 higher** (6.78 higher to 8.43 higher)
GMFM-66 at 12 months											
230 (4 RCTs)	serious[e]	not serious	not serious	serious[c]	None	⊕⊕◯◯ Low[c,e]	-	-	-	-	MD **1.94 higher** (0.14 lower to 4.01 higher)

Evidence profile:

Stem cell therapy as compared to usual care for cerebral palsy

Certainty assessment							Summary of findings				
CFA at 12 months											
54 (1 RCT)	very serious[a]	Inevaluable[b]	not serious	serious[c]	None	⊕◯◯◯ very low[a,b,c]	-	-	-	-	MD **10.83** **higher** (8.34 higher to 13.32 higher)
WeeFIM at 6 months											
63 (1 RCT)	not serious	Inevaluable[b]	not serious	serious[c]	None	⊕⊕◯◯ Low[b,c]	-	-	-	-	MD **0.3** **higher** (0.41 lower to 1.01 higher)
BSID-Mental scale at 6 months											
185 (3 RCTs)	not serious	not serious	not serious	Serious[c]	None	⊕⊕⊕◯ Moderate[c]	-		-	-	MD **1.64** **higher** (3.88 lower to 7.16 higher)
BSID- Motor scale at 6 months											
185 (3 RCTs)	not serious	not serious	not serious	Serious[c]	None	⊕⊕⊕◯ Moderate[c]	-		-	-	MD **1.31** **higher** (1.69 lower to 4.32 higher)
CPQoL at 12 months											
99 (2 RCTs)	very serious[a]	not serious	not serious	Serious[c]	None	⊕◯◯◯ very low[a,c]	-	-	-	-	MD **26.82** **higher** (6.35 lower to 60 higher)
MAS at 12 months											
99 (2 RCTs)	very serious[a]	not serious	not serious	Serious[c]	None	⊕◯◯◯ very low[a,c]	-	-	-	-	MD **0.69** **lower** (1.19 lower to 0.18 lower)

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

Explanations

a. downgraded two levels for risk of bias as more than 2/3rd of studies (by wt.) are at high risk of bias
b. downgraded one level for inconsistency as single study is inevaluable for inconsistency
c. downgraded one level for imprecision due to small sample size
d. downgraded one level for inconsistency due to inconsistent results across studies
e. downgraded one level for risk of bias as 1/3rd – 2/3rd of studies are at high risk of bias

D. SUMMARY OF JUDGMENTS:

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

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

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

E. CAVEATS IN EXISTING EVIDENCE:

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

- Heterogeneity across trials in patient population and type of stem cell therapy, cell dosage, route of administration and time of administration
- Use of different diagnostic and evaluation tools by studies
- Lack of long term follow up of participants thus providing insufficient evidence on the safety of this experimental therapy
- Lack of cost effectiveness data

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3. MUSCULAR DYSTROPHY

A. BACKGROUND:

Muscular dystrophies are a heterogeneous group of genetic disorders affecting the key structural and functional proteins in the muscle cell plasma membrane, resulting in impaired muscle regeneration subsequent inflammation and ending up with progressive muscular weakness, atrophy, functional dependency, and early mortality.[1] Amongst various muscular dystrophies, Duchenne Muscular Dystrophy (DMD) is the most common. There are no definitive therapeutic options available in routine use and the treatment mostly includes oral anti-inflammatory glucocorticoids aiming to prolong ambulation and minimize cardiac fibrosis but have limitations because of associated adverse effects.[2]

B. RECOMMENDATIONS:

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

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

*This recommendation is not applicable to gene therapy.
** The evidence for this recommendation is derived from RCTs that included participants with Duchenne Muscular dystrophy only.

Rationale/Justification:

This recommendation has been made as there is very low certainty evidence of trivial improvement in muscle strength and functional ability of patients with muscular dystrophy. There is a small increase in undesirable effects with stem cell therapy. In addition, the follow up period 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 muscular dystrophies, what is the efficacy and safety of stem cell therapy as compared to usual care?

Included Studies: Initially, 4,328 citations were screened followed by the 23 citations included for second screening of full text. Among these, 20 studies were excluded from the systematic review because of the virtue of being non-randomized studies, experimental studies without comparator

arm and pilot studies. The remaining three randomised controlled trials were finalized with the inclusion in this review.[3-5]

Among the three RCTs, one study has compared the efficacy and safety of muscle-derived CD133+ stem cells with sham therapy, while two studies compared the CAP1002 as a stem cell therapy with usual care or placebo in patients with DMD. These two trials named as Halt Cardiomyopathy Progression; HOPE(NCT02485938)[4] and HOPE-2 (NCT03406780)[3] trials on CAP1002 in patients with DMD were sponsored by Capricor Therapeutics (Beverly Hills, CA, USA). In HOPE trial, CAP-1002 was given through intracoronary infusion while, HOPE 2 followed the intravenous infusions route of administration. CAP1002 were formulated by using the donor myocardial tissue culture to create CDCs, and formulated as CAP 1002, and then cryopreserved. One trial reported the efficacy and safety of muscle-derived CD133+ stem cells (n=5) isolated from tibialis anterior muscle of all included patients.[5]

Critical outcomes reviewed:

S. No.	Outcomes	What does it measure?
1.	Performance of upper limb (PUL) PUL 1.2:0-74 PUL 2.0: 42 Higher score is better	PUL is a clinician rated tool which is tailored to evaluate the upper limb function in both ambulant and non-ambulant patients with DMD. It consists of two versions (PUL1.2 and PUL 2.0) with 22 items in each. Out of which one item is entry item to define the starting functional level and 21 items are subdivided into high (shoulder), middle (elbow) and distal (wrist) levels.
2.	Pediatric Outcomes Data Collection Instrument (PODCI) 0-100 Higher is better	The pediatric outcomes data collection instrument (PODCI) assesses the usual performance of daily tasks and health-related quality of life (HRQoL) among children with various chronic or musculoskeletal conditions, such as Muscular Dystrophy. The PODCI comprises 83 questions and generates 5 subscale scores: upper extremity and physical functioning, transfer and basic mobility, sports and physical functioning, pain/comfort, and happiness, along with a PODCI global function score. Scores for each PODCI subscale range from 0 to 100, with high scores indicating high HRQoL.
3.	Quality of Life (QoL) Range: 0-100 Higher is better	PedsQL is a generic HRQoL questionnaire with 4 dimensions including Daily Activities (5 items), Treatment (4 items), Worry (6 items), and Communication (3 items). Scoring is on 5-point Likert scale from: 0 (Never) to 4 (Almost always) and transformed from 0 to 100. Items are reverse scored and linearly transformed to a 0-100 scale as follows: 0=100, 1=75, 2=50, 3=25, 4=0.

Risk of Bias Assessment:

PUL and PODCI:

Study ID	Experimental intervention	Comparator	Outcome	Weight	D1	D2	D3	D4	D5	Overall
Taylor M et al. (2019)[4]	Allogeneic CDCs-Intracoronary CAP-1002	Usual care	PUL	1	+	+	+	+	+	+

Quality of Life:

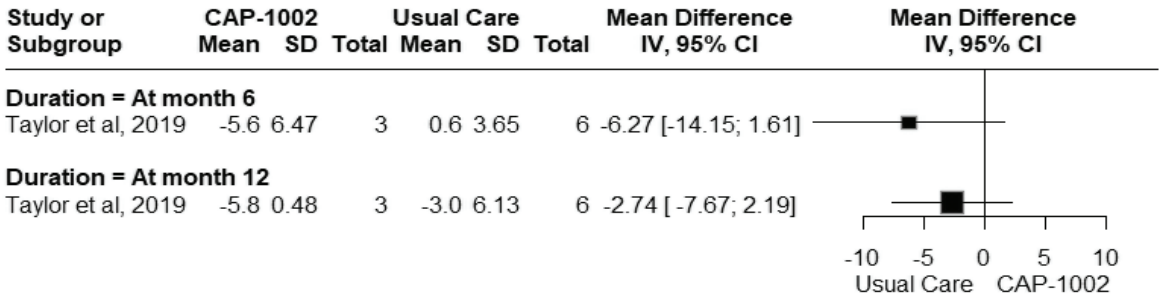
Study ID	Experimental intervention	Comparator	Outcome	Weight	D1	D2	D3	D4	D5	Overall
Taylor M et al. (2019)[4]	Allogeneic CDCs-Intracoronary CAP-1002	Usual care	Quality of life	1	+	!	+	+	+	!

+	Low risk
!	Some concerns

D1	Randomisation process
D2	Deviations from the intended interventions
D3	Missing outcome data
D4	Measurement of the outcome
D5	Selection of the reported result

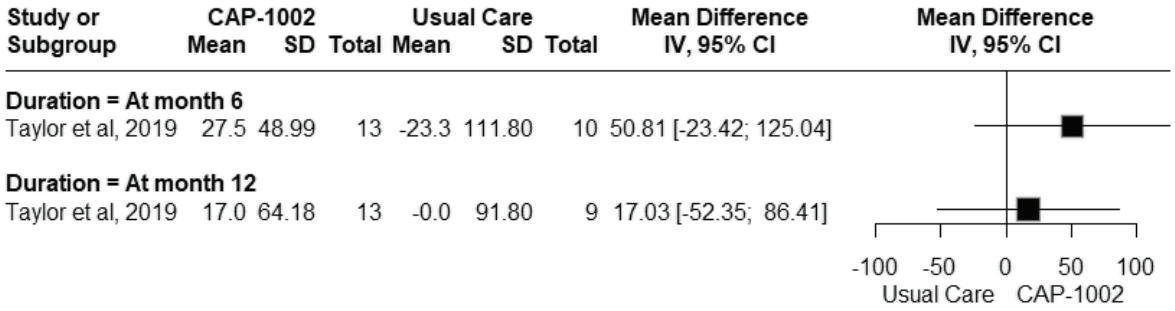
Desirable effects:

1. **PUL 1.2:** Evidence from HOPE trial reporting the total PUL scale score yielded a mean difference of -6.27 (95% CI: -14.15 to 1.61) at the end of six months and -2.74 (95%CI: -7.68 to 2.20) at the end of 12 months between the stem cell arm and usual care arm. The differences were statistically non-significant at both time points.

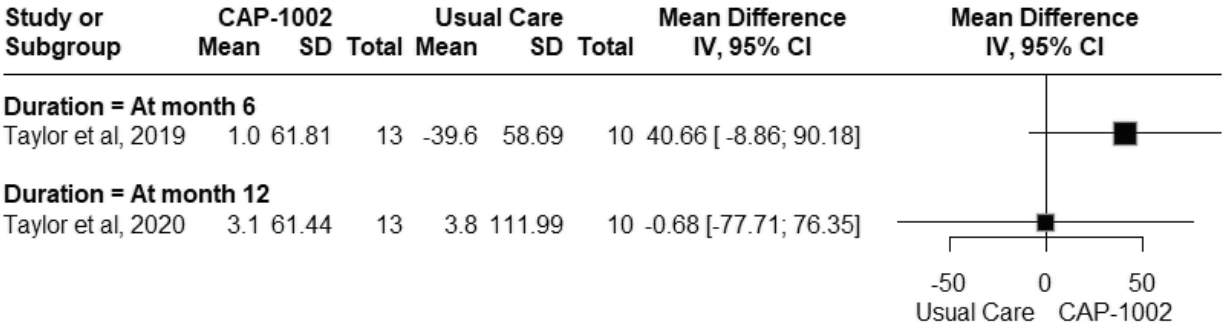


2. PODCI:

2.1. Patient reported PODCI: Global Function outcome of Patient PODCI: Evidence from HOPE trial reporting the Global Function outcome of Patient PODCI scale yielded a mean difference of 50.81 (95% CI: -23.42 to 125.04) at the end of six months and 17.03 (95%CI: -52.35 to 86.41) at the end of 12 months between the stem cell arm and usual care arm. The differences were statistically non-significant at both time points.

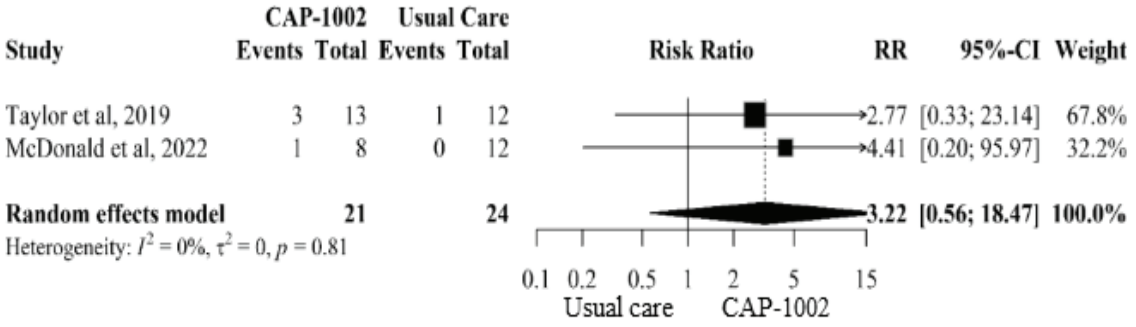


2.2 Parent-reported PODCI: Global Function outcome: Evidence from HOPE trial reporting the Global Function outcome of Parent PODCI scale yielded a mean difference of 40.66 (95% CI: -8.86 to 90.18) at the end of six months and -0.68 (95%CI: -77.71 to 76.35) at the end of 12 months between the stem cell arm and usual care arm. The differences were statistically non-significant at both time points.



Undesirable effects:

3. Serious Adverse Events: Among the included three trials, two trials had reported the higher numbers of serious AEs among 4/21 (19%) patients in CAP-1002 treated group versus 1/24 (4%) patients in control group. However, the pooled estimates were not statistically significant (RR: 3.22; 95% CI: 0.56 to 18.47; I^2: 0%).



One patient treated with intravenous CAP-1002 had reported the acute allergic reaction as a serious AE during the second dose of CAP-1002, while intracoronary CAP-1002 treated patients reported four serious AEs such as fever and confusion (1 patient), ventricular fibrillation (1 patient), and urinary tract infection (1 patient). Torrente et al did not observe the presence of any local or systemic AEs in both the treatment groups (muscle-Derived CD133+ stem cells group and sham therapy).[5]

Summary of findings: Grade

Stem Cell Therapy as compared to usual care for Muscular dystrophy

Patient or population: Muscular dystrophy patients
Setting: Tertiary care/ Hospitals
Intervention: Stem cell therapy
Comparison: control/usual care

Outcomes	Anticipated absolute effects*(95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with control	**Risk with SCT**				
Total PUL 1.2 follow-up: 6 months	-	MD **6.27 points lower** (14.15 lower to 1.61 higher)	-	9 (1 RCT)	⊕⊕◯◯ Low[a,b]	
Total PUL 1.2 follow-up: 12 months	-	MD **2.74 points lower** (7.68 lower to 2.2 higher)	-	9 (1 RCT)	⊕⊕◯◯ Low[a,b]	
Patient-reported PODCI parameter: Global Function follow-up: 6 months	-	MD **50.81 points higher** (23.42lower to 125.04higher)	-	23 (1 RCT)	⊕◯◯◯ Very low[a,b,c]	
Patient-reported PODCI parameter: Global Function follow-up: 12 months	-	MD **17.03 points higher** (52.35lower to 86.41higher)	-	22 (1 RCT)	⊕◯◯◯ Very low[a,b,c]	
Parent-reported PODCI parameter: Global Function follow-up: 6 months	-	MD **40.66 points higher** (8.86lower to 90.18higher)	-	23 (1 RCT)	⊕◯◯◯ Very low[a,b,c]	
Parent-reported PODCI parameter: Global Function follow-up: 12 months	-	MD **0.68 points lower** (77.71 lower to 76.35 higher)	-	23 (1 RCT)	⊕◯◯◯ Very low[a,b,c]	
Serious Adverse Events	42 per 1,000	**134 per 1,000** (23 to 770)	**RR 3.22** (0.56 to 18.47)	45 (2 RCTs)	⊕⊕◯◯ Low[a,b]	

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

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

Summary of findings: Grade

Stem Cell Therapy as compared to usual care for Muscular dystrophy

Patient or population: Muscular dystrophy patients
Setting: Tertiary care/ Hospitals
Intervention: Stem cell therapy
Comparison: control/usual care

Outcomes	**Anticipated absolute effects***(95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with control	**Risk with SCT**				

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

Explanations

a Downgraded by one level for inconsistency as for single study, inconsistency is inevaluable
b Downgraded by one level for imprecision due to small sample size and event rate not meeting the optimal information size criteria
c. Downgraded by two levels for high risk of bias in single study

Evidence Profile:

Stem Cell Therapy as compared to usual care for Muscular dystrophy

Certainty assessment							Summary of findings				
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With control	With SCT		Risk with control	Risk difference with SCT
Total PUL 1.2 (follow-up: 6 months)											
25 (1 RCT)	not serious	Inevaluable[a]	not serious	Serious[b]	None	⊕⊕◯◯ Low[a,b]	-	-	-	-	MD **6.27 lower** (14.15 lower to 1.61 higher)
Total PUL 1.2 (follow-up: 12 months)											
25 (1 RCT)	not serious	Inevaluable[a]	not serious	Serious[b]	None	⊕⊕◯◯ Low[a,b]	-	-	-	-	MD **2.74 lower** (7.68 lower to 2.2 higher)
Patient-reported PODCI parameter: Global Function (follow-up: 6 months)											
25 (1 RCT)	very Serious[c]	Inevaluable[a]	not serious	Serious[b]	None	⊕◯◯◯ Very low[a,b,c]	-	-	-	-	MD **50.81 higher** (23.42 lower to 125.04 higher)
Patient-reported PODCI parameter: Global Function (follow-up: 12 months)											
25 (1 RCT)	very Serious[c]	Inevaluable[a]	not serious	Serious[b]	None	⊕◯◯◯ Very low[a,b,c]	-	-	-	-	MD **17.03 higher** (52.35 lower to 86.41 higher)
Parent-reported PODCI parameter: Global Function (follow-up: 6 months)											
25 (1 RCT)	very Serious[c]	Inevaluable[a]	not serious	Serious[b]	None	⊕◯◯◯ Very low[a,b,c]	-	-	-	-	MD **40.66 higher** (8.86 lower to 90.18 higher)

Stem Cell Therapy as compared to usual care for Muscular dystrophy

Certainty assessment							Summary of findings				
Parent-reported PODCI parameter: Global Function (follow-up: 12 months)											
25 (1 RCT)	very Serious[c]	Inevaluable[a]	not serious	Serious[b]	None	⊕◯◯◯ Very low[a,b,c]	-	-	-	-	MD **0.68 lower** (77.71 lower to 76.35 higher)
Serious Adverse Events											
45 (2 RCTs)	Not serious	Inevaluable[a]	not serious	Serious[b]	None	⊕⊕◯◯ Low[a,b]	1/24 (4.2%)	4/21 (19.0%)	**RR 3.22** (0.56 to 18.47)	1/24 (4.2%)	**93 more per 1,000** (from 18 lower to 728 higher)

Explanations
a Downgraded by one level for inconsistency as for single study, inconsistency is inevaluable
b Downgraded by one level for imprecision due to small sample size and event rate not meeting the optimal information size criteria
c Downgraded by two levels for high risk of bias in single study

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	Small**
Certainty of evidence	Very low
Values	Probably no important uncertainty or variability
Balance of effects	Does not favor either the intervention or the comparison
Resources required	Large costs***
Certainty of evidence of required resources	Moderate
Cost effectiveness	Probably favors the comparison
Equity	Probably reduced
Acceptability	Probably yes
Feasibility	Probably yes
Recommendations: Stem Cell Therapy is **not recommended**# in routine practice for the treatment of muscular dystrophies##. It may be used only in the context of rigorously conducted clinical trials.	

***This judgment was made as there is very low certainty evidence of trivial improvement in muscle strength and functional ability of patients with muscular dystrophy.
**This judgment was made as there is a small increase in undesirable effects with stem cell therapy.
*** The committee opined that stem cell treatment is associated with large costs.
#This recommendation is not applicable to gene therapy.
##The evidence for this recommendation is derived from RCTs that included participants with Duchenne Muscular dystrophy only.

E. CAVEATS IN EXISTING EVIDENCE:

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

- Lack of sufficient number of RCTs with low risk of bias
- Small number of participants and events in the included trials
- Heterogeneity across trials in patient population and type of stem cell therapy, cell dosage, route of administration and time of administration as well as outcomes reported
- Lack of long term follow up of participants thus providing insufficient evidence on the safety of this experimental therapy
- Lack of cost effectiveness data

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4. BRONCHOPULMONARY DYSPLASIA

A. BACKGROUND

Bronchopulmonary dysplasia (BPD) is a chronic respiratory condition that impacts premature infants who need mechanical ventilation and oxygen therapy.[1] A study by Bhunwal et al reported an incidence of 11.2% in preterm neonates (<33 week gestation) with respiratory distress and a higher incidence in infants <1 kg and <28 weeks gestation.[2] Despite the progress made in the field of newborn care, bronchopulmonary dysplasia (BPD) continues to be a substantial contributor to illness and death among premature neonates.[1]

B. RECOMMENDATIONS:

a) Stem Cell Therapy is **not recommended** in routine clinical practice for the prevention of BPD in high-risk preterm neonates.
Strength: Conditional#
Certainty of Evidence: Low

b) Stem Cell Therapy is **not recommended** in routine clinical practice for the treatment of moderate and severe BPD.
Strength: Conditional#
Certainty of Evidence: No included studies

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

Rationale/Justification

a. This recommendation has been made as the evidence is inadequate in quality and quantity to determine the safety and efficacy of stem cell therapy for the prevention of BPD in high-risk preterm neonates. In addition, the reported follow up period is too small to comment on the side effect profile and long-term safety is not known.

b. There is lack of evidence to determine the safety and efficacy of stem cell therapy in treatment of infants with moderate and severe BPD.

C. SUMMARY OF EVIDENCE:

Key Question 1: In preterm neonates that are at high risk of Bronchopulmonary Dysplasia, what is the efficacy and safety of stem cell therapy as compared to usual care for prevention of BPD?

Key Question 2: In Infants with moderate and severe Bronchopulmonary Dysplasia, what is the efficacy and safety of stem cell therapy as compared to usual care for treatment of BPD?

Included Studies: An initial search based on MESH terms in 4 databases identified 383 records, 373 studies were manually screened after duplicate removal, and only 1 RCT fitting the inclusion criteria was included for prevention of Bronchopulmonary Dysplasia in preterm neonates. No RCT was found for the use of stem cells in established BPD.
The included study encompassed 66 neonates enrolled at 23 to 28 gestational weeks (G.W.) receiving mechanical ventilator support with respiratory deterioration between postnatal days 5 and 14.[3] A 5-year follow-up study of respiratory and neurodevelopmental outcomes of the same phase II trial was available and included as a supplementary report to the primary RCT.[4] One unpublished RCT was found through a hand search of the references terminated early due to non-safety reasons. No data analysis from the study was available, so the study was excluded.

Critical outcomes reviewed:

S. no.	Outcomes	What does it measure?
1.	Incidences of BPD	It measures the probability of BPD occurrence in preterm infants that depends upon the gestational age and birth weight. The probability is high in infants born at less than 28 GW.
2.	Mortality by one year	Risk of mortality by one year of age
3.	Composite of mortality or moderate/severe BPD	The included study defined it as the need for supplemental oxygen/respiratory support to maintain oxygen saturation >90% at 36 GW.
4.	Adverse Neurodevelopmental outcome at 18-24 months	It measures the risk of neurological disabilities including Cerebral Palsy, Deafness, Motor skill delay, Mental delay, Social delay and Blindness.
5.	Serious Adverse Events	-

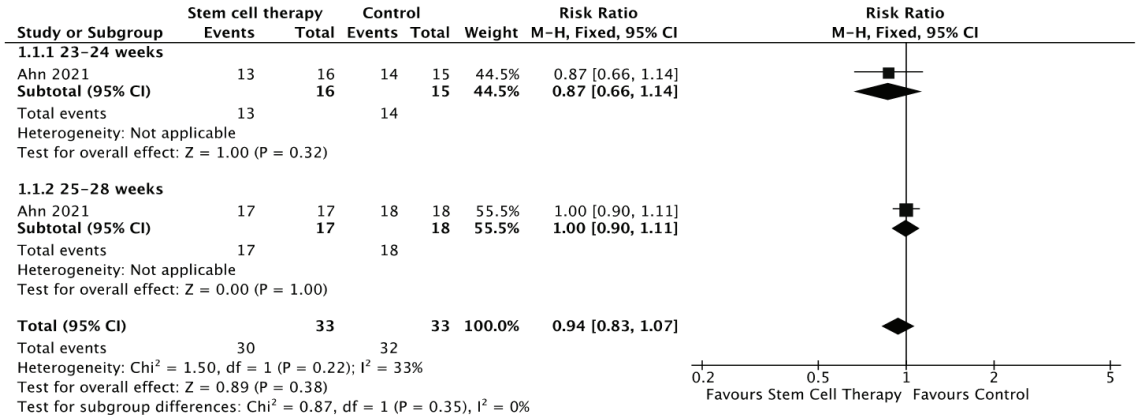
Risk of Bias Assessment:

Study ID	Outcomes	Randomization process	Deviation from intended intervention	Missing outcome data	Measurement of outcome	Selection of reported results	Overall risk of bias
Ahn 2021 & Ahn 2022	BPD	+	+	+	+	+	+
Ahn 2021 & Ahn 2022	Moderate to severe BPD	+	+	+	+	+	+
Ahn 2021 & Ahn 2022	Mortality or BPD	+	+	+	+	+	+
Ahn 2021 & Ahn 2022	Mortality at discharge	+	+	+	+	+	+
Ahn 2021 & Ahn 2022	Blindness	+	+	+	+	+	+
Ahn 2021 & Ahn 2022	Deafness	+	+	+	+	+	+
Ahn 2021 & Ahn 2022	Cerebral palsy	+	+	+	+	+	+
Ahn 2021 & Ahn 2022	Motor delay	+	+	+	+	+	+
Ahn 2021 & Ahn 2022	Mental delay	+	+	+	+	+	+
Ahn 2021 & Ahn 2022	Social delay	+	+	+	+	+	+

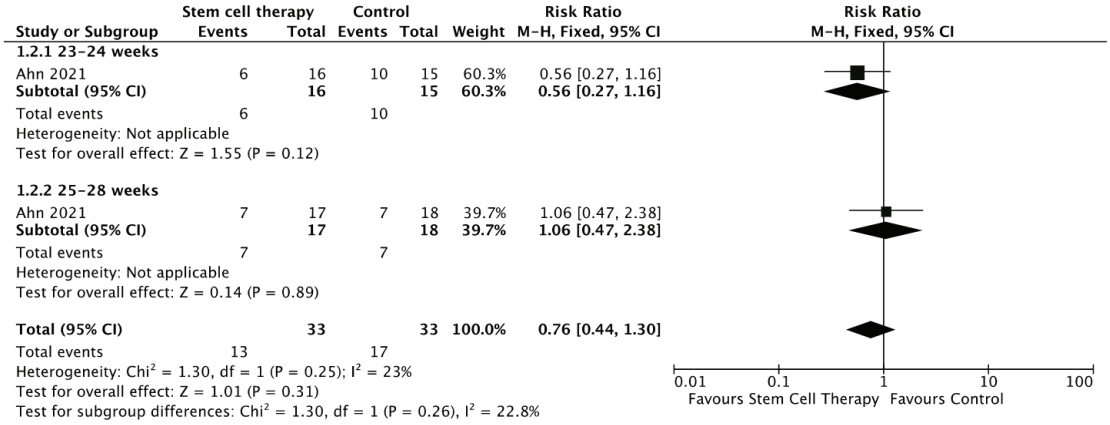
Desirable Effects:

1. Incidence of BPD:

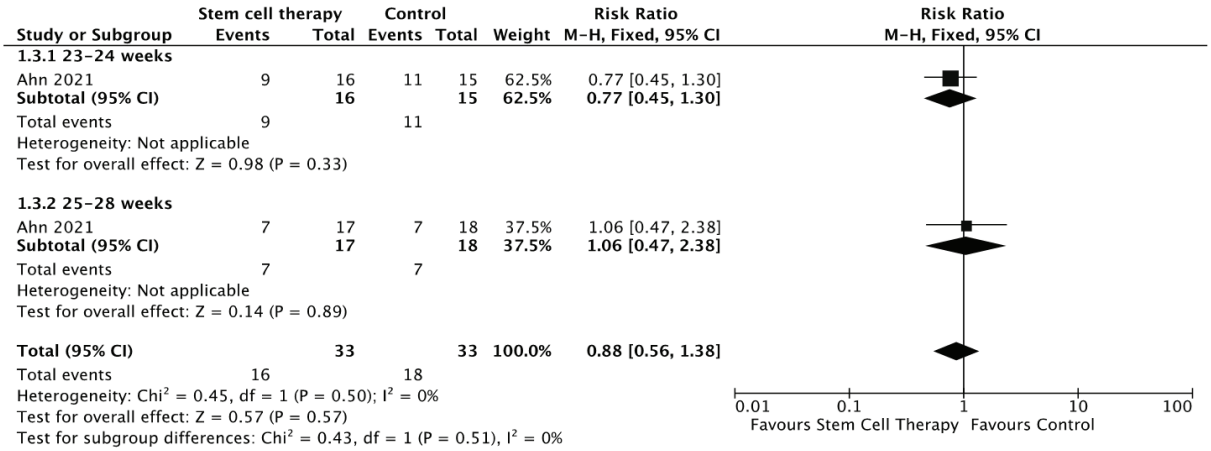
1.1. Incidence of BPD of any severity in all neonates ≤ 28 weeks gestation: Evidence from 1 RCT with 66 participants reporting the incidence of BPD of any severity yielded a risk ratio of RR 0.94 (95% CI: 0.83 to 1.07) in all neonates ≤ 28 weeks gestation. Subgroup analysis revealed a risk ratio of 0.87 (95% CI: 0.66 to1.14) in neonates born at 23-24 weeks gestation and 1.00 (95% CI: 0.90 to 1.11) in neonates born at 25-28 weeks gestation. The differences were statistically non-significant.



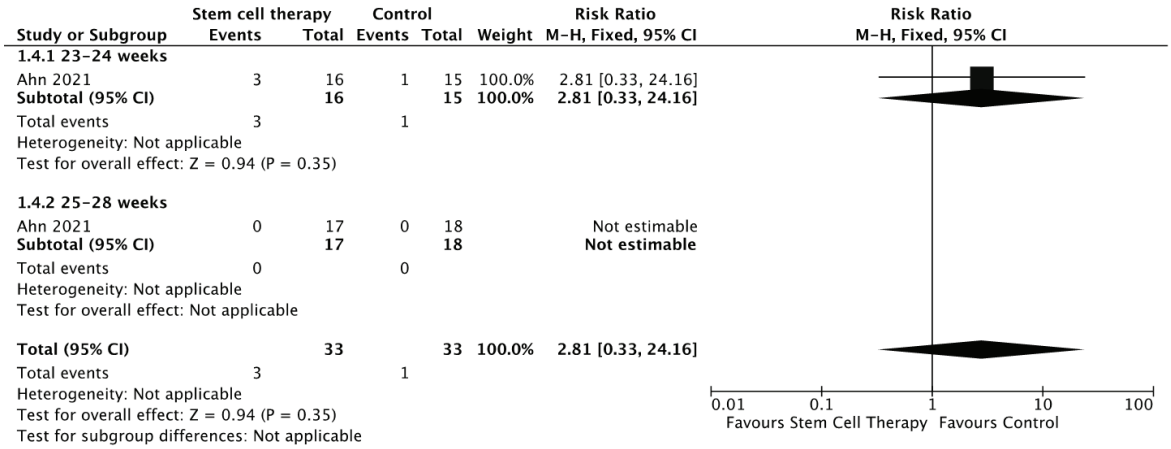
1.2. Incidence of BPD of moderate to severe in all neonates ≤ 28 weeks gestation: Evidence from 1 RCT with 66 participants reporting the incidence of BPD of moderate to severe BPD yielded a risk ratio of RR 0.76 (95% CI: 0.44 to 1.30) in all neonates ≤ 28 weeks gestation between the stem cell transplantation and the usual care arm. Subgroup analysis revealed a risk ratio of 0.56 (95% CI: 0.27 to 1.16) in neonates born at 23-24 weeks gestation and 1.06 (95% CI: 0.47 to 2.38) in neonates born at 25-28 weeks gestation. The differences were statistically non-significant.



2. Composite outcome of mortality or moderate to severe BPD at 36 weeks P.M.A: Evidence from 1 RCT with 66 participants reporting the composite outcome of mortality or moderate to severe BPD at 36 weeks P.M.A. in all neonates born ≤ 28 weeks gestation yielded a risk ratio of 0.88 (95% CI: 0.56 to 1.38) between the stem cell transplantation arm and the usual care arm. Sub-groups analysis for neonates born at 23-24 weeks gestation had a risk ratio of 0.77 (95% CI: 0.45 to 1.30) and for 25-28 weeks gestation, a risk ratio of 1.06 (95% CI: 0.47 to 2.38) was yielded. The differences were statistically non-significant.

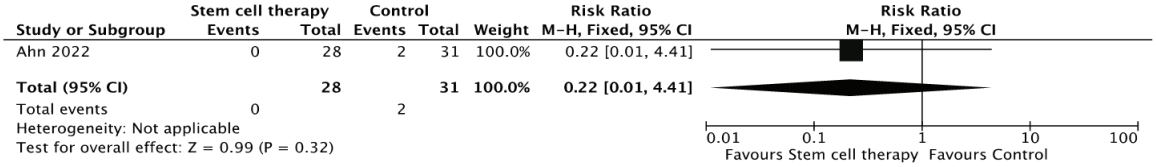


3. Mortality at discharge in all neonates ≤ 28 weeks gestation: Evidence from 1 trial with 66 participants reporting mortality in the sub-groups of neonates born at 23-24 weeks gestation yielded a risk ratio of 2.81 (95% CI: 0.33 to 24.16) between the stem cell transplantation arm and the usual care arm. The difference was statistically non-significant.

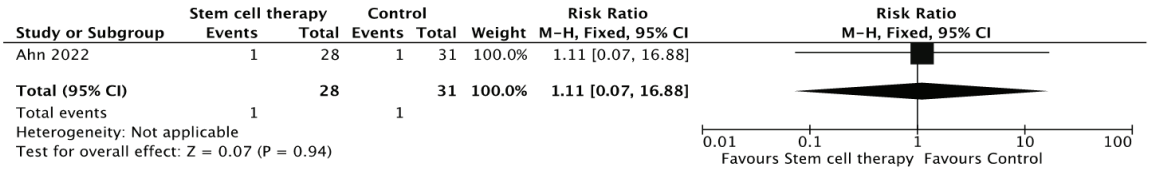


4. Adverse neurodevelopment outcomes: The trial reported the risk ratios for the following adverse outcomes at 5 years: cerebral palsy [0.22 (95% CI: 0.01 to 4.41)], deafness requiring hearing aid or cochlear implant [1.11 (95% CI: 0.07 to 16.88)], motor delay [0.24 (95% CI: 0.06 to 1.05)], mental delay [0.08 (95% CI: 0.00 to 1.44)] and social delay [0.12 (95% CI: 0.01 to 2.18)]; between the stem cell transplantation arm and the usual care arm. The impact on blindness was not estimable. The differences in all estimable parameters were statistically non-significant.

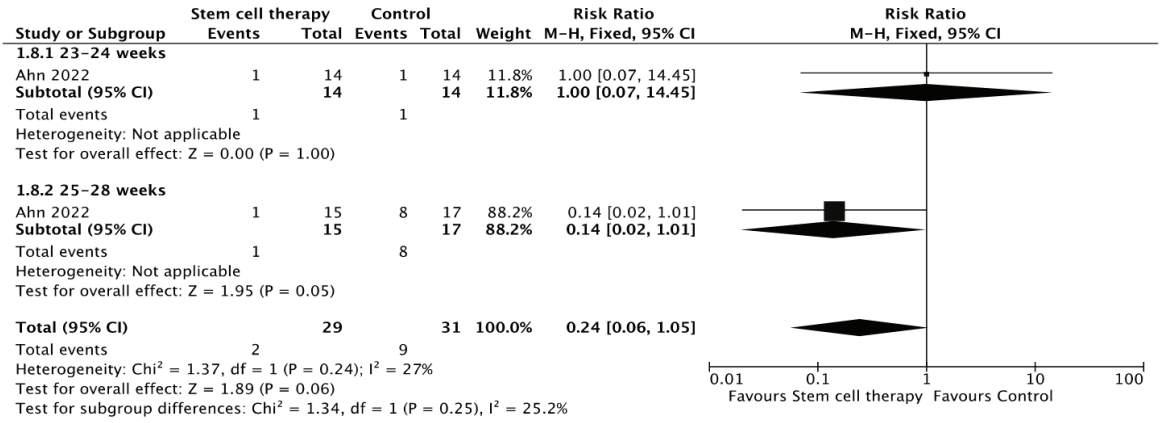
4.1. Cerebral palsy at 5 years:



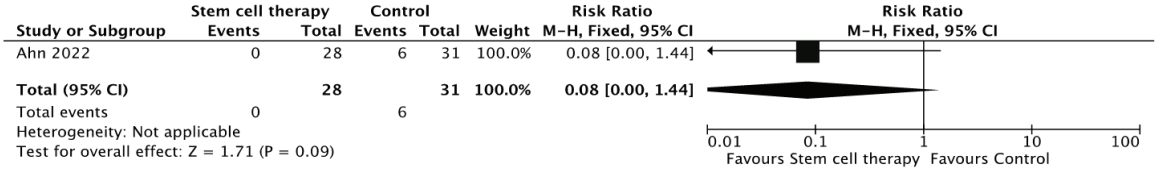
4.2. Deafness at 5 years:



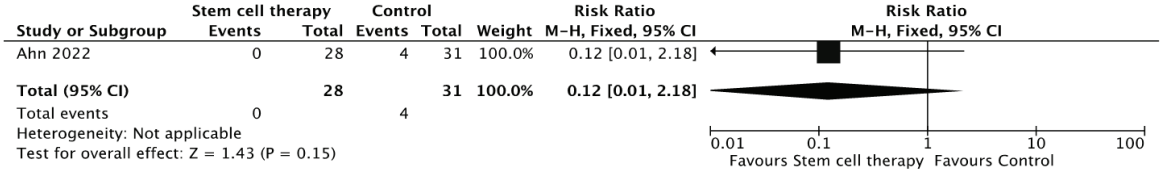
4.3. Motor delay at 5 years:



4.4. Mental delay at 5 years:



4.5. Social delay at 5 years:



Undesirable Effects:

5. Serious adverse events: No SAEs were reported in the included study.

SUMMARY OF FINDINGS: GRADE

Stem cell therapy as compared to usual care for prevention of BPD

Patient or population: BPD high risk preterm neonates
Setting: Tertiary Care/ Hospital
Intervention: Stem cell therapy
Comparison: Usual care for prevention of bronchopulmonary dysplasia

Outcomes	**Anticipated absolute effects***(95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with usual care for prevention of BPD	**Risk with Stem cell therapy**				
Bronchopulmonary dysplasia, any severity, at 36 weeks PMA	970 per 1,000	**912 per 1,000** (805 to 1,000)	**RR 0.94** (0.83 to 1.07)	66 (1 RCT)	⊕⊕◯◯ Low[a,b]	
Moderate to severe bronchopulmonary dysplasia	515 per 1,000	**392 per 1,000** (227 to 670)	**RR 0.76** (0.44 to 1.30)	66 (1 RCT)	⊕⊕◯◯ Low[a,b]	
Composite outcome of mortality or moderate/ severe BPD at 36 weeks PMA	545 per 1,000	**480 per 1,000** (305 to 753)	**RR 0.88** (0.56 to 1.38)	66 (1 RCT)	⊕⊕◯◯ Low[a,b]	
Mortality at discharge	30 per 1,000	**85 per 1,000** (10 to 732)	**RR 2.81** (0.33 to 24.16)	66 (1 RCT)	⊕⊕◯◯ Low[a,b]	
Cerebral palsy at 5 years	65 per 1,000	**14 per 1,000** (1 to 285)	**RR 0.22** (0.01 to 4.41)	59 (1 RCT)	⊕⊕◯◯ Low[a,b]	
Blindness at 5 years	0 per 1,000	**0 per 1,000** (0 to 0)	not estimable	59 (1 RCT)	⊕⊕◯◯ Low[a,b]	
Deafness at 5 years	32 per 1,000	**36 per 1,000** (2 to 545)	**RR 1.11** (0.07 to 16.88)	59 (1 RCT)	⊕⊕◯◯ Low[a,b]	
Motor delay at 5 years	290 per 1,000	**70 per 1,000** (17 to 305)	**RR 0.24** (0.06 to 1.05)	60 (1 RCT)	⊕◯◯◯ Very low[a,b,c]	

Stem cell therapy as compared to usual care for prevention of BPD

Patient or population: BPD high risk preterm neonates
Setting: Tertiary Care/ Hospital
Intervention: Stem cell therapy
Comparison: Usual care for prevention of bronchopulmonary dysplasia

Outcomes	Anticipated absolute effects*(95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with usual care for prevention of BPD	**Risk with Stem cell therapy**				
Mental delay at 5 years	194 per 1,000	**15 per 1,000** (0 to 279)	**RR 0.08** (0.00 to 1.44)	59 (1 RCT)	⊕◯◯◯ Very low[a,b,c]	
Social delay at 5 years	129 per 1,000	**15 per 1,000** (1 to 281)	**RR 0.12** (0.01 to 2.18)	59 (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; **RR:** risk ratio

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

Explanations
a Downgraded by one level for inconsistency as for single study, inconsistency is inevaluable
b Downgraded by one level for imprecision due to small sample size and event rate not meeting the optimal information size criteria
c Downgraded by one level for serious indirectness due to indirectness in the measurement of outcome (parental assessment)

EVIDENCE PROFILE:

Stem cell therapy as compared to usual care for prevention of BPD in preterm infants

Certainty assessment							Summary of findings				
							Study event rates (%)			Anticipated absolute effects	
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	With usual care for prevention of BPD	With Stem cell therapy	Relative effect (95% CI)	Risk with routine care for prevention of BPD	Risk difference with Stem cell therapy
Bronchopulmonary dysplasia, any severity, at 36 weeks PMA											
66 (1 RCT)	not serious	Inevaluable[a]	not serious	Serious[b]	none	⨁⨁◯◯ Low[a,b]	32/33 (97.0%)	30/33 (90.9%)	**RR 0.94** (0.83 to 1.07)	32/33 (97.0%)	**58 lower per 1,000** (from 165 lower to 68 higher)
Moderate to severe bronchopulmonary dysplasia											
66 (1 RCT)	not serious	Inevaluable[a]	not serious	Serious[b]	none	⨁⨁◯◯ Low[a,b]	17/33 (51.5%)	13/33 (39.4%)	**RR 0.76** (0.44 to 1.30)	17/33 (51.5%)	**124 lower per 1,000** (from 288 lower to 155 higher)
Composite outcome of mortality or moderate to severe BPD at 36 weeks' PMA											
66 (1 RCT)	not serious	Inevaluable[a]	not serious	Serious[b]	none	⨁⨁◯◯ Low[a,b]	18/33 (54.5%)	16/33 (48.5%)	**RR 0.88** (0.56 to 1.38)	18/33 (54.5%)	**65 lower per 1,000** (from 240 lower to 207 higher)
Mortality at discharge											
66 (1 RCT)	not serious	Inevaluable[a]	not serious	Serious[b]	none	⨁⨁◯◯ Low[a,b]	1/33 (3.0%)	3/33 (9.1%)	**RR 2.81** (0.33 to 24.16)	1/33 (3.0%)	**55 higher per 1,000** (from 20 lower to 702 higher)
Cerebral palsy at 5 years											
59 (1 RCT)	not serious	Inevaluable[a]	not serious	Serious[b]	none	⨁⨁◯◯ Low[a,b]	2/31 (6.5%)	0/28 (0.0%)	**RR 0.22** (0.01 to 4.41)	2/31 (6.5%)	**50 lower per 1,000** (from 64 lower to 220 higher)
Blindness at 5 years											
59 (1 RCT)	not serious	Inevaluable[a]	not serious	Serious[b]	none	⨁⨁◯◯ Low[a,b]	0/31 (0.0%)	0/28 (0.0%)	not estimable	0/31 (0.0%)	

Stem cell therapy as compared to usual care for prevention of BPD in preterm infants

Certainty assessment							Summary of findings				
Deafness at 5 years											
59 (1 RCT)	not serious	Inevaluable[a]	not serious	Serious[b]	none	⨁⨁◯◯ Low[a,b]	1/31 (3.2%)	1/28 (3.6%)	**RR 1.11** (0.07 to 16.88)	1/31 (3.2%)	**4 higher per 1,000** (from 30 lower to 512 higher)
Motor delay at 5 years											
60 (1 RCT)	not serious	Inevaluable[a]	Serious[c]	Serious[b]	none	⨁◯◯◯ Very low[a,b,c]	9/31 (29.0%)	2/29 (6.9%)	**RR 0.24** (0.06 to 1.05)	9/31 (29.0%)	**221 lower per 1,000** (from 273 lower to 15 higher)
Mental delay at 5 years											
59 (1 RCT)	not serious	Inevaluable	Serious[c]	Serious[b]	none	⨁◯◯◯ Very low[a,b,c]	6/31 (19.4%)	0/28 (0.0%)	**RR 0.08** (0.00 to 1.44)	6/31 (19.4%)	**178 lower per 1,000** (from -- to 85 higher)
Social delay at 5 years											
59 (1 RCT)	not serious	Inevaluable[a]	serious[b]	serious[c]	none	⨁◯◯◯ Very low[a,b,c]	4/31 (12.9%)	0/28 (0.0%)	**RR 0.12** (0.01 to 2.18)	4/31 (12.9%)	**114 lower per 1,000** (from 128 lower to 152 higher)

CI: confidence interval; **RR:** risk ratio

Explanations:

a Downgraded by one level for inconsistency as for single study, inconsistency is inevaluable
b Downgraded by one level for imprecision due to small sample size and event rate not meeting the optimal information size criteria
c. Downgraded by one level for serious indirectness due to indirectness in the measurement of outcome (parental assessment)

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. For prevention of BPD in high-risk preterm neonates:

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	Probably favors the comparison
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: Stem Cell Therapy is **not recommended** in routine practice for the prevention of BPD in high-risk preterm neonates. It may be used only in the context of rigorously conducted randomized controlled trials.	

*This judgment has been made as the evidence is inadequate in quality and quantity to determine the safety and efficacy of stem cell therapy for the prevention of BPD in high-risk preterm neonates.
**The committee opined that stem cell treatment is associated with large costs.

b. For treatment of established moderate and severe BPD in premature infants:

Desirable Effects	Don't know*
Undesirable Effects	Don't know*
Certainty of evidence	No included studies
Values	Probably no important uncertainty or variability
Balance of effects	Don't Know
Resources required	Large costs**
Certainty of evidence of required resources	Moderate
Cost effectiveness	Probably favors the comparison
Equity	Probably reduced
Acceptability	Probably yes
Feasibility	Probably yes
Recommendations: Stem Cell Therapy is **not recommended** in routine practice for the treatment of established moderate and severe BPD in premature infants. It may be used only in the context of rigorously conducted randomized controlled trials.	

*This judgment has been made as here is lack of evidence to determine the safety and efficacy of stem cell therapy in treatment of infants with moderate and severe BPD.
**The committee opined that stem cell treatment is associated with large costs.

E. CAVEATS IN EXISTING EVIDENCE:

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

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

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1. Omar SA, Abdul-Hafez A, Ibrahim S, et al. Stem-Cell Therapy for Bronchopulmonary Dysplasia (BPD) in Newborns. *Cells*; 11. Epub ahead of print 2022. DOI: 10.3390/cells11081275.
2. Bhunwal S, Mukhopadhyay K, Bhattacharya S, Dey P, Dhaliwal LK. Bronchopulmonary dysplasia in preterm neonates in a level III neonatal unit in India. Indian Pediatrics. 2018 Mar;55:211-5.
3. Ahn SY, Chang YS, Lee MH, et al. Stem cells for bronchopulmonary dysplasia in preterm infants: A randomized controlled phase II trial. *Stem Cells Transl Med*; 10. Epub ahead of print 2021. DOI: 10.1002/sctm.20-0330.
4. Ahn SY, Chang YS, Lee MH, Sung S, Kim AR, Park WS. Five-year follow-up of phase II trial of stromal cells for bronchopulmonary dysplasia. Thorax. 2023 Nov;78(11):1105-1110. doi: 10.1136/thorax-2022-219622. Epub 2023 Aug 21. PMID: 37604693.

5. SPINAL MUSCULAR ATROPHY

A. BACKGROUND:

Spinal muscular atrophy (SMA), an autosomal recessive neurodegenerative disorder of alpha motor neurons of spinal cord associated with progressive muscle weakness and hypotonia, is the most common genetic cause of infant mortality. The incidence of SMA is approximately 1 in 10,000 to 20,000 live births, and the carrier frequency is 1/40 to 1/70 in the general population.[1,2]

B. RECOMMENDATIONS:

Stem cell therapy is **not recommended*** in routine clinical practice for the treatment of spinal muscular atrophy.
Strength: Conditional#
Certainty of Evidence: Very low

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

*This recommendation is not applicable to gene therapy.

Rationale/Justification:

The evidence is inadequate in quantity and quality to determine the safety and efficacy of stem cell therapy in spinal muscular atrophy. 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 a single study with high risk of bias and small number of participants and/or events.

C. SUMMARY OF EVIDENCE

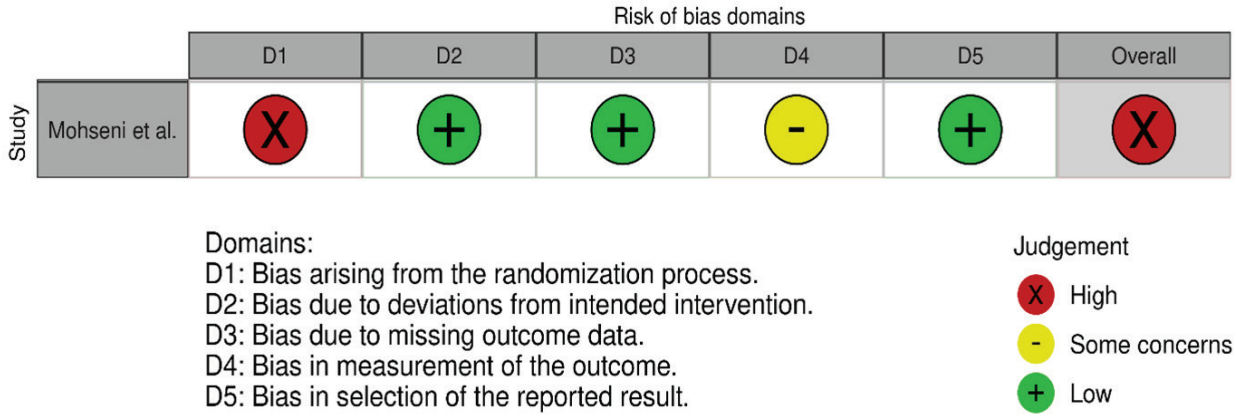
Key Question: In patients with spinal muscular atrophy, what is the efficacy and safety of stem cell therapy as compared to usual care?

Included Studies: An initial search based on MESH terms in 4 databases identified 965 records, 374 studies were manually screened after duplicate removal, and only 1 RCT fitting the inclusion criteria was included. This RCT was a Phase 1 clinical trial in patients with SMA1 who received side population adipose-derived mesenchymal stem cells (SPADMSCs).

Critical outcomes reviewed:

S. no.	Outcomes	What does it measure?
1.	Mortality	Number of deaths over a given period of time.
2.	Life expectancy	It is the survival measure that depends on the type of SMA and age of onset. In general, severe type of SMA has a life expectancy of less than 2 years.
3.	Ballard score	Scoring system used to assess baby's gestational age.
4.	Nerve conduction velocity (NCV)	It measures the flow of an electrical impulse through the nerves that can identify nerve damage.
5.	Serious Adverse Events	-

Risk of bias Assessment:



Desirable effects:

1. **Survival:** One of the patients in the intervention group was alive after 24 months of study follow-up. He is a non-sitter 62-month-old boy with appropriate weight gain and need for noninvasive ventilation (NIV) for about 8 h per day.

2. **Life expectancy:** The mean life expectancy of the intervention group was 11.17 months and the mean lifetime of the control group was 8.52 months.

3. **Ballard Score:** The mean Ballard score in the intervention arm was 10.6 immediately after the first injection as compared to a score of 9.2 in the control arm. The mean score just before the third injection in the transplantation group was 11 and in the control group was 9.6. Also,

the mean scores just after the third injection in the transplantation group was 11.6 and in the control group, was 9.6.

4. **Nerve conduction velocity studies:** The single trial involving 10 participants reporting the nerve conduction velocity yielded a mean difference of 0.40 (95 % CI: 0.116 to 0.684) in the median nerve, 0.10 (95% CI: -0.172 to 0.372) in the ulnar nerve, 0.26 (95% CI: -0.017 to 0.537) in the tibial nerve and -0.15 (95% CI: -0.339 to 0.039) in the peroneal nerve between the stem cell transplantation arm and the usual care arm. The difference in median nerve was statistically significant whereas the differences in ulnar nerve, tibial nerve and peroneal nerve were statistically non-significant.

Undesirable effects:

5. **Serious Adverse events:** The treatment was safe and well tolerated, without any adverse effect.

Summary of findings: GRADE

Stem cell therapy as compared to standard care for treating spinal muscular atrophy

Patient or population: Treating spinal muscular atrophy
Setting: Tertiary care/Hospital
Intervention: Stem cell therapy
Comparison: Standard care

Outcomes	Anticipated absolute effects*(95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with standard care	**Risk with stem cell therapy**				
Safety and tolerability of the allogeneic SPADMSCs assessed with: Neurological criteria of Ballard scores follow-up: mean 12 months		• The intervention was safe and well tolerated • Two patients had mild fever after intervention, but no significant complications or side effects		10 (1 RCT)	⊕◯◯◯ very low[a,b,c]	
Survival at 24 months follow up assessed with: Alive status follow-up: mean 24 months	At 24 months of follow up, one child survived in the intervention group and none in the control group.			10 (1 RCT)	⊕◯◯◯ very low[a,b,c]	
Life expectancy assessed with: Regular follow up		mean **3.05 Months higher**	-	10 (1 RCT)	⊕◯◯◯ very low[a,b,c]	
Ballard Score assessed with: After 3rd injection Scale from: -6 to 36		MD **2 higher**	-	10 (1 RCT)	⊕◯◯◯ very low[a,b,c]	
NCV: Median nerve assessed with: After 4 weeks of 3rd injection		MD **0.4 mV higher** (0.16 higher to 0.68 higher)	-	10 (1 RCT)	⊕◯◯◯ very low[a,b,c]	
NCV: Ulnar nerve assessed with: After 3rd injection		MD **0.1 mV higher** (0.172 lower to 0.372 higher)	-	10 (1 RCT)	⊕◯◯◯ very low[a,b,c]	
NCV: Tibial Nerve assessed with: After 3rd injection		MD **0.26 mV higher** (0.17 lower to 0.537 higher)	-	10 (1 RCT)	⊕◯◯◯ very low[a,b,c]	

Summary of findings: GRADE

Stem cell therapy as compared to standard care for treating spinal muscular atrophy

Patient or population: Treating spinal muscular atrophy
Setting: Tertiary care/Hospital
Intervention: Stem cell therapy
Comparison: Standard care

Outcomes	Anticipated absolute effects*(95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with standard care	**Risk with stem cell therapy**				
NCV: Peroneal nerve assessed with: After 3rd injection		MD **0.15 mV lower** (0.339 lower to 0.039 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

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. No information about allocation concealment
b. downgraded one level for inconsistency as single study is inevaluable for inconsistency
c. downgraded one level for imprecision due to small sample size

EVIDENCE PROFILE:
Stem cell therapy as compared to standard care for treating spinal muscular atrophy

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 care	With stem cell therapy		Risk with standard care	Risk difference with stem cell therapy
Safety and tolerability of the allogeneic SPADMSCs (follow-up: mean 12 months; assessed with: Neurological criteria of Ballard scores)											
10 (1 RCT)	serious[a]	Inevaluable[b]	not serious	Serious[c]	None	⊕◯◯◯ very low[a,b,c]	• The intervention was safe and well tolerated • Two patients had mild fever after intervention, but no significant complications or side effects				
Survival at 24 months follow up (follow-up: mean 24 months; assessed with: Alive status)											
10 (1 RCT)	serious[a]	Inevaluable[b]	not serious	Serious[c]	None	⊕◯◯◯ very low[a,b,c]	At 24 months of follow up., one child survived in the intervention group and none in the control group.				
Life expectancy (assessed with: Regular follow up)											
10 (1 RCT)	serious[a]	inevaluable	not serious	serious[b]	None	⊕◯◯◯ very low[a,b,c]	-	-	-	-	mean **3.05 Months higher** (0 to 0)
Ballard Score (assessed with: After 3rd injection; Scale from: -6 to 36)											
10 (1 RCT)	serious[a]	inevaluable	not serious	serious[b]	None	⊕◯◯◯ very low[a,b,c]	-	-	-	-	MD **2 higher** (0 to 0)
NCV: Median nerve (assessed with: After 4 weeks of 3rd injection)											
10 (1 RCT)	serious[a]	not serious	not serious	serious[b]	None	⊕◯◯◯ very low[a,b,c]	-	-	-	-	MD **0.4 mV higher** (0.16 higher to 0.68 higher)
NCV: Ulnar nerve (assessed with: After 3rd injection)											

EVIDENCE PROFILE:
Stem cell therapy as compared to standard care for treating spinal muscular atrophy

Certainty assessment							Summary of findings				
10 (1 RCT)	serious[a]	not serious	not serious	serious[b]	None	⊕◯◯◯ very low[a,b,c]	-	-	-	-	MD **0.1 mV higher** (0.172 lower to 0.372 higher)
NCV: Tibial Nerve (assessed with: After 3rd injection)											
10 (1 RCT)	serious[a]	not serious	not serious	serious[b]	None	⊕◯◯◯ very low[a,b,c]	-	-	-	-	MD **0.26 mV higher** (0.17 lower to 0.537 higher)
NCV: Peroneal nerve (assessed with: After 3rd injection)											
10 (1 RCT)	serious[a]	not serious	not serious	serious[b]	None	⊕◯◯◯ very low[a,b,c]	-	-	-	-	MD **0.15 mV lower** (0.339 lower to 0.039 higher)

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

Explanations

a. No information about allocation concealment
b. downgraded one level for inconsistency as single study is inevaluable for inconsistency
c. downgraded one level for imprecision due to small sample size

D. SUMMARY OF JUDGEMENTS:

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

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

*This judgment has been made as the evidence was inadequate in quantity and quality to determine the safety and efficacy of stem cell therapy in spinal muscular atrophy.
** The committee opined that stem cell treatment is associated with large costs.
#This recommendation is not applicable to gene therapy.

E. CAVEATS IN EXISTING EVIDENCE:

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

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

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REFERENCES:

1. Verhaart I.E.C, Robertson A, Wilson I.J, Aartsma-Rus A, Cameron S, Jones C.C, Cook S.F, Lochmülle, H. Prevalence, Incidence and Carrier Frequency of 5q-Linked Spinal Muscular Atrophy—A Literature Review. Orphanet J. Rare Dis. 2017, 12, 124.
2. Lunn M R, Wang C H. Spinal Muscular Atrophy. Lancet 2008, 371, 2120–2133.
3. Mohseni R, Hamidieh A, Shoae-Hassani A, Ghahvechi-Akbari M, Majma A, Mohammadi M, et al. An open-label phase 1 clinical trial of the allogeneic side population adipose-derived mesenchymal stem cells in SMA type 1 patients. Neurol Sci. 2022 Jan;43(1):399–410.

6. HYPOXIC ISCHEMIC ENCEPHALOPATHY

A. BACKGROUND:

Hypoxic-ischaemic encephalopathy (HIE) stands as a prominent cause of both mortality and enduring neurological consequences, impacting a substantial number of infants globally. Current therapeutic approaches for HIE are predominantly limited to cooling treatments. The exploration of stem cell-based therapies presents a promising avenue for addressing and potentially repairing damaged brain tissue.[1]

B. RECOMMENDATIONS:

Stem cell therapy is **not recommended** in routine clinical practice for the treatment of hypoxic ischemic encephalopathy.
Strength: Conditional[#]
Certainty of Evidence: No included studies

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

Rationale/Justification:

This recommendation has been made as there is lack of evidence to determine the safety and efficacy of stem cell therapy for treatment of hypoxic ischemic encephalopathy.

C. SUMMARY OF EVIDENCE:

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

Included Studies: The search strategy yielded 3175 search items. No completed RCTs, which were peer-reviewed and published for inclusion, were identified. The list of ongoing trials has been included in the supplement.

Critical outcomes reviewed:

S. no.	Outcomes	What does it measure?
1.	Mortality by one year	Risk of mortality by one year of age
2.	Adverse Neurodevelopmental outcome at 18-24 months	It measures the risk for neurological disabilities that causes physical, emotional and behavioral symptoms.
3.	Serious Adverse Events	-

Risk of Bias Assessment:

No evidence identified

Desirable Effects:

No evidence identified

Undesirable Effects:

No evidence identified.

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	No included studies
Values	Probably no important uncertainty or variability
Balance of effects	Don't Know
Resources required	Large costs**
Certainty of evidence of required resources	Moderate
Cost effectiveness	Probable favors the comparison
Equity	Probably reduced
Acceptability	Probably yes
Feasibility	Probably yes
Recommendations: Stem Cell Therapy is **not recommended** in routine practice for the treatment of Hypoxic ischemic encephalopathy. It may be used only in the context of rigorously conducted randomized controlled trials.	

*This judgment has been made as there is lack of evidence to determine the safety and efficacy of stem cell therapy for treatment of hypoxic ischemic encephalopathy.
** The committee opined that stem cell treatment is associated with large costs.

E. CAVEATS IN EXISTING EVIDENCE:

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

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

----**

REFERENCES:

1. Executive summary: Neonatal encephalopathy and neurologic outcome, second edition. Report of the American College of Obstetricians and Gynecologists' Task Force on Neonatal Encephalopathy. ObstetGynecol2014;123:896-901

7. OSTEOGENESIS IMPERFECTA

A. BACKGROUND:

Osteogenesis imperfecta (OI), or "brittle bone disease," is a condition of joint tissue with a wide range of symptoms and causes. OI affects 1 in 15,000 to 1 in 20,000 people. The disease has a wide variation in presentation. The most severe forms result in death of fetus in utero or immediately after birth. The milder versions of the disease affect the musculoskeletal system of the person. Clinical and MRI data are used to diagnose Osteogenesis imperfecta. Traditionally bisphosphonates, denosumab, and teriparatide are used to strengthen the bone and prevent frequent fractures with some success. The fractures are treated as required and the growing children are offered surgical treatment to treat or prevent severe deformities. Transforming growth factor, and gene-targeted methods are a few of the newer treatments that have shown promise in terms of preventing the disease from manifesting by correcting the genetic disorders.[1]

B. RECOMMENDATIONS:

Stem cell therapy is **not recommended** in routine clinical practice for the treatment of osteogenesis imperfecta.
Strength: Conditional[#]
Certainty of Evidence: No included studies

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

Rationale/Justification:
This recommendation has been made as there is lack of evidence to determine the safety and efficacy of stem cell therapy in treatment of osteogenesis imperfecta.

C. SUMMARY OF EVIDENCE:

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

Included Studies: Electronic database search identified a total of 592 studies. After removal of duplicates (n = 109), 483 studies were undertaken for title and abstract screening. A total of 33 studies were found eligible for full text screening. Out of these, 6 studies were identified which reported the use of stem cell therapy in osteogenesis imperfecta. However, none of these studies were randomized and apart from one study they had no control group. Hence, none of the studies qualified for inclusion as per the inclusion and exclusion criteria. Hence, no evidence could be generated, as none of the studies on stem cell therapy for patients of osteogenesis imperfecta were found eligible as per inclusion criteria.

Critical outcomes reviewed:

S. no.	Outcomes	What does it measure?
1.	Incidence/frequency of fracture	-
2.	Growth	It evaluates delayed growth/development including physical and neurological delays.
3.	Serious Adverse Events	-

Risk of Bias Assessment:

No evidence identified

Desirable Effects:

No evidence identified

Undesirable Effects:

No evidence identified

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	No included studies
Values	Probably no important uncertainty or variability
Balance of effects	Don't Know
Resources required	Large costs**
Certainty of evidence of required resources	Moderate
Cost effectiveness	Probable favors the comparison
Equity	Probably reduced
Acceptability	Probably yes
Feasibility	Probably yes
Recommendations: Stem Cell Therapy is **not recommended** in routine practice for the treatment of Osteogenesis imperfecta. It may be used only in the context of rigorously conducted clinical trials.	

*This judgment has been made as there is lack of evidence to determine the safety and efficacy of stem cell therapy in treatment of osteogenesis imperfecta.

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

E. CAVEATS IN EXISTING EVIDENCE:

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

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

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REFERENCES:

1. Milena Jovanovic, Gali Guterman-Ram, Joan C Marini, Osteogenesis Imperfecta: Mechanisms and Signaling Pathways Connecting Classical and Rare OI Types, Endocrine Reviews, Volume 43, Issue 1, February 2022, Pages 61–90, https://doi.org/10.1210/endrev/bnab017

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

- Autism Spectrum Disorder
- Cerebral Palsy

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

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IV. ANNEXURES

Annexure 1: CONTRIBUTORS

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Annexure 2: DECLARATION OF INTEREST (DoI)

Name	Declaration 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
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Dr. Satinder Aneja, Sharda University, Gr. Noida	None declared	Not applicable
Dr. Sheffali Gulati, All India Institute of Medical Sciences, New Delhi	None declared	Not applicable
Dr. Pratibha Singhi, Amrita Hospital, Faridabad	None declared	Not applicable
Dr. Suvarna Alladi, National Institute of Mental Health and Neuro Sciences (NIMHANS), Bangalore	None declared	Not applicable
Dr. Suvasini Sharma, Lady Hardinge Medical College (LHMC), New Delhi	None declared	Not applicable
Dr. Madhulika Kabra, Professor, Department of Pediatrics, New Delhi	None declared	Not applicable
Dr. Deepak Chawla, Professor | Department of Neonatology, Government Medical College and Hospital, Chandigarh	None declared	Not applicable
Dr. Ketan Kumar,Assistant Professor, Department of Pediatrics, AIIMS Bhubhaneshwar	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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