Evidence-based Guidelines for the use of Stem Cell Therapy

Pediatric Conditions Supplement

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Department of Health Research
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CONTENTS

ABBREVIATIONS

ABC	:	Adaptive Behaviour Composite
AEs	:	Adverse Events
ASD	:	Autism Spectrum Disorder
ASM	:	Anti-Seizure Medication
AUCB	:	Autologous Umbilical Cord Blood
BMMSCs	:	Bone Marrow Mesenchymal Stem Cells
BMMNCs	:	Bone Marrow Mononuclear Cells
BPD	:	Bronchopulmonary Dysplasia
CARS	:	Childhood Autism Rating Scale
CB	:	Cord Blood
CDCs	:	Cardiosphere-Derived Cells
CGI	:	Clinical Global Impression
CI	:	Confidence Interval
CP	:	Cerebral Palsy
DMD	:	Duchenne Muscular Dystrophy
DMSO	:	Dimethyl Sulfoxide
DSM-5	:	Diagnostic and Statistical Manual of Mental Disorders, 5th edition
DSM-IV	:	Diagnostic and Statistical Manual of Mental Disorders, 4th Edition
ECMO	:	Extracorporeal Membrane Oxygenation
EtD	:	Evidence to Decision
FEV	:	Forced Expiratory Volume
FVC	:	Forced Vital Capacity
GARS-II	:	Gilliam Autism Rating Scale-Second Edition
GW	:	Gestational Week
HINE	:	Hammersmith Infant Neurological Examination
HOPE	:	Halt Cardiomyopathy Progression
HRQoL	:	Health-Related Quality of Life
iNO	:	Inhaled Nitric Oxide
MD	:	Muscular Dystrophy
MDs	:	Mean Differences
MeSH	:	Medical Subject Heading
MSCs	:	Mesenchymal Stem/Stromal Cells
NCV	:	Nerve Conduction Velocity
NICU	:	Neonatal Intensive Care Unit
NIV	:	Non-Invasive Ventilation
NNTB	:	Numbers Needed to Treat for an Additional Beneficial Outcome
NNTH	:	Numbers Needed to Treat for an Additional Harmful Outcome
OI	:	Osteogenesis Imperfecta
PANDAS	:	Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal infection
PDD-NOS	:	Pervasive Developmental Disorder - Not Otherwise Specified
PedsQL	:	Pediatric Quality of Life Inventory
PICO	:	Population Intervention, Comparator and Outcome
PODCI	:	Pediatric Outcomes Data Collection Instrument
PRA	:	Panel Reactive Antibody
PRISMA	:	Preferred Reporting Items for Systematic Reviews and Meta-

		Analyses
PUL	:	Performance of Upper Limb
RCT	:	Randomized Controlled Trial
RDs	:	Risk Differences
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
SPA	:	Spinal Muscular Atrophy
SPADMSCs	:	Side Population Adipose-Derived Mesenchymal Stem Cells
TA	:	Tibialis Anterior
UCB	:	Umbilical Cord Blood
VABS	:	Vineland Adaptive Behaviour and Socialization subscale
VABS-3	:	Vineland Adaptive Behaviour Scale third edition
WHO	:	World Health Organization

1. AUTISM SPECTRUM DISORDER

i. **Key question in PICO format**

ii. **Search strategy**

iii. **PRISMA flow diagram**

iv. **Summary of included studies**

v. **Evidence to decision framework**

vi. **Data extraction**

vii. **List of excluded studies**

i. Key question in PICO format:

In patients with autism spectrum disorder (ASD), what is the efficacy and safety of stem cell therapy as compared to usual care?

Population: Children and adolescents with autism spectrum disorder
Intervention: Any stem cell and product derived from stem cells or their derivatives
Comparator: Usual Care/Conventional Care
Critical Outcomes: Childhood Autism Rating Scale (CARS), Vineland Adaptive Behavior Scales and Socialization Subscale (VABS SS); Safety: Serious Adverse Events (SAEs)

ii. Search Strategy (October 2023):

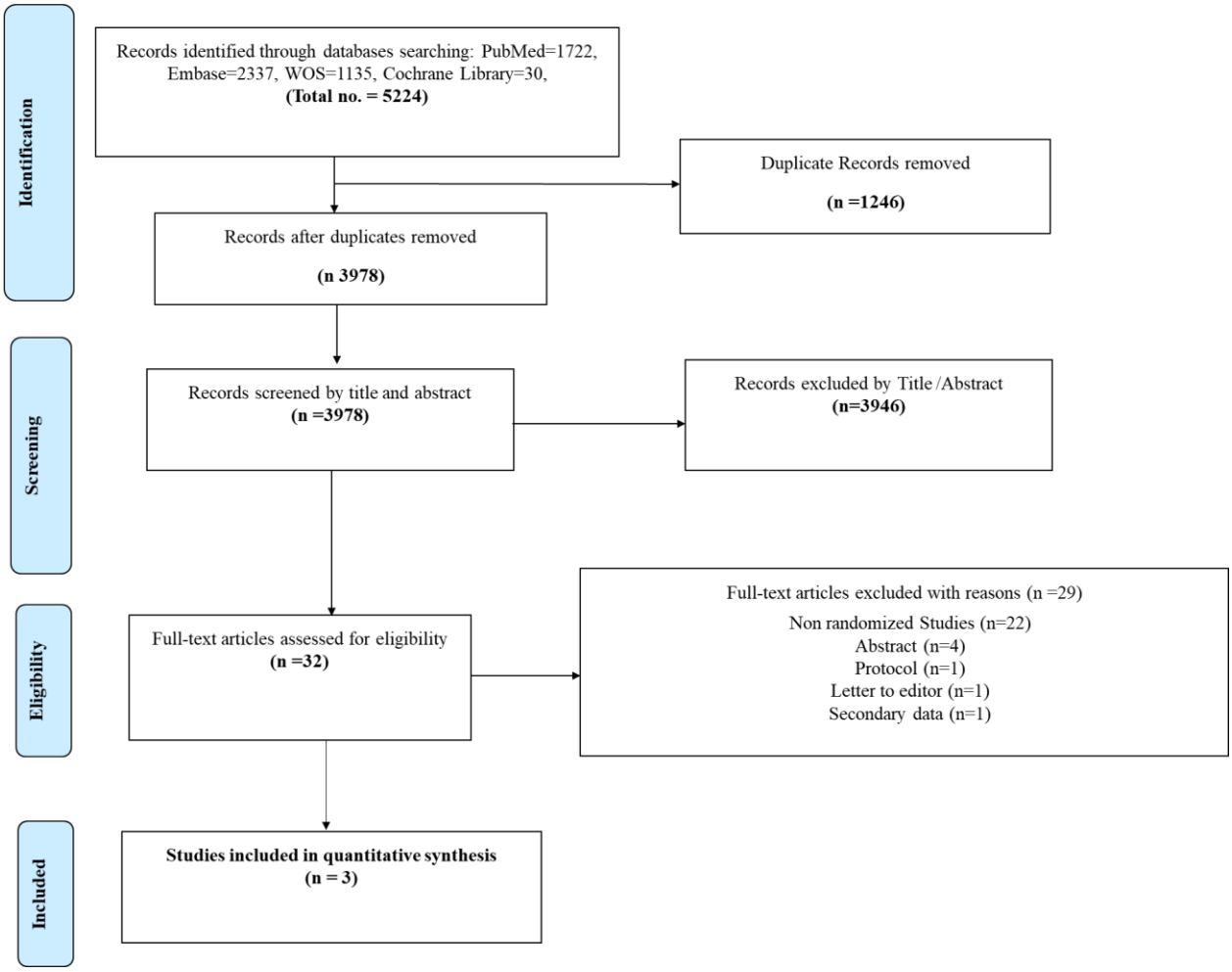
PubMed	((((((((("Child"[Mesh]) OR ("Adolescent"[Mesh])) OR ("Infant"[Mesh])) OR ("Pediatrics"[Mesh])) OR ("Minors"[Mesh])) OR ("Child, Preschool"[Mesh]))) OR ("Infant, Newborn"[Mesh])) OR ((preschool children) OR (preschool*) OR (pre-school*) OR (neonate) OR (newborn) OR (perinatal) OR (kids) OR (baby) OR (babies) OR (child*) OR (infant*) OR (pediatric*) OR (paediatric*) OR (adolescen*) OR (toddler*) OR (juvenil*))) AND ((((((("Autism Spectrum Disorder"[Mesh]) OR ("Autistic Disorder"[Mesh])) OR ("Asperger Syndrome"[Mesh])) OR ("Child Development Disorders, Pervasive"[Mesh])) OR ("Developmental Disabilities"[Mesh])) OR ((autism spectrum disorders) OR (ASD) OR (ASDs) OR (autism spectrum) OR (developmental disorder) OR (pervasive developmental disorders) OR (PDD) OR (PDDs) OR (disorders asperger) OR (syndrome asperger) OR (disease asperger) OR (disorder autistic) OR (disorder autistic spectrum) OR (childhood disintegrative disorder) OR (childhood pervasive disorder*) OR (disorder pervasive) OR (pervasive disorder*) OR (autis*) OR (asperger*) OR (kanner*)))) AND ((((((("Stem Cells"[Mesh] OR "Mesenchymal Stem Cell Transplantation"[Mesh] OR "Stem Cell Research"[Mesh] OR "Peripheral Blood Stem Cell Transplantation"[Mesh] OR "Cord Blood Stem Cell Transplantation"[Mesh] OR "Stem Cell Transplantation"[Mesh] OR "Hematopoietic Stem Cell Mobilization"[Mesh] OR "Hematopoietic Stem Cell Transplantation"[Mesh] OR "Mesenchymal Stem Cells"[Mesh]) OR ("Fetal Stem Cells"[Mesh])))))) OR ((stem cell) OR (stem cell transplantation) OR (stem cell treatment) OR (SCT) OR (cell transplantation) OR (HSCT) OR (hematopoietic stem cell mobilization) OR (peripheral stem cell transplantation) OR (PSCT) OR (bone marrow transplantation) OR (BMT) OR (placental blood stem cell transplantation) OR (umbilical cord stem cell transplantation) OR (mesenchymal stem cells) OR (Wharton's jelly-derived MSCs) OR (bone marrow-derived MSCs) OR (umbilical cord blood-derived MSCs) OR (BM-MSCs) OR (fetal derived MSCs) OR (foetal-derived MSCs) OR (embryonic stem cells) OR (allogeneic mesenchymal stem cells) OR (progenitor cells) OR (mother cells) OR (colony-forming unit) OR (erythroid

	progenitor cells) OR (pluripotent stem cells) OR (totipotent stem cells)))
EMBASE	(('child'/exp OR 'adolescent'/exp OR 'infant'/exp OR 'pediatrics'/exp OR 'minor (person)'/exp OR 'preschool child'/exp OR 'newborn'/exp) OR ('preschool children' OR neonate OR perinatal OR kids OR baby OR babies OR child* OR infant* OR pediatric* OR paediatric* OR adolescen* OR toddler* OR preschool* OR 'pre school*' OR juvenil*)) AND (('autism'/exp OR 'asperger syndrome'/exp OR 'developmental disorder'/exp) OR ('autism spectrum disorders' OR 'autism spectrum disorder' OR asd OR asds OR 'autism spectrum' OR 'developmental disorder' OR 'pervasive developmental disorders' OR 'pervasive disorder*' OR pdd OR pdds OR 'child development disorders, pervasive' OR 'autistic disorder' OR 'disorder autistic' OR 'disorder autistic spectrum' OR 'childhood disintegrative disorder' OR 'disorders asperger' OR 'syndrome asperger' OR 'disease asperger' OR autis* OR asperger* OR kanner*)) AND (('stem cell'/exp OR 'mesenchymal stem cell transplantation'/exp OR 'stem cell research'/exp OR 'peripheral blood stem cell transplantation'/exp OR 'cord blood stem cell transplantation'/exp OR 'stem cell transplantation'/exp OR 'mesenchymal stem cell'/exp OR 'fetalstem cell'/exp) OR ('stem cell transplantation' OR sct OR 'hematopoietic stem cell transplantation' OR 'hematopoietic stem cell mobilization' OR hsct OR 'peripheral stem cell transplantation' OR psct OR 'stem cell' OR 'bone marrow transplantation' OR bmt OR 'umbilical cord stem cell transplantation' OR 'stem cell treatment' OR 'mesenchymal stem cells' OR 'cell transplantation' OR 'whartons jelly derived mscs' OR 'bone marrow-derived mscs' OR 'umbilical cord blood-derived mscs' OR 'bmmscs' OR 'fetal derived mscs' OR 'embryonic stem cells' OR 'allogeneic mesenchymal stem cells' OR 'progenitor cells' OR 'mother cells' OR 'colony-forming unit' OR 'erythroid progenitor cells' OR 'pluripotent stem cells' OR 'totipotent stem cells'))
Web of Science	ALL=(child OR adolescent OR adolescen* OR Infant OR pediatrics OR pediatric* OR paediatric* OR minors OR "child, preschool" OR "preschool children" OR preschool* OR pre-school* OR "infant, newborn" OR infant* OR neonate OR newborn OR perinatal OR kids OR baby OR babies OR child* OR toddler* OR juvenil*) AND ALL=("autism spectrum disorder" OR "autism spectrum disorders" OR ASD OR ASDs OR "autism spectrum" OR "developmental disorder" OR "child development disorders, pervasive" OR "pervasive developmental disorder" OR PDD OR PDDs OR "asperger syndrome" OR "disorders asperger" OR "syndrome asperger" OR "disease asperger" OR "Autistic Disorder" OR "disorder autistic" OR "disorder autistic spectrum" OR "developmental disabilities" OR "childhood disintegrative disorder" OR "childhood pervasive disorder*" OR "pervasive disorder*" OR autis* OR asperger* OR kanner*) AND ALL=("stem cells" OR "stem cell" OR "stem cell transplantation" OR "stem cell treatment" OR SCT OR "cell transplantation" OR HSCT OR "hematopoietic stem cell transplantation" OR "hematopoietic stem cell mobilization" OR "stem cell research" OR "peripheral stem cell transplantation" OR PSCT OR "peripheral blood stem cell transplantation" OR "cord blood stem cell transplantation" OR "mesenchymal stem cells" OR "mesenchymal stem cell

	transplantation" OR "fetal stem cells" OR "bone marrow transplantation" OR BMT OR "placental blood stem cell transplantation" OR "umbilical cord stem cell transplantation" OR "umbilical cord blood-derived MSCs" OR "wharton's jelly-derived MSCs" OR "bone marrow-derived MSCs" OR "BM-MSCs" OR "fetal derived MSCs" OR "foetal-derived MSCs" OR "embryonic stem cells" OR "allogeneic mesenchymal stem cells" OR "progenitor cells" OR "mother cells" OR "colony-forming unit" OR "erythroid progenitor cells" OR "pluripotent stem cells" OR "totipotent stem cells")
Cochrane Library	1. MeSH descriptor: [Child] explode all trees 2. MeSH descriptor: [Adolescent] explode all trees 3. MeSH descriptor: [Infant] explode all trees 4. MeSH descriptor: [Pediatrics] explode all trees 5 .MeSH descriptor: [Minors] explode all trees 6 .MeSH descriptor: [Infant, Newborn] explode all trees 7. MeSH descriptor: [Child, Preschool] explode all trees 8. (preschool children OR preschool* OR pre-school* OR neonate OR newborn OR perinatal OR kids OR baby OR babies OR child* OR infant* OR pediatric* OR paediatric* OR adolescen* OR toddler* OR juvenil*) 9. #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 10. MeSH descriptor: [Autism Spectrum Disorder] explode all trees 11. MeSH descriptor: [Autistic Disorder] explode all trees 12. MeSH descriptor: [Asperger Syndrome] explode all trees 13. MeSH descriptor: [Child Development Disorders, Pervasive] explode all trees 14. MeSH descriptor: [Developmental Disabilities] explode all trees 15. (autism spectrum disorders OR ASD OR ASDs OR autism spectrum OR developmental disorder OR pervasive developmental disorder OR PDD OR PDDs OR childhood disintegrative disorder OR disorders asperger OR syndrome asperger OR disease asperger OR disorder autistic OR disorder autistic spectrum childhood disintegrative disorder OR childhood pervasive disorder* OR disorder pervasive OR pervasive disorder* OR autis* OR asperger* OR kanner*) 16. #10 OR #11 OR #12 OR #13 OR #14 OR #15 17. MeSH descriptor: [Stem Cells] explode all trees 18. MeSH descriptor: [Mesenchymal Stem Cell Transplantation] explode all trees 19. MeSH descriptor: [Peripheral Blood Stem Cell Transplantation] explode all trees 20. MeSH descriptor: [Cord Blood Stem Cell Transplantation] explode all trees 21. MeSH descriptor: [Stem Cell Transplantation] explode all trees 22. MeSH descriptor: [Hematopoietic Stem Cell Mobilization] explode all trees 23. MeSH descriptor: [Hematopoietic Stem Cell Transplantation] explode all trees 24. stem cell OR stem cell transplantation OR stem cell treatment OR SCT OR cell

	transplantation OR HSCT OR hematopoietic stem cell mobilization OR peripheral stem cell transplantation OR PSCT OR bone marrow transplantation OR BMT OR stem cell research OR placental blood stem cell transplantation OR umbilical cord stem cell transplantation OR mesenchymal stem cells OR fetal stem cells OR Wharton's jelly- derived MSCs OR bone marrow-derived MSCs OR umbilical cord blood-derived MSCs OR BM-MSCs OR fetal derived MSCs OR foetal-derived MSCs OR embryonic stem cells OR allogeneic mesenchymal stem cells OR progenitor cells OR mother cells OR colony- forming unit OR erythroid progenitor cells OR pluripotent stem cells OR totipotent stem cells 25. #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 26. #9 AND #16 AND #25

iii. PRISMA Flow Diagram:



iv. Summary of included studies:

RCTs from Iran[1] and USA[2,3] evaluated autologous bone marrow derived stem cells and umbilical cord blood total nucleated cells respectively. Sharifzadeh et al. 2020 was a parallel single-blinded RCT in children from Iran aged 5 to 15 years, with ASD diagnosed according to the DSM-5 criteria.[1] The mean (SD) age of the participants was 9.5 (2.1) years. A total of 36 children were randomly assigned to two groups- intervention & comparator group. The intervention group received two injections of autologous bone marrow mesenchymal stem cells (BMMSCs) through the intrathecal route during a period of one month. Both groups received ASD rehabilitation therapies in addition to risperidone (0.06 mg/kg/day), a second-generation antipsychotic agent used for the treatment of behavioral symptoms in children with ASD. All patients were followed-up for at least 12 months. The authors reported that 4 children revoked consent before receiving the allocated treatment; hence analysis of only 32 children was published. The main outcomes assessed were efficacy in terms of Childhood Autism Rating Scale (CARS) scores, Gilliam Autism Rating Scale-second edition (GARS-II) scores, CGI Severity of illness scores and CGI Global improvement scores. Both the total scores and subscales were evaluated at baseline, 6 months and 12 months after intervention. Safety was assessed by the frequency of side effects (injection related effects, such as hospital complications, short-term and long-term complications during the 12 months).

Dawson et al. 2020 was a randomized, double-blinded, study conducted in North Carolina, USA.[2] It evaluated a single intravenous autologous or allogeneic unrelated cord blood (CB) infusion versus placebo (TC199 + 1% DMSO) in children aged 2 to 7 years with ASD who met the DSM-5 diagnosis criteria. The mean (SD) age of the participants was 5.5 (1.7) years; and the gender ratio was 143 males: 37 females. The participants were allocated as intervention or comparator in a 2:1 ratio. Although the RCT was not described as cross-over trial, the authors mentioned that participants who randomly received cord blood cells at baseline, received placebo infusion after the primary outcome and was measured at 6 months post infusion and vice-versa. However, the publication did not mention any washout period, or other description related to a cross-over trial. Participants with an autologous CB received autologous cells and those without a suitable autologous CB unit received cells from a ≥4/6 HLA-matched, allogeneic unrelated donor. Efficacy was assessed through measurement of the change in the Vineland Adaptive Behavior Scale Third edition (VABS-3) score after 6 months. The VABS-3 is a caregiver interview measuring domains of adaptive functioning, socialization, communication, daily living skills, and motor skills. In this trial, it was recorded at baseline and at 6-month time point. In addition, the number of participants with "improvement in CGI scores" was also evaluated, although the definition of "improvement" was not specified. CGI-Improvement ratings were calculated after 6 months of treatment, using a seven-point scoring system; wherein a score of 1 represented marked improvement, and a score of 7 denoted worse than the baseline condition. Eye tracking as an index of attention to dynamic stimuli, post 6-month treatment was also assessed. Safety was assessed by the number of serious adverse events (SAEs) in the first 12 months post treatment and non-serious AEs in the first 6 months.

Chez et al. 2018 was a randomized, blinded, placebo-controlled, cross-over trial conducted in California, USA.[3] Children aged 2 to 7 years with ASD diagnosed by the DSM-IV criteria, were intravenously infused with either CB total nucleated count (>10 million/kg) or placebo (0.9% saline). The mean age of the participants was 4.5 years (range 2.4 to 6.8); and the gender ratio was 25 males: 4 females. Outcomes were evaluated at baseline, 12 weeks and 24 weeks. The participants were then infused with the opposite product, and the outcomes were evaluated again at 12- and 24- weeks post infusion. Although the trial was conducted as a cross-over study, there was no description of a washout period. Efficacy of treatment was expressed in terms of Vineland scores at baseline, 12 weeks and 24 weeks post treatment. In addition, CGI improvement at 12 and 24 weeks was also assessed. The safety was assessed by the number of SAEs and non-serious AEs in the first 6 months.

v. Evidence to Decision Framework:

QUESTION

Should Stem cell therapy vs. standard therapy be used for children with ASD?	
POPULATION:	Patients with ASD
INTERVENTION:	Stem cell therapy
COMPARISON:	Usual care
MAIN OUTCOMES:	Efficacy: Childhood Autism Rating Scale, Vineland Adaptive Behavior and Socialization subscales; Safety: Serious adverse events
SETTING:	Tertiary care/ Hospital
PERSPECTIVE:	Population
BACKGROUND:	The Autism Spectrum Disorders (ASD) includes Autism, Asperger Syndrome and Pervasive Developmental Disorders-Not Otherwise Specified (PDD-NOS). This spectrum of disorders is characterized by a triad of core symptoms that include: (a) qualitative impairment in social interaction, (b) delays in the development of communication, and (c) restrictive interests and/or repetitive body movements.[4] In addition to these behavioural deficits and excesses, many individuals with ASD have co-morbid intellectual disability and psychiatric conditions.[5] The range of behavioural deficits/excesses and co-morbid conditions greatly complicates treatment planning, particularly with respect to identifying treatment priorities.
CONFLICT OF INTERESTS:	None

ASSESSMENT

Problem Is the problem a priority?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	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%.[6] 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%).[7]	

Desirable Effects How substantial are the desirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
●Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	**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. **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. **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 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 to 0.02) at the end of 12 months. The differences were statistically non-significant at both time points.	

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ●Small ○ Moderate ○ Large ○ Varies ○ Don't know	Sharifzadeh et al[1] 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[2] 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[3] 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.	

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ● Low ○ Moderate ○ High ○ No included studies	The certainty of evidence is low due to small sample size and heterogeneity in the outcomes reported by the trials.	
Values Is there important uncertainty about or variability in how much people value the main outcomes?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability	Main outcome is improvement in cognitive, communication and social abilities which is highly valued by most people. Research identified self-help skills as the top priority, as these were considered to be the foundation for all other skills.[8,9]	
Balance of effects Does the balance between desirable and undesirable effects favor the intervention or the comparison?		

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ● Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	Based on limited evidences, it is unclear if benefits of stem cell therapy outweigh the harms.	
Resources required How large are the resource requirements (costs)?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
● Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	No direct evidence of the resources required in stem cell transplantation in patients with ASD has been identified. On a global scale, the most frequently reported range for single treatment is $10,000 to $20,000. However, the cost is influenced by several factors such as type, quality, source of stem cells, the condition to be treated, and the location of the treatment facility.[10]	

Certainty of evidence of required resources What is the certainty of the evidence of resource requirements (costs)?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Very low ○ Low ● Moderate ○ High ○ No included studies	No research evidence was identified.	The GDG members were fairly certain about the large resources required for providing stem cell treatment.
Cost effectiveness Does the cost-effectiveness of the intervention favor the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Favors the comparison ● Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ No included studies	No research evidence for stem cell therapy was identified.	The intervention was not found to be effective and hence the committee deferred to comment on cost effectiveness.

Equity What would be the impact on health equity?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Reduced ● Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	No research evidence was identified.	As stem cell therapy is an expensive treatment offered only at tertiary centers, it is likely to reduce equity.
Acceptability Is the intervention acceptable to key stakeholders?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	Despite uncertainty regarding the medical risks and benefits associated with stem cell injections, parents may still consider undergoing treatment in private, unregulated clinics for their autistic children in the hope for improvement.	
Feasibility Is the intervention feasible to implement?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**

○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	No research evidence was identified.	Feasible to implement in tertiary care centers.

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	**Trivial**	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Trivial	**Small**	Moderate	Large		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	**Low**	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	**Does not favor either the intervention or the comparison**	Probably favors the intervention	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	**Large costs**	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	**Moderate**	High			No included studies

COST EFFECTIVENESS	Favors the comparison	**Probably favors the comparison**	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	No included studies
EQUITY	Reduced	**Probably reduced**	Probably no impact	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Use only in the context of rigorously conducted RCTs	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	○	●	○	○	○

CONCLUSIONS

Recommendation

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.

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.

vi. Data Extraction:

Data Extraction Methods:

Two reviewers independently extracted the data from the included studies. A pre-tested data extraction form was used to record the extracted data. The following data was extracted:

1. Publication details: Author name, citation, publication date, country of study, study design
2. Participants: Number, age, gender
3. Intervention: Type, dosage and route
4. Comparison: Type, dosage and route
5. Outcomes: Efficacy, safety

For estimating efficacy, total scores of various scales were noted and the mean difference with 95% CI in the treatment group versus the control group at different time-points was calculated using the Cochrane Collaboration Review Manager software version. This was done independently by both the authors. For the safety outcomes, frequency of adverse events was compared in both the groups and results were expressed as risk ratio (RR) with 95% CI.

Data Extraction Sheet:

The three RCTs recorded multiple efficacy outcome measures. However, the scales used and methods to report results, were different. Therefore, none of the data from the included studies that reflected efficacy, could be pooled though meta-analysis. Therefore, the results of individual studies are summarized below.

Table 1: Efficacy outcome: Sharifzadeh et al. 2020[1]

	Stem cell therapy (n=14)	**Comparator (n=18)**	**Effect size**
	Autologous BMMSCs + ASD rehabilitation therapies and risperidone	**ASD rehabilitation therapies and risperidone**	**Mean Difference [95% CI]**
CARS Total Scores			
Mean (SD) at baseline	36.36 (3.61)	38.72 (7.23)	-2.36 [-6.20, 1.48]
Mean (SD) at 6 months	34.43 (3.98)	36.94 (7.42)	-2.51 [-6.52, 1.50]
Mean (SD) at 12 months	30.75 (5.00)	35.06 (8.45)	-4.31 [-9.01, 0.39]

GARS-II Total Scores			
Mean (SD) at baseline	19.29 (6.79)	19.11 (6.93)	0.18 [-4.61, 4.97]
Mean (SD) at 6 months	16.64 (6.90)	17.44 (6.14)	-0.80 [-5.39, 3.79]
Mean (SD) at 12 months	13.21 (7.08)	14.33 (6.34)	-1.12 [-5.85, 3.61]
CGI Severity of illness Scores			
Mean (SD) at baseline	4.43 (0.65)	4.44 (0.86)	-0.01 [-0.53, 0.51]
Mean (SD) at 6 months	3.71 (0.61)	4.06 (0.87)	-0.35 [-0.86, 0.16]
Mean (SD) at 12 months	3.07 (0.73)	3.78 (1.11)	-0.71 [-1.35, -0.07]
CGI Global improvement Scores			
Mean (SD) at baseline	3.36 (0.50)	3.56 (0.51)	-0.20 [-0.55, 0.15]
Mean (SD) at 6 months	3.29 (0.47)	3.72 (0.83)	-0.43 [-0.89, 0.03]
Mean (SD) at 12 months	2.86 (0.77)	3.56 (1.29)	-0.70 [-1.42, 0.02]

Table 2: Efficacy outcome: Dawson et al. 2020[2]

	Stem cell (n=119)	**Comparator (n=57)**	**Effect size**
	Autologus or Allogeneic Umbilical Cord Blood total nucleated cell at baseline followed by placebo infusion	**placebo infusion at baseline followed by CB infusion.**	
Mean change in Vineland scores (VABS-3 SS) at 6-months	3.13 (8.76)	1.98 (8.41)	1.15 [-1.54, 3.84]*
No. with improvement in CGI scores at 6 months	64/117	29/57	1.08 [0.79, 1.46]**
Eye Tracking (Attention to dynamic stimuli) post 6 months treatment ***	No data shown	No data shown	

*Mean Difference [95% CI]

** RR [95% CI]

***No data were shown, but the authors reported RR 1.43 [1.15, 1.78]

Table 3: Efficacy outcome: Chez et al. 2018[3]

	Autologous umbilical cord blood (AUCB) n=14*	Placebo n=15*	Effect size
Mean (SD) Vineland scores (total)			
Baseline	68.50 (14.18)	77.17 (15.60)	-8.67 [-19.51, 2.17]
12 weeks	68.89 (15.25)	78.525 (13.13)	-9.63 [-20.02, 0.76]
24 weeks	68.91 (16.66)	78.08 (12.96)	-9.17 [-20.09, 1.75]
Mean (SD) Adaptive Behavior Composite (ABC)			
Baseline	66.00 (12.20)	74.27 (16.00)	-8.27 [-18.59, 2.05]
12 weeks	66.15 (15.05)	74.93 (12.40)	-8.78 [-18.86, 1.30]
24 weeks	67.57 (16.52)	75 (11.60)	-7.43 [-17.88, 3.02]
Communication			
Baseline	66.00 (15.56)	79.60 (17.18)	-13.60 [-25.52, -1.68]
12 weeks	67.79 (16.21)	81.47 (14.63)	-13.68 [-24.95, -2.41]
24 weeks	68.00 (18.82)	83.33 (15.46)	-15.33 [-27.92, -2.74]
Motor			
Baseline	73.86 (13.17)	77.67 (13.57)	-3.81 [-13.54, 5.92]
12 weeks	73.5 (15.09)	79.57 (11.51)	-6.07 [-15.89, 3.75]
24 weeks	69.71 (15.10)	76.67 (7.61)	-6.96 [-15.76, 1.84]
Daily			
Baseline	68.14 (15.55)	77.13 (16.61)	-8.99 [-20.69, 2.71]
12 weeks	68.13 (15.32)	78.13 (14.21)	-10.00 [-20.78, 0.78]
24 weeks	70.36 (17.73)	77.33 (15.30)	-6.97 [-19.06, 5.12]
CGI improvement after 12 weeks (n/Total)	(n/Total)	(n/Total)	OR [95% CI]
1. Expressive	15/29	15/29	1.00 [0.36, 2.80]
2. Receptive	17/29	14/29	1.52 [0.54, 4.28]
3. Social	16/29	14/29	1.32 [0.47, 3.70]
CGI improvement after 24 weeks			
1. Expressive	16/29	16/29	1.00 [0.63, 1.59]

2. Receptive	18/29	17/29	1.06 [0.70, 1.61]
3. Social	18/29	16/29	1.13 [0.73, 1.74]

*This study was a cross-over RCT. Therefore, the data should show 29 children in each arm; however, the authors have not shown it as such.

Safety outcomes:

Sharifzadeh et al. 2020[1] 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. 2020[2] reported the frequency of SAEs in both the groups of children; 3/119 (2.5%) of the children in the cord blood group experienced moderate SAEs while 3/61 (4.9%) in the control group experienced SAEs. For non-serious AE also, the proportion of children were comparable; 97/119 (81.5%) in the intervention group and 51/61 (83.6%) in the comparison group. These events were further categorized as episodes of mild, moderate and severe infusion reactions. These data are summarized in Table 4.

Chez et al. 2018[3] reported no serious adverse events in either group. This trial did not compare (non-serious) adverse events in the two groups but only reported them in the intervention group (Table 5). There were no observed allergic reactions or serious adverse events associated with the administration of cord blood cells.

Thus, the data of safety could not be pooled through meta-analysis.

Table 4: Summary of safety: Dawson et al. 2020[2]

No. of participants with events	**Autologus or Allogeneic Umbilical Cord Blood total nucleated cell at baseline followed by placebo infusion**	**Placebo infusion at baseline followed by CB infusion.**	**Effect size RR [95% CI]**
SAEs in first 12 months	3/119	3/61	0.51 [0.11, 2.46]
AEs in the first 6 months (Overall Frequency)	97/119	51/61	0.87 [0.42, 1.80]
1. Infusion reactions Mild	5/119	4/61	0.63 [0.16, 2.42]

2. Infusion reactions Moderate	3/119	0/61	3.70 [0.19, 72.70]
3. Infusion reactions Severe	4/119	0/61	4.79 [0.25, 90.47]
1. Psychiatric reactions Mild	52/119	27/61	0.98 [0.52, 1.82]
2. Psychiatric reactions Moderate	3/119	2/61	0.76 [0.12, 4.69]
3. Psychiatric reactions Severe	0/119	0/61	Not estimable

Table 5: Episodes of adverse events associated with cord blood infusion Chez et al. 2018[3]

Event	**No. of episodes**
Constitutional Symptoms	37
Skin and subcutaneous tissue disorders	3
Gastrointestinal disorders	26
Musculoskeletal and connective tissue disorder	0
Neurological disorders	0
Pain	0
Pulmonary/Upper respiratory disorders	11
Reproductive system and breast disorders	0
Psychiatric disorders	0
Renal and urinary disorders	9

vii. List of excluded studies:

No.	Citation	Reason for exclusion
1.	Bradstreet JJ, Sych N, Antonucci N, et al. Efficacy of fetal stem cell transplantation in autism spectrum disorders: an open-labeled pilot study. Cell Transplant. 2014;23 Suppl 1: S105-S112.	Non-randomized study
2.	Bansal H, Verma P, Agrawal A, Leon J, Sundell IB, Koka PS. A Short Study Report on Bone Marrow Aspirate Concentrate Cell Therapy in Ten South Asian Indian Patients with Autism. J Stem Cells. 2016;11(1):25-36.	Non-randomized study
3.	Carpenter KLH, Major S, Tallman C, et al. White Matter Tract Changes Associated with Clinical Improvement in an Open-Label Trial Assessing Autologous Umbilical Cord Blood for Treatment of Young Children with Autism. Stem Cells Transl Med. 2019;8(2):138-147. doi:10.1002/sctm.18-0251	Non-randomized study
4.	Chez M, Lepage C, Parise C, Dang-Chu A, Hankins A. A Randomized, Blinded, Placebo-controlled, Crossover Study to Assess the Efficacy of Stem Cells from Autologous Umbilical Cord Blood to Improve Language and Behavior in Children with Autism. Cytotherapy. 2016;18(6):S112.	Only abstract available
5.	Dawson G, Sun JM, Davlantis KS, et al. Autologous Cord Blood Infusions Are Safe and Feasible in Young Children with Autism Spectrum Disorder: Results of a Single-Center Phase I Open-Label Trial. Stem Cells Transl Med. 2017;6(5):1332-1339. doi:10.1002/sctm.16-0474	Non-randomized study
6.	Liu M, Lü Y, Huan Y, Ge R, Zhang J, Jiang S, et al. Safety and efficacy of cord blood mononuclear cells and umbilical cord mesenchymal stem cells therapy for childhood autism. Journal of Clinical Rehabilitative Tissue Engineering Research. 2011;15:4359-62.	Non-randomized study
7.	Liu WP, Wang J, Qu SQ, et al. Transplantation of human neural precursor cells in the treatment of children with pervasive developmental disorder. Zhongguo Dang Dai Er Ke Za Zhi. 2013;15(10):860-865.	Non-randomized study
8.	Lv YT, Zhang Y, Liu M, et al. Transplantation of human cord blood mononuclear cells and umbilical cord-derived mesenchymal stem cells in autism. J Transl Med. 2013;11:196. Published 2013 Aug 27.	Non-randomized study
9.	McLaughlin C, West T, Hollowell R, et al. Expanded Access Protocol of Umbilical Cord Blood Infusion for Children with Neurological Conditions: An Update. Stem Cells Transl Med. 2021;10(S1):S7-S8. doi:10.1002/sct3.13016	Protocol update

10.	Mucha, A., et al. Wharton's jelly-derived mesenchymal stem cells treatment in children with neurological diseases. Bone Marrow Transplant 53 (Suppl 1), 145–805 (2019)	Non randomized study
11.	Murias M, Major S, Compton S, et al. Electrophysiological Biomarkers Predict Clinical Improvement in an Open-Label Trial Assessing Efficacy of Autologous Umbilical Cord Blood for Treatment of Autism. Stem Cells Transl Med. 2018;7(11):783-791.	Non-randomized study
12.	Nguyen Thanh L, Nguyen HP, Ngo MD, et al. Outcomes of bone marrow mononuclear cell transplantation combined with interventional education for autism spectrum disorder [published correction appears in Stem Cells Transl Med. 2021 Dec;10(12):1721]. Stem Cells Transl Med. 2021;10(1):14-26.	Non-randomized study
13.	Nguyen LT, Nguyen PH, Hoang DM. 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. J Pediatr. 2021;230:271-272.	Letter to editor
14.	Petriv T, Tatarchuk M, Skuratov A, Rybachuk O, Tsymbaliuk V. Safety of Combined Autistic Spectrum Disorders Treatment with Umbilical Cord Mesenchymal Stem Cells Application: Clinical Investigation. Stem Cells Transl Med. 2021;10(S1): S10.	Only abstract available
15.	Ramírez Durán, Hernán & Lopez-Quezada, Jane & García, Sandra & de la Cruz-de la Cruz, Carlos & Velasco-Ruiz, Ileana & González-Llano, Oscar &Mancias-Guerra, Consuelo (2022). P106 Stem cell therapy in children with neurological disease: Association between adverse effects and total nucleated cells parameters.	Only abstract available
16.	Sharma AK, Gokulchandran N, Kulkarni PP, et al. Cell transplantation as a novel therapeutic strategy for autism spectrum disorders: a clinical study. Am J Stem Cells. 2020;9(5):89-100.	Non-randomized study
17.	Sharma A, Gokulchandran N, Chopra G, et al. Administration of autologous bone marrow-derived mononuclear cells in children with incurable neurological disorders and injury is safe and improves their quality of life. Cell Transplant. 2012;21 Suppl1: S79-S90.	Non-randomized study
18.	Sharma A, Gokulchandran N, Sane H, et al. Autologous bone marrow mononuclear cell therapy for autism: an open label proof of concept study. Stem Cells Int. 2013; 2013:623875.	Non-randomized study
19.	Siniscalco, D., et al. "Fetal stem cell transplantation in autism spectrum disorders."Cell Journal. 2016;18: 63-64.	Non-randomized study
20.	Simhal AK, Carpenter KLH, Kurtzberg J, et al. Changes in the geometry and robustness of diffusion tensor imaging networks: Secondary analysis from a randomized controlled trial of young	Secondary data

	autistic children receiving an umbilical cord blood infusion. Front Psychiatry. 2022; 13:1026279. Published 2022 Oct 20	
21.	Sun JM, Dawson G, Franz L, et al. Infusion of human umbilical cord tissue mesenchymal stromal cells in children with autism spectrum disorder. Stem Cells Transl Med. 2020;9(10):1137-1146.	Non-randomized study
22.	Tanchanco, Lourdes & Vera, Michelle & Bernal, Samuel & Bengzon, Alfredo. Effect of mesenchymal stem cell treatment on autism spectrum disorder. Cytotherapy. 2015;17. S39-S40.	Only abstract available
23.	Nguyen Thanh L, Nguyen HP, Ngo MD, et al. Outcomes of bone marrow mononuclear cell transplantation combined with interventional education for autism spectrum disorder [published correction appears in Stem Cells Transl Med. 2021 Dec;10(12):1721]. Stem Cells Transl Med. 2021;10(1):14-26.	Non-randomized study
24.	Villarreal-Martinez L, MartÍnez-Garza LE, Rodriguez-Sanchez IP, et al. Correlation Between $CD133^{+}$ Stem Cells and Clinical Improvement in Patients with Autism Spectrum Disorders Treated with Intrathecal Bone Marrow-derived Mononuclear Cells. InnovClinNeurosci. 2022;19(4-6):78-86.	Non-randomized study
25.	Zakerinia M, Kamgarpour A, Nemati H, et al. Intrathecal Autologous Bone Marrow-Derived Hematopoietic Stem Cell Therapy in Neurological Diseases. Int J Organ Transplant Med. 2018;9(4):157-167.	Non-randomized study
26.	Gomes, A., et al."Allogeneic Stem Cell Transplantation in Children with Autism." Haematologica. 2017;102: 865-865	Non-randomized study
27.	Tyumina O.V., Volchkov S.E., Ovchinnikov P.A., Trusova L.M., Bugakov A.I., Romanova S.A., Bumagina L.V., Galahova O. Clinical Evaluation of the efficiency of allogeneic cord blood transfusion in patients with autism // Genes & Cells. - 2020. - Vol. 15. - N. 3. - P. 74-79.	Non-randomized study
28.	Smirnov VN, Neznanov NG, Morozova YV, et al. Allogeneic umbilical cord blood cell therapy for children with autism: safety and efficacy of the method. ZhNevrolPsikhiatrIm S SKorsakova. 2021;121(11. Vyp. 2):31-37.	Non-randomized study
29.	Smirnov, V., et al. The use of allogeneic human umbilical cord blood cells in children with autism: the effectiveness and safety of the method. European Neuropsychopharmacology 2021; **53**: S250-S251.	Non-randomized study

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2. 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.
3. 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.
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9. Lavelle TA, Weinstein MC, Newhouse JP, Munir K, Kuhlthau KA, Prosser LA. Parent Preferences for Health Outcomes Associated with Autism Spectrum Disorders. Pharmacoeconomics. 2019; Apr;37(4):541-551. doi:10.1007/s40273-019-00783-8. PMID: 30895565; PMCID: PMC6469598.
10. https://www.startstemcells.com/stem-cell-therapy-cost.html

2. CEREBRAL PALSY

i. **Key question in PICO format**

ii. **Search strategy**

iii. **PRISMA flow diagram**

iv. **Summary of included studies**

v. **Evidence to decision framework**

vi. **Data extraction**

vii. **List of excluded studies**

i. Key Question in PICO format:

In patients with Cerebral Palsy, what is the efficacy and safety of stem cell therapy as compared to usual care?

Population: Children diagnosed with cerebral palsy
Intervention: Any stem cell and product derived from stem cells
Comparator: Usual Care/ Conventional Care
Critical Outcomes: Efficacy: Gross & fine motor function, Tonal ability, Functional ability
Safety: Serious Adverse Events (general & specific- e.g. stroke)
Additional/Important outcome: Quality of life, Cognition, Other adverse events

ii. Search Strategy (October 2023):

The MeSH and keywords search terms included were Stem Cells, Progenitor Cells, Mother Cells, CP, Dystonic-Rigid Cerebral Palsies. The terminologies (MeSH terms or entry terms) used were divided into two basic groups: study population related to cerebral palsy and terms describing or related to stem cell products (stem cell, regenerative cell, mesenchymal cell, cord blood cell, mononuclear cell). Using these MeSH/ entry terms and suitable Boolean operators, specific search strategies were developed for each search engine. The electronic search was later supplemented by a manual search of the references from the included articles, to identify additional articles. Truncation was used for terms like “stem cell” and “cerebral palsy” to widen the search and include all relevant keywords. The Boolean function “OR” was used to find articles that use different spellings. The only filter applied was to include human studies and randomized controlled trials. No limitation to the date of publishing was applied and articles up to September 2023 were included. All the articles were reviewed by two independent authors.

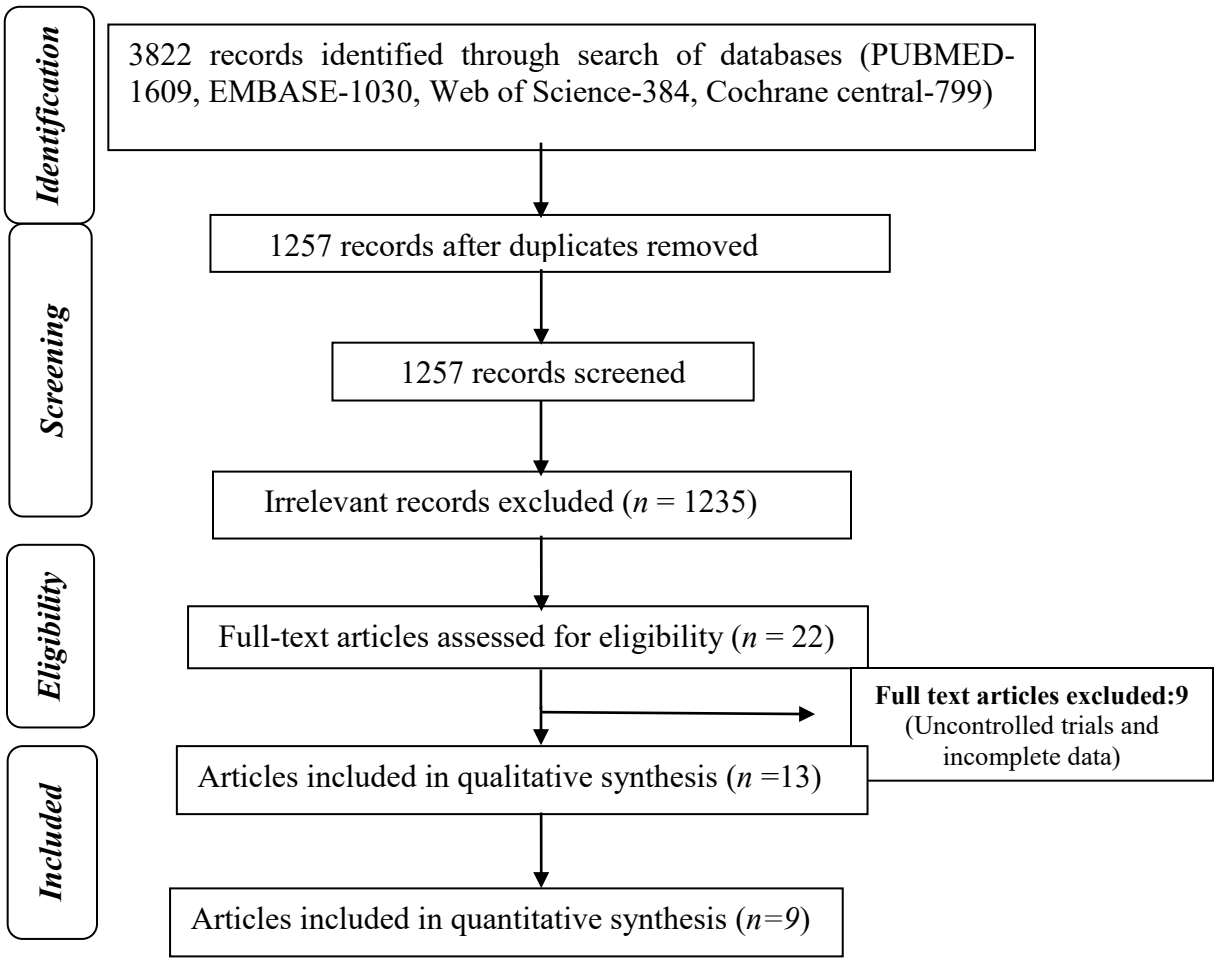
PubMed Search:

We used the advanced search syntax provided by the platform.

(("Cerebral Palsy"[Mesh]) OR ((CP (Cerebral Palsy)[Title/Abstract])) OR (Cerebral Palsy, Dystonic-Rigid[Title/Abstract])) OR (Cerebral Palsies, Dystonic-Rigid[Title/Abstract])) OR (Cerebral Palsy, Dystonic Rigid[Title/Abstract])) OR (Dystonic-Rigid Cerebral Palsies[Title/Abstract])) OR (Dystonic-Rigid Cerebral Palsy[Title/Abstract])) OR (Cerebral Palsy, Mixed[Title/Abstract])) OR (Mixed Cerebral Palsies[Title/Abstract])) OR (Mixed Cerebral Palsy[Title/Abstract])) OR (Cerebral Palsy, Monoplegic, Infantile[Title/Abstract])) OR (Monoplegic Infantile Cerebral Palsy[Title/Abstract])) OR (Infantile Cerebral Palsy, Monoplegic[Title/Abstract])) OR (Cerebral Palsy, Quadriplegic, Infantile[Title/Abstract])) OR (Quadriplegic Infantile Cerebral Palsy[Title/Abstract])) OR (Infantile Cerebral Palsy, Quadriplegic[Title/Abstract])) OR (Cerebral Palsy, Rolandic Type[Title/Abstract])) OR (Rolandic Type Cerebral Palsy[Title/Abstract])) OR (Cerebral Palsy, Congenital[Title/Abstract])) OR (Congenital Cerebral Palsy[Title/Abstract])) OR (Little Disease[Title/Abstract])) OR (Little's Disease[Title/Abstract])) OR (Spastic Diplegia[Title/Abstract])) OR (Diplegias, Spastic[Title/Abstract])) OR (Spastic Diplegias[Title/Abstract])) OR (Diplegia, Spastic[Title/Abstract])) OR (Monoplegic Cerebral Palsy[Title/Abstract])) OR (Cerebral Palsies, Monoplegic[Title/Abstract])) OR (Cerebral Palsy, Monoplegic[Title/Abstract])) OR (Monoplegic Cerebral Palsies[Title/Abstract])) OR (Cerebral Palsy, Athetoid[Title/Abstract])) OR (Athetoid

Cerebral Palsy[Title/Abstract])) OR (Cerebral Palsies, Athetoid[Title/Abstract])) OR (Cerebral Palsy, Dyskinetic[Title/Abstract])) OR (Cerebral Palsies, Dyskinetic[Title/Abstract])) OR (Dyskinetic Cerebral Palsy[Title/Abstract])) OR (Cerebral Palsy, Atonic[Title/Abstract])) OR (Atonic Cerebral Palsy[Title/Abstract])) OR (Cerebral Palsy, Hypotonic[Title/Abstract])) OR (Hypotonic Cerebral Palsies[Title/Abstract])) OR (Hypotonic Cerebral Palsy[Title/Abstract])) OR (Cerebral Palsy, Diplegic, Infantile[Title/Abstract])) OR (Diplegic Infantile Cerebral Palsy[Title/Abstract])) OR (Infantile Cerebral Palsy, Diplegic[Title/Abstract])) OR (Cerebral Palsy, Spastic[Title/Abstract])) OR (Spastic Cerebral Palsies[Title/Abstract])) OR (Spastic Cerebral Palsy[Title/Abstract]))) AND (("Stem Cells"[Mesh]) OR ((((((((((((((Cell, Stem[Title/Abstract]) OR (Cells, Stem[Title/Abstract])) OR (Stem Cell[Title/Abstract])) OR (Progenitor Cells[Title/Abstract])) OR (Cell, Progenitor[Title/Abstract])) OR (Cells, Progenitor[Title/Abstract])) OR (Progenitor Cell[Title/Abstract])) OR (Mother Cells[Title/Abstract])) OR (Cell, Mother[Title/Abstract])) OR (Cells, Mother[Title/Abstract])) OR (Mother Cell[Title/Abstract])) OR (Colony-Forming Unit[Title/Abstract])) OR (Colony Forming Unit[Title/Abstract])) OR (Colony-Forming Units[Title/Abstract])) OR (Colony Forming Units[Title/Abstract]))). This strategy searched for the specified terms using MeSH (Medical Subject Headings) terms in PubMed/MEDLINE. We adjusted the MeSH Terms as needed based on the controlled vocabulary of PubMed/MEDLINE. Similar search strategies were developed for other search engines

iii. PRISMA Flow Diagram:



iv. Summary of included studies:

Research studies were conducted in Iran, USA, China, and South Korea. Specifically, four studies were from Iran and USA, while five were from China, and four were from South Korea. Out of these, most studies were double-blind RCTs, except for a few like Huang et al. 2018 conducted a single-blind RCT, Sun et al. 2022 conducted an open-label RCT, and Luan et al. 2012 did not specify any blinding. Additionally, Sun et al. 2017 and Rah et al. 2017 utilized crossover study designs.[1-5]

Liu et al. 2017 examined two types of stem cells—bone marrow mesenchymal stem cells (BMMSCs) and bone marrow mononuclear cells (BMMNCs)—in children with CP, separating them into distinct groups for data extraction.[6] Similarly, Sun et al. 2022 evaluated cord blood and cord tissue-derived mesenchymal stromal cells, also grouping them separately for analysis.[2] Both Liu et al. 2017 and Amanat et al. 2021 focused on children with spastic CP.[6,7] Zarrabi et al. in 2022 carried out a double-blind, placebo-controlled study comparing umbilical cord blood mononuclear cells with a placebo.[8] In a 2020 study, Min et al. evaluated erythropoietin combined with allogenic umbilical cord blood in a placebo-controlled trial involving children with CP.[9] This review concentrated on the efficacy of stem cell therapy versus standard care, and extracted data from groups treated with allogenic umbilical cord blood (UCB) and placebo groups. Lv et al. 2023 conducted a phase 1/2 open-label RCT administering neural stem cells intranasally. Despite a higher risk of bias and its uniqueness as the only trial using the intranasal route and neural stem cells, this study was included in the analysis.[10]

The sample sizes of the studies varied from 36 to 105 participants, with publication dates 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 below 5 years of age.

Study	Type of study and Population	Intervention (I)	Comparison (C)	Outcomes (including SAE)	Comments
Huang et al. 2018, China (IV)[1]	Placebo-controlled, observer-blind RCT Children between 3 to 12 years of age	hUCB-MSC 4 intravenous infusions (n=27)	Placebo (0.9% saline) (n=27)	Change in GMFM-88 total score at 3 months from baseline: 4.59±1.352 in intervention and 1.74 ±2.02 in control group Change in GMFM-88 total score at 6 months from baseline:7.62±2.444 in intervention and 2.96 ±1.664 in control group Change in GMFM-88 total score at 12 months from baseline:10.27±2.964 in intervention and 4.75 ±1.456 in control group Change in GMFM-88 total score at 24 months from baseline:12.66±3.432 in intervention and 4.81	Flow cytometry for cell surface markers done Scales used- -GMFM-88 -CFA Follow up was done at- 0,3, 6, 12, 24 months. Change score has been reported.

				±2.028 in control group Change in CFA total score at 3 months: 7.2±3.796 in intervention and 2.9±1.716 in control group Change in CFA total score at 6 months: 12.0±5.044 in intervention and 5.5±2.704 in control group Change in CFA total score at 12 months: 18.9±5.98 in intervention and 8.07±2.808 in control group Change in CFA total score at 24 months:25.0±6.396 in intervention and 10.6±3.38in control group No SAE at 24-month follow-up URI: 10 (I), 8 (C); Diarrhoea: 5 (I), 6 (C); Anorexia: 3 (I), 1 (C); Constipation: 2 (I), 2 (C); Urticaria: 0 (I), 1 (C)	
Liu et al. 2017, China (IT)[6]	Double blind RCT 105 patients, 6 to 150 months with spastic cerebral palsy, randomly assigned to three groups: the BMMSC group, the BMMNC group and the control group (35 in each group).	Bone marrow MNCs BMMSC (n=35) BMMNC (n=35) 4 intrathecal injections	Bobath therapy (n=35)	GMFM total score in BMMSC group at baseline: 95.21±32.69 GMFM total score in BMMSC group at 3 months:113.15±34.93 GMFM total score in BMMSC group at 6 months:122±35.50 GMFM total score in BMMSC group at 12 months: 127.03±35.80 GMFM total score in BMMNC group atbaseline:95.68±30.79 GMFM total score in BMMNC group at 3 months: 99.47±30.89 GMFM total score in BMMNC group at 6 months:104.76±31.39 GMFM total score in BMMNC group at 12 months:111.91±31.68 GMFM total score in control group at baseline:95.26±29.19 GMFM total score in control group at 3 months: 97.34±28.96 GMFM total score in control group at 6 months: 99.86±28.48 GMFM total score in control group at 12	Two children in the BMMSC group and one child in the BMMNC group left due to parental withdrawal. Scales used- -GMFM -FMFM Fever: 3-BMMNC 2- BMMSC Signs of low ICP: 6-BMMNC 4- BMMSC No serious adverse Reactions in any group. *Change in values not given

				months:102.51±28.30 FMFM total score in BMMSC group at baseline: 40.45±18.31 FMFM total score in BMMSC group at 3 months:52.94±20.94 FMFM total score in BMMSC group at 6 months:69.76±21.67 FMFM total score in BMMSC group at 12 months: 79.39±21.95 FMFM total score in BMMNC group at baseline:40.56±17.57 FMFM total score in BMMNC group at 3 months: 44.03±17.99 FMFM total score in BMMNC group at 6 months:48.38±18.47 FMFM total score in BMMNC group at 12 months:52.59±18.89 FMFM total score in control group at baseline:40.43±15.88 FMFM total score in control group at 3 months: 42.91±15.84 FMFM total score in control group at 6 months:44.77±16.27 FMFM total score in control group at 12 months:46.71±16.07	

Gu et al. 2020, China (IV)[11]	-Double blind placebo controlled RCT -40 patients, 2 to 12 years with spastic cerebral palsy (20 in each group)	hUCB-MSC 4 intravenous infusions (n=20)	Placebo (n=19)	Change in GMFM-88 total score at 3 months from baseline: 32.053±22.626 in intervention and 15.700±29.682 in control group Change in GMFM-88 total score at 6 months from baseline:59.00±40.261 in intervention and 28.900±38.750 in control group Change in GMFM-88 total score at 12 months from baseline:64.526±43.2 in intervention and 36.800±38.72 in control group Change in CFA total score at 3 months from baseline: 17.947±14.594 in intervention and 7.425±12.393 in control group Change in CFA total score at 6 months from baseline: 23.790±16.605 in intervention and 11.925±14.638 in control group Change in CFA total score at 12 months from baseline: 25.737±17.366 in intervention and 15.175±17.032in control group Change in ADL score from baseline to 3 months: 12.447±9.486 in intervention and 5.975±8.019 in control group Change in ADL score from baseline to 6 months: 21.053±12.584 in intervention and 10.125±10.125 in control group Change in ADL score from baseline to 12 months: 22.974±12.918in intervention and 12.775±11.092 in control group	GMFM-88 CFA ADL Retrospective registration of trial. Study duration not mentioned. Specific inclusion criteria not given. URI: 10 (I), 14 (C) Diarrhoea: 6(I), 9 (C) Fever: 7 (I), 4 (C) Vomiting: 5 (I), 3 (C) Constipation: 1 (I), 3 (C) Change score given
Rah et al. 2017, S. Korea (IV)[5]	Randomized, double-blind, cross-over study. 57 patients, 2 to 10 years with spastic cerebral palsy.	G-CSF followed by Intravenous infusion of mobilized peripheral blood mononuclear cells (mPBMCs)	Placebo	Change in neurodevelopment test scores according to randomization: GMFM-88: 0.3725 in intervention and 0.4000 in control arm PEDI-self-care: 0.4928 in intervention and 0.5180 in control arm QUEST: 1.3392 in intervention and 1.0815 in control arm Improvement in cognitive function: 23 children in	Method of randomization not mentioned. Although, it was mentioned as double blinded in title but who was blinded not mentioned in

	G-CSF was given for 5 days. One month later (M1), recipients were randomized to receive either mPBMCs or a placebo infusion, and these treatment groups were switched at 7 months (M7) and observed for another 6 months (M13).			intervention and 31 in control arm	methods. This was a cross-over study and both the groups received intervention and placebo. Outcome measures were not assessed separately before crossover. Transient hemoglobinuria (n = 3) and abdominal pain (n = 1) were reported during the mPBMC infusion.
Amanat et al. 2021, Iran (IT)[7]	Multicenter randomized double-blind sham-controlled trial 72 patients, 4 to 14 years with spastic cerebral palsy (36 in each group)	hUCB-MSC, Single dose of 2×10^7 cells via intrathecal route (n=36)	Sham controlled (n=36)	Mean changes in GMFM-66 from Baseline to 3 months: 6.85±16.39 in intervention and 2.03±15.32 in control arm Baseline to 6 months: 11.27±16.10 in intervention and (-)0.58±14.49 in control arm Baseline to 12 months: 10.65±16.10 in intervention and 1.23±13.97 in control arm Mean changes in MAS from Baseline to 3 months: (-)1.0±0.90 in intervention and (−)0.66±0.99 in control arm Baseline to 6 months: (-)1.26±0.93 in intervention and (−)0.69±1.04 in control arm Baseline to 12 months: (-)1.0±0.94 in intervention and (−)0.28±1.02 in control arm	5 lost follow-up or withdrew consent. Fever: 2 (I), 0 (C) Irritability: 6 (I), 3 (C) Headache: 5 (I), 1 (C) Low back pain: 8 (I), 0 (C) Vomiting: 1 (I), 0 (C) No SAE were reported.

				Mean changes in PEDI from Baseline to 6 months: PEDI total: 6.08± 10.39 in intervention and 5.09±11.44 in control arm Baseline to 12 months: PEDI total: 8.53±10.86 in intervention and 1.58±11.87 in control arm Mean changes in CPQoL from Baseline to 6 months: CPQoL total: 12.5±45.15 in intervention and (-)18.3±55.95 in control arm Baseline to 12 months: 0.05±46.42 in intervention and (−)29.3±89.84	
Sun et al. 2022, USA (IV)[2]	Open label RCT 68 patients, 2 to 5 years with spastic cerebral palsy	Umbilical cord blood (1) the AlloCB group received 10 ×10^7 total nucleated cells per kg at baseline (n=20) (2) hCT-MSC group received 2×10^6 at baseline, 3months, and 6months (n=23)	Natural history control group received 10×10^7AlloCB TNC/kg at 12months (n=25)	Changes in GMFM-66 from baseline to 12 months AlloCB: 9.5±6.39 hCT-MSC: 7.5±5.87 Control: 6.7±4.97 Changes in PDMS from baseline to 12 months AlloCB: 3.6±7.40 hCT-MSC: 3.2±5.75 Control: 0.2±4.21 No serious infusion related reactions in any group	Allo CB group Fever: 1 Tachycardia:1 Cough:2 Dyspnea:1 Hypoxia:1 hCT-MSC group Fever: 1 Vomiting:2 Dyspnea:1 Hypoxia:2
Kang et al. 2015, S Korea (IV or IA)[12]	Randomized, placebo-controlled, double-blind trial -34 patients, 6 months to 20 years with spastic cerebral palsy	hUCB intravenous (15) or intra-arterial (2) routes (n=17)	Placebo (n=17) (IV-14, IA-3)	Change from baseline to 3 months GMFM: 3.65±4.83 in intervention and 2.61±2.70 in control arm GMPM: 3.76±4.05 in intervention and 3.7±2.46 in control arm WeeFIM: 1.59±3.15 in intervention and 1.12±5.53 in control arm Change from baseline to 6 months GMFM: 7.08 ±7.34 in intervention and 3.85±3.73 in control arm	URI: 7 (I), 4(C) Fever: 6 (I), 7(C) Vomiting: 5 (I), 1(C) Irritability: 3 (I), 2(C) Urticaria: 4 (I), 2(C) No SAEs

	(17 in each group)			GMPM: 8.54±5.99 in intervention and 2.60±2.92 in control arm PEDI self-care: 4.41±1.25 in intervention and 4.88±0.98 in control arm BSID: Mental score:8.94±8.24 in intervention and 9.82±8.48 in control arm Mental score:3.25±4.2 in intervention and 3.12±3.69 in control arm	
Luan et al. 2012, China (Intraventricular)[3]	-Single blind RCT -94 children with CP	Neural (fetal brain) progenitor cells Intraventricular route (n=45)	Standard care (n=49)	The scores improved per month were 2.22 ± 3.54 (PDMS-FM) and 0.31 ± 0.52 (GMFM) before intervention, and 2.17±3.27 (PDMS-FM) and 5.35±2.67 (GMFM) within 1 month after intervention. SAE: Frontal hemorhhage:1 Facial weakness:1	Six patients developed fever. No control data given in table-9
Sun et al. 2017, USA (IV)[4]	Double-blind, placebo-controlled, crossover study 63 children ages 1 to 6 years with CP	hUCB Single intravenous (n=32)	Placebo (n=31)	Change in score from baseline to 1-year GMFM-66 score was 7.5±6.8 in intervention group and 6.9±5.5 in the placebo group PDMS-2: The median change from baseline did not differ significantly between randomized groups (ACB 1.0, IQR 24.5 to 4.5 vs. placebo 20.5, IQR 24.0 to 2.0	Two unplanned interim analyses were conducted for the primary endpoint. No SAEs reportedUrticaria-1 (I)
Min et al. 2013, S Korea (IV)[13]	Placebo-controlled, double-blind RCT 96 children with CP	The first group received UCB potentiated with rhEPO (n-31). The second group received rhEPO (n-33) Intravenous route	Placebo (n-32)	Change scores from baseline to 3 months GMPM: 11.5±8.4 in pUCB, 7.5±4.56 in EPO and 8.1±6.84 in control group GMFM: 6.5±5.04 in pUCB, 6.8±4.56 in EPO and 6.4±3.99 in control group BSID-II Mental scale raw score: 12±7.84 in pUCB, 7.4±5.13 in EPO and 5.8±4.56 in control group BSID-II Motor scale raw score: 9.5±10.64 in pUCB, 4.8±4.56 in EPO and 4.3±4.56 in control group WeeFIM: 0.9±1.68 in pUCB, 0.0±0.57 in EPO and 0.6±1.14 in control group Change scores from baseline to 6 months GMPM: 14.5±10.08 in pUCB, 9.2±4.56 in EPO and	Nine dropped out Ten serious adverse events that required the hospitalization of nine patients were reported. The death of a 25-month-old female patient occurred in the pUCB group at 14 weeks post-treatment

				9.6±6.84 in control group GMFM: 9.1±6.72 in pUCB, 9.0±6.27 in EPO and 7.8±5.13 in control group BSID-II Mental scale raw score: 17.6±10.08 in pUCB, 11.5±7.41 in EPO and 9.9±9.12 in control group BSID-II Motor scale raw score: 11.7±11.2 in pUCB, 5.6±4.56 in EPO and 5.2±5.13 in control group WeeFIM: 1.3±1.68 in pUCB, 0.1±1.14 in EPO and 0.4±1.14 in control group Pneumonia, seizures, influenza, UTI and death in 1,0,1,0,1 and 2,1,0,0,0 and 1,0,1,1,0 in pUCB, EPO and control groups	(unrelated). Serious adverse events: Gp:1-3 Gp:2-3 Gp:3-3 Other events URI: 18, 19, 21 Fever: 12,4,8 Diarrhoea: 6,2,2 Pneumonia: 6,0,0 Vomiting: 6,5,2 Constipation: 5,4,5
Min et al. 2020 S Korea (IV)[9]	Randomized, blinded, placebo-controlled, Study 88 children aged 10 months–6 years with CP (gp-A: 22, gp B-24, gp C-20, gp D-22)	Four groups: (A) UCB+EPO, (B) UCB +placebo EPO, (C) placebo UCB+EPO, and (D) placebo UCB +placebo EPO. UCB: single dose IV EPO: six doses	Placebo (n-22)	Change scores from baseline to 3 months GMPM: 13.11±2.77 in A, 3.42±3.52 in B, 1.80±3.10 in C, and 1.93±4.77 in D group GMFM: 5.23±3.29 in A, 4.25±3.33 in B, 6.85±5.44 in C, and 5.05±4.74 in D group BSID-II Mental scale raw score: 7.55±5.78 in A, 9.33±9.21 in B, 8.90±6.07 in C, and 8.14±6.48 in D group BSID-II Motor scale raw score: 5.14±8.64 in A, 4.33±4.36 in B, 5.80±7.92 in C, and 4.50±5.54 in D group Change scores from baseline to 6 months GMPM: 3.90±3.71 in A, 4.93±4.55 in B, 2.43±3.6 in C, and 2.42±5.5 in D group GMFM: 6.50±3.33 in A, 6.92±5.39 in B, 10.20±6.75 in C, and 6.86±5.40 in D group BSID-II Mental scale raw score: 12.86±8.60 in A, 13.38±10.58 in B, 16.0±11.61 in C, and 10.50±7.70 in D group BSID-II Motor scale raw score: 4.91±7.28 in A, 5.96±4.94 in B, 9.05±9.04 in C, and 3.36±13.34 in D group Change scores from baseline to 12 months	Eleven serious AEs were reported. No death SAEs A-3; B-1, C-2, D-4 AEs A-42, B-38, C-41, D-35

				GMPM: 6.8±6.11 in A, 5.58±6.41 in B, 3.67±4.86 in C, and 2.34±5.78 in D group GMFM: 8.86±5.04 in A, 9.33±7.93 in B, 13.30±8.23 in C, and 8.27±6.06 in D group BSID-II Mental scale raw score: 21.18±16.35 in A, 19.91±13.27 in B, 23.95±18.13 in C, and 15.05±11.42 in D group BSID-II Motor scale raw score: 8.45±8.74 in A, 9.05±9.84 in B, 12.40±10.62 in C, and 7.18±6.72 in D group	
Zarrabi et al. 2022, Iran (IT)[8]	Multi-center, randomized, double-blind study 72 children, aged 4-14 years with spastic CP (36 in each group)	A single dose UCB-MNCs (n-36) Intrathecal route	Placebo(n-36)	Change scores from baseline to 3 months GMFM-66: 9.17±8.41 in intervention and 2.03±15.32in control MAS: (-) 0.97±3.0 in intervention and (−) 0.66±0.99in control Change scores from baseline to 6 months GMFM-66: 11.26±8.78 in intervention and (-) 0.58±14.49in control MAS: (-) 0.91±2.72 in intervention and (−) 0.69±1.04 in control PEDI: 8.77±12.27 in intervention and 5.09±11.44 in control CPQoL: (-) 8.42±60.73 in intervention and (-) 18.3±55.95in control Change scores from baseline to 12 months GMFM-66: 9.62±8.78 in intervention and 1.23±13.97in control MAS: (-) 0.87±2.66 in intervention and (−) 0.28±1.02 in control PEDI: 9.95±12.91 in intervention and 1.58±11.87 in control CPQoL: (-) 5.33±59.17 in intervention and (−) 29.3±89.84 in control	The NCT no and control data of this study and study by Amanat and colleagues are exactly similar Total 30 adverse events Fever- I-2; C- 0 Headache- I-9; C- 1 Irritability- I-7; C- 3 Low back pain- I-11; C- 0 Vomiting- I-1; C- 0 No SAEs were reported
Lv et al. 2023 China	Open label randomized controlled	Neural stem cells from aborted fetal	Standard therapy (n-10)	Baseline assessment in intervention group GMFM-88: 52.41±24.44 ADL: 34.54±20.90	Seizure: I-1, C-0 Nasal mucosa hemorrhage: I-1, C-

(IN)[10]	trial 25 children, aged 3-12 years with spastic CP	brain Intranasal, 3 doses (n-15)		SDSC: 49.43±14.27 FMFM: 24.00±15.85 Baseline assessment in control group GMFM-88:47.43±27.30 ADL: 40.65±31.72 SDSC: 47.90±19.81 FMFM: 26.50±14.99 Follow up assessment in intervention group (24 months) GMFM-88:74.95±23.84 ADL: 61.68±26.16 SDSC: 39.14±9.77 FMFM: 36.56±17.86 Follow up assessment in control group (24 months) GMFM-88:41.94±24.50 ADL: 32.81±20.09 SDSC: 47.50±18.54 FMFM: 24.56±14.25	0 Fever: I-2, C-0 No severe AEs related to the intranasal delivery

v. Evidence to Decision Framework:

Should stem cell therapy vs. standard therapy be used for cerebral palsy?	
POPULATION:	Cerebral Palsy
INTERVENTION:	Stem cell therapy
COMPARISON:	Control/ Usual care
MAIN OUTCOMES:	GMFM; CFA; PEDI; WeeFIM; BSID; CPQoL; PDMS; MAS; Fever; Vomiting; Serious adverse effects; GMPM
SETTING:	In children with Cerebral Palsy
PERSPECTIVE:	Population

BACKGROUND:	The term 'Cerebral Palsy' is defined as a group of permanent disorders in the development of movement and posture, that cause activity limitation and are attributed to non-progressive insults to the developing fetal or infant brain. The motor impairment of cerebral palsy is often accompanied by sensory disturbances, perception, intellectual disability, communication, behavior, 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 to 3.88].[14]
CONFLICT OF INTERESTS:	None

ASSESSMENT

Problem Is the problem a priority?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Cerebral palsy (CP) is one of the most common cause of motor deficiency in childhood, with an approximate prevalence of 2 to 3 per thousand live births.[15]	
Desirable Effects How substantial are the desirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**

● Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	**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-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 (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. **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. **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. **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. **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. **BSID Mental scale:** Evidence from 3 trials involving 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. **CP Quality of Life (QoL):** Evidence from 2 trials involving 99 participants reported the CP QoL 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. **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.

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ○ Moderate ○ Large ● Varies ○ Don't know	The likelihood of having an adverse event appears variable for stem cell therapy when compared to usual care [RR=0.72 (0.25 to 2.04)].	

Study[9,13]	Intervention	Control
Pneumonia	1	1
Influenza	1	1
Death	1	0
UTI	0	1
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

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

● Very low ○ Low ○ Moderate ○ High ○ No included studies	The overall certainty of evidence is very low due to high risk of bias in the trials as well as inconsistency and imprecision in the effect shown by stem cell therapy.	
Values Is there important uncertainty about or variability in how much people value the main outcomes?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability	Main outcome is improvement in motor function and quality of life valued by most patients, parents and caregivers.[16]	
Balance of effects Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**

○ Favors the comparison ○ Probably favors the comparison ● Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	It is less clear if benefits of stem cell intervention outweigh the harms, based on limited evidence.	
Resources required How large are the resource requirements (costs)?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
● Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	No direct evidence identified.	
Certainty of evidence of required resources What is the certainty of the evidence of resource requirements (costs)?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Very low ○ Low ● Moderate ○ High ○ No included studies	No research evidence was identified.	The GDG is fairly confident that the required resources for stem cell therapy are large.

Cost effectiveness Does the cost-effectiveness of the intervention favor the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Favors the comparison ● Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ No included studies	No research evidence for stem cell therapy was identified.	The intervention was not found to be effective and hence the committee deferred to comment on cost effectiveness.
Equity What would be the impact on health equity?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Reduced ● Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	No research evidence was identified.	Due to expensive treatment of stem cell therapy offered only at tertiary care centres, it might reduce equity.
Acceptability Is the intervention acceptable to key stakeholders?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**

○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	A study done by Smith et al stated that people in the Australian CP community were supportive of Neural Stem Cell therapy even when ethical and practical considerations were provided.[17]	
Feasibility Is the intervention feasible to implement?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	No research evidence was identified.	Feasible to implement in tertiary care centers.

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	**Trivial**	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Trivial	Small	Moderate	Large		**Varies**	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies

VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	**Does not favor either the intervention or the comparison**	Probably favors the intervention	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	**Large costs**	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	**Moderate**	High			No included studies
COST EFFECTIVENESS	Favors the comparison	**Probably favors the comparison**	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	No included studies
EQUITY	Reduced	**Probably reduced**	Probably no impact	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	**Conditional recommendation against the intervention**	**Use only in the context of rigorously conducted RCTS**	**Conditional recommendation for either the intervention or the comparison**	**Conditional recommendation for the intervention**	**Strong recommendation for the intervention**
○	○	●	○	○	○

CONCLUSIONS

Recommendation

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 randomized controlled trials.

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.

vi. Data Extraction:

Data Extraction Methods:

A predesigned, standardized, well-structured proforma was developed for data extraction. Two investigators independently reviewed the eligible articles and extracted data from their full text. The extracted data included as much information available from the following:- administrative details: study author(s), published or unpublished, year of publication, year in which the study was conducted, presence of vested interest, details of other relevant papers cited; details of the study: study design, type, duration, and completeness of follow-up (e.g., greater than 80%), country and location of the study, informed consent, ethics approval; details of participants: sex, age, type of cerebral palsy, number of participants; details of interventions: initiation, dose, and duration of MSCs administration; details of outcomes as mentioned before as types of outcome measures. We resolved disagreements by discussion. We described ongoing studies identified by our search, when available, detailing the primary author, research question(s), methods, and outcome measures, together with an estimate of the reporting date. For any queries or additional data requirement, the study investigators/authors were contacted.

Measures of treatment effect

Treatment effect measures used were risk ratios (RRs), risk differences (RDs), numbers needed to treat for an additional beneficial outcome (NNTB) or numbers needed to treat for an additional harmful outcome (NNTH) for categorical variables, and mean differences (MDs) for continuous variables. Any within-group SEM reported in a trial was replaced by its corresponding SD, using the formula "SD = SEM × √n", where, n is the number of participants. Also, 95% confidence intervals (CIs) was reported for each statistics.

Unit of analysis issues

All RCTs in which the unit of allocation was the individual i.e. child with cerebral palsy were included.

Dealing with missing data

A dropout rate for each study was obtained. When a significant dropout rate (e.g. greater than 20%) was found, additional data was requested by contacting the study author(s). A sensitivity analysis was performed to evaluate the overall results with and without the inclusion of studies with a significant dropout rate. If a study reported outcomes, only for participants completing the trial or only for participants who followed the protocol, the study author(s) were contacted to provide additional information to facilitate an intention-to-treat analysis. In instances when this was not possible, a complete-case analysis was performed.

Data Extraction Sheet:

Study	**Huang et al. 2018[1]**	**Liu et al. 2017[6]**	**Gu et al. 2020[11]**	**Rah et al. 2017[5]**	**Amanat et al. 2021[7]**	**Sun et al. 2022[2]**
Study type	Placebo-controlled, observer-blind RCT	Prospective, double blind, randomised, parallel group Study	Double blind placebo controlled RCT	Randomized, double-blind, cross-over study.	Multi-center, population-based randomized double blind sham-controlled trial	Randomized, open-label
Number of participants	56, 2 lost to follow up before second dose	105, 35 in each group	40, 20 in each group	57 patients, 2 to 10 years with spastic cerebral palsy.	72, 36 in each arm	68 children
Countries and setting	China	China	China	S Korea	Iran	USA
Duration of study Follow up (Post intervention)	24 months	12 months	12 months	12 months	12 months	12 months
Method of assessment of disease condition	Clinical	Clinical	Clinical	Clinical	Clinical	Clinical

Subgroup analysis within study	Outcomes at 3,6,12 and 24 months	Outcomes at 3,6, and months	Change in ADL, CFA and GMFM-88 at 3, 6, and 12 months	GMFM, PEDI and QUEST	Change in GMFM-66, MAS, PEDI and CPQoL at 3,6,12 months	Change in GMFM-66, PDMS-2 scores at 6 and 12 months
Inclusion criteria:	1. must be diagnosed with CP according to the national standard criteria including clinical history and physical examination, 2. aged between 3 and 12 years 3. no prior history of epilepsiagravior within 15 d of infusion and no seizure attack within 24 h of treatment, 4. must be able to comply with scheduled visits, treatment plans, physical examinations, laboratory tests, performance scales, and	1. children 6 to 150 months of age diagnosed with spastic CP, 2. gross motor function classification system (GMFCS) score between levels II and V, 3. no interferences due to other related treatments within 3 months prior to the enrolment and during the treatment, such as rehabilitation, traditional Chinese medicine, and surgery, and 4. parents voluntarily accepted UCMSC	Not given	2 and 10 years of age and had a non-severe type of CP	Males and females aged 4 to 14 years old who were diagnosed with spastic CP according to standard criteria, gross motor function classification system (GMFCS) level 2–5, and white matter lesions in brain magnetic resonance imaging (MRI) (e.g., periventricular leukomalacia) were included in the study.	Children aged 2 to 5 years with hypertonic CP due to hypoxic–ischemic encephalopathy, periventricular leukomalacia, or in utero stroke or bleed were eligible to participate if they were classified in Gross Motor Function Classification System (GMFCS) levels I to IV and their history and routine brain imaging did not suggest a genetic condition or brain malformation as the cause of their CP.

	other study procedures, and 5. showing willingness by signing the informed consent form, which was approved by the IRB for patients or parents.	transplantation therapy and agreed to cooperate with follow-up studies.				
Exclusion criteria:	Patients having liver or renal dysfunction at enrollment, any known genetic or immunological disorder, coagulation disorder, malignancy history, known allergy to more than 2 kinds of food or medications, current severe infection, or any other features that hampered the compliance with the requirement of the protocol	1. patients with a history of severe allergic or autoimmune disease, 2. patients with a history of intractable seizures, 3. patients with AIDS, hepatitis, or positive serology for syphilis, 4. patients with hereditary metabolic diseases of the nervous system, 5. patients with tumours and/or blood disease history,	1. grand mal seizure within 15 days or seizure attack within 24 h prior to treatment, 2. congenital heart disease, 3.any known genetic or immunological disease, 4. coagulation disorder, 5. serious liver or renal dysfunction, 6. malignancy history, 7. serious allergy history or known allergy to more than two kinds of food or medications,	Not mentioned	Individuals with other types of CP (e.g., athetoid, ataxic, or mixed CP), co-morbid neurological disorders (e.g., untreated epilepsy), or congenital infections (TORCH Syndrome) were excluded. Severe anemia (hemoglobins< 8 mg/dl), coagulation disorders, history of	autism spectrum disorder, legal blindness, hypsarrhythmia, intractable seizures, uncontrolled infections, progressive neurological or genetic diseases, impaired organ function, immunosuppression, classification in GMFCS level V, or hypotonic or ataxic CP without hypertonicity. Children with an available autologous umbilical cord blood unit or who had previously received any form of cellular

	according to the clinical judgment of the investigator were excluded from study.	and 6. patients who were rejected due to other serious diseases, such as brain tumours or mental and psychological disorders.	8. active serious infection, 9. participation in other clinical trials within 3 months prior to screening, and 10. any other concerns that hampered the compliance or safety as judged by the investigator.		malignancy, prior cell infusion, renal insufficiency, and liver failure were other exclusion criteria.	therapy were also ineligible.
Recruitment/ selection of patients:	From China	From China	From China	S Korea	From Iran	Duke University, North Carolina, USA
Intervention: Type of stem cells with method of their characterization, Route of administration, Dose	Human umbilical cord blood-derived MSCs (hUCB-MSCs) Flow cytometry for cell surface markers done Intravenous 2 doses, ($5X10^7$ cell/mL) each	BM-MSCs-BMMSC and BMMNC Flow cytometry for cell surface markers done Intrathecal 4 doses, 1×10^6/kg body weight each	hUCB-MSC 4 intravenous infusions Flow cytometry for cell surface markers done Intravenous 4 doses, 5×10^7/kg body weight each	peripheral blood mononuclear cells (mPBMCs Flow cytometry for cell surface markers done Intravenous $5.97 \pm 1.99 \times 10^8$ /Kg	Allogenic UCT-MSCs (cord blood) Flow cytometry for cell surface markers done Intrathecal Single dose of 2×10^7 cells	AlloCB TNCs and hCT-MSC Flow cytometry for cell surface markers done Intravenous One dose for AlloCB and 3 doses for hCT-MSC
Outcomes reported with time points	Change in GMFM-88 total score at 3 months from baseline: 4.59±1.352 in intervention and 1.74±2.02	GMFM total score in BMMSC group at baseline: 95.21±32.69 GMFM total score in BMMSC group	Change in GMFM-88 total score at 3 months from baseline: 32.053±22.626 in intervention and	Change in neurodevelopment test scores according to randomization: GMFM-88: 0.3725 in intervention and 0.4000 in	Mean changes in GMFM-66 from Baseline to 3 months: 6.85±16.39 in intervention and	Changes in GMFM-66 from baseline to 12 months AlloCB: 9.5±6.39 hCT-MSC: 7.5±5.87 Control: 6.7±4.97 Changes in PDMS from baseline to 12

	in control group Change in GMFM-88 total score at 6 months from baseline: 7.62±2.444 in intervention and 2.96±1.664 in control group Change in GMFM-88 total score at 12 months from baseline: 10.27±2.964 in intervention and 4.75±1.456 in control group Change in GMFM-88 total score at 24 months from baseline: 12.66±3.432 in intervention and 4.81±2.028 in control group Change in CFA total score at 3 months: 7.2±3.796 in intervention and 2.9±1.716 in control group Change in CFA	at 3 months: 113.15±34.93 GMFM total score in BMMSC group at 6 months: 122±35.50 GMFM total score in BMMSC group at 12 months: 127.03±35.80 GMFM total score in BMMNC group at baseline: 95.68±30.79 GMFM total score in BMMNC group at 3 months: 99.47±30.89 GMFM total score in BMMNC group at 6 months: 104.76±31.39 GMFM total score in BMMNC group at 12 months: 111.91±31.68 GMFM total score in control group at baseline:	15.700±29.682 in control group Change in GMFM-88 total score at 6 months from baseline: 59.00±40.261 in intervention and 28.900±38.750 in control group Change in GMFM-88 total score at 12 months from baseline: 64.526±43.2 in intervention and 36.800±38.72 in control group Change in CFA total score at 3 months from baseline: 17.947±14.594 in intervention and 7.425±12.393 in control group Change in CFA total score at 6 months from baseline: 23.790±16.605 in intervention and	control arm PEDI-self-care: 0.4928 in intervention and 0.5180 in control arm QUEST: 1.3392 in intervention and 1.0815 in control arm Improvement in cognitive function: 23 children in intervention and 31 in control arm	2.03±15.32 in control arm Baseline to 6 months: 11.27±16.10 in intervention and (-) 0.58±14.49 in control arm Baseline to 12 months: 10.65±16.10 in intervention and 1.23±13.97 in control arm Mean changes in MAS from Baseline to 3 months: (-) 1.0±0.90 in intervention and (–) 0.66±0.99 in control arm Baseline to 6 months: (-) 1.26±0.93 in intervention and (–) 0.69±1.04 in control arm Baseline to 12 months: (-) 1.0±0.94 in intervention	months AlloCB: 3.6±7.40 hCT-MSC: 3.2±5.75 Control: 0.2±4.21

	total score at 6 months: 12.0±5.044 in intervention and 5.5±2.704 in control group Change in CFA total score at 12 months: 18.9±5.98 in intervention and 8.07±2.808 in control group Change in CFA total score at 24 months: 25.0±6.396 in intervention and 10.6±3.38 in control group	95.26±29.19 GMFM total score in control group at 3 months: 97.34±28.96 GMFM total score in control group at 6 months: 99.86±28.48 GMFM total score in control group at 12 months: 102.51±28.30 FMFM total score in BMMSC group at baseline: 40.45±18.31 FMFM total score in BMMSC group at 3 months: 52.94±20.94 FMFM total score in BMMSC group at 6 months: 69.76±21.67 FMFM total score in BMMSC group at 12 months: 79.39±21.95	11.925±14.638 in control group Change in CFA total score at 12 months from baseline: 25.737±17.366 in intervention and 15.175±17.032 in control group Change in ADL score from baseline to 3 months: 12.447±9.486 in intervention and 5.975±8.019 in control group Change in ADL score from baseline to 6 months: 21.053±12.584 in intervention and 10.125±10.125 in control group Change in ADL score from baseline to 12 months: 22.974±12.918 in intervention and 12.775±11.092		and (−) 0.28±1.02 in control arm Mean changes in PEDI from Baseline to 6 months: PEDI total: 6.08± 10.39 in intervention and 5.09±11.44 in control arm Baseline to 12 months: PEDI total: 8.53±10.86 in intervention and 1.58±11.87 in control arm Mean changes in CPQoL from Baseline to 6 months: CPQoL total: 12.5±45.15 in intervention and (-) 18.3±55.95 in control arm Baseline to 12 months: 0.05±46.42 in intervention and (−)	

		FMFM total score in BMMNC group at baseline: 40.56±17.57 FMFM total score in BMMNC group at 3 months: 44.03±17.99 FMFM total score in BMMNC group at 6 months: 48.38±18.47 FMFM total score in BMMNC group at 12 months: 52.59±18.89 FMFM total score in control group at baseline: 40.43±15.88 FMFM total score in control group at 3 months: 42.91±15.84 FMFM total score in control group at 6 months: 44.77±16.27 FMFM total	in control group		29.3±89.84	

		score in control group at 12 months: 46.71±16.07				
Funding	Hubei Province Technology Fund No. 2013BCB002	The National Natural Science Foundation of China (NSFC), NO. 81571165	Science and Technology Research Project of Hubei Province, China (no. 2013BCB002), and Science and Technology Program of Shaanxi Province, China (no. 2016SF-145)	Korea Healthcare Technology R&D Project of the Ministry for Health & Welfare Affairs of the Republic of Korea (A101712)	Research Deputy of Tehran University of Medical Sciences (No funding no)	The Marcus Foundation, Atlanta, GA, USA

vii. List of Excluded Studies:

The following studies were excluded from quantitative synthesis (meta-analysis) because of the mentioned reasons: -

- Cox Jr et al. 2022, USA[18]: This study does not provide change in efficacy outcomes in placebo group at various time points before going to cross over and receiving stem cell therapy. So as such according to PICO strategy it does not get included in the review. Regarding safety, they didn't mention the adverse effects in placebo group in the initial 12 months. They only had a blanket statement which says no adverse effect of stem cell infusion. Hence, we can't compare between intervention and control group regarding safety or efficacy.
- Chen et al. 2013, China[19]: Non-randomized trial
- Liu et al. 2017[6] and Lv et al. 2023[10]: Change scores at the follow-up were not given.
- Rah et al. 2017[5]: This was a crossover study. Outcome measures were not assessed separately before crossover. Baseline characteristics not given.
- Luan et al. 2012[3]: They changed GMFM to goal attainment scale and changed quantitative variables to qualitative.
- Apart from these, the RCTs conducted by Amanat and Zarrabi et al, were probably three-arm single trial, because both these trials have the same clinical trial registration number and control data.[7,8] This raises the suspicion of salami slicing and even the authenticity of data represented in the studies. Similarly, in the RCT by Gu et al, change in GMFM-88 looks unrealistic (64.526 at 12 months). We tried to address these issues by sensitivity analysis.[11]

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3. MUSCULAR DYSTROPHY

i. **Key question in PICO format**

ii. **Search strategy**

iii. **PRISMA flow diagram**

iv. **Summary of included studies**

v. **Additional forest plots**

vi. **Evidence to decision framework**

vii. **Data extraction**

viii. **List of excluded studies**

i. Key question in PICO format:

In patients with muscular dystrophy, what is the efficacy and safety of stem cell therapy as compared to usual care?

Population: Patients with Muscular Dystrophy
Sub-groups: Age, Type of muscle dystrophy
Intervention: Any stem cell and product derived from stem cells or their derivatives
Comparator: Usual Care/ Conventional Care
Critical Outcomes: Improvement in Muscle strength beyond 6 months of treatment; Functional ability (like motor, independent ambulation, need for respiratory); Safety: Serious Adverse Events- mortality, tumor formation

ii. Search strategy

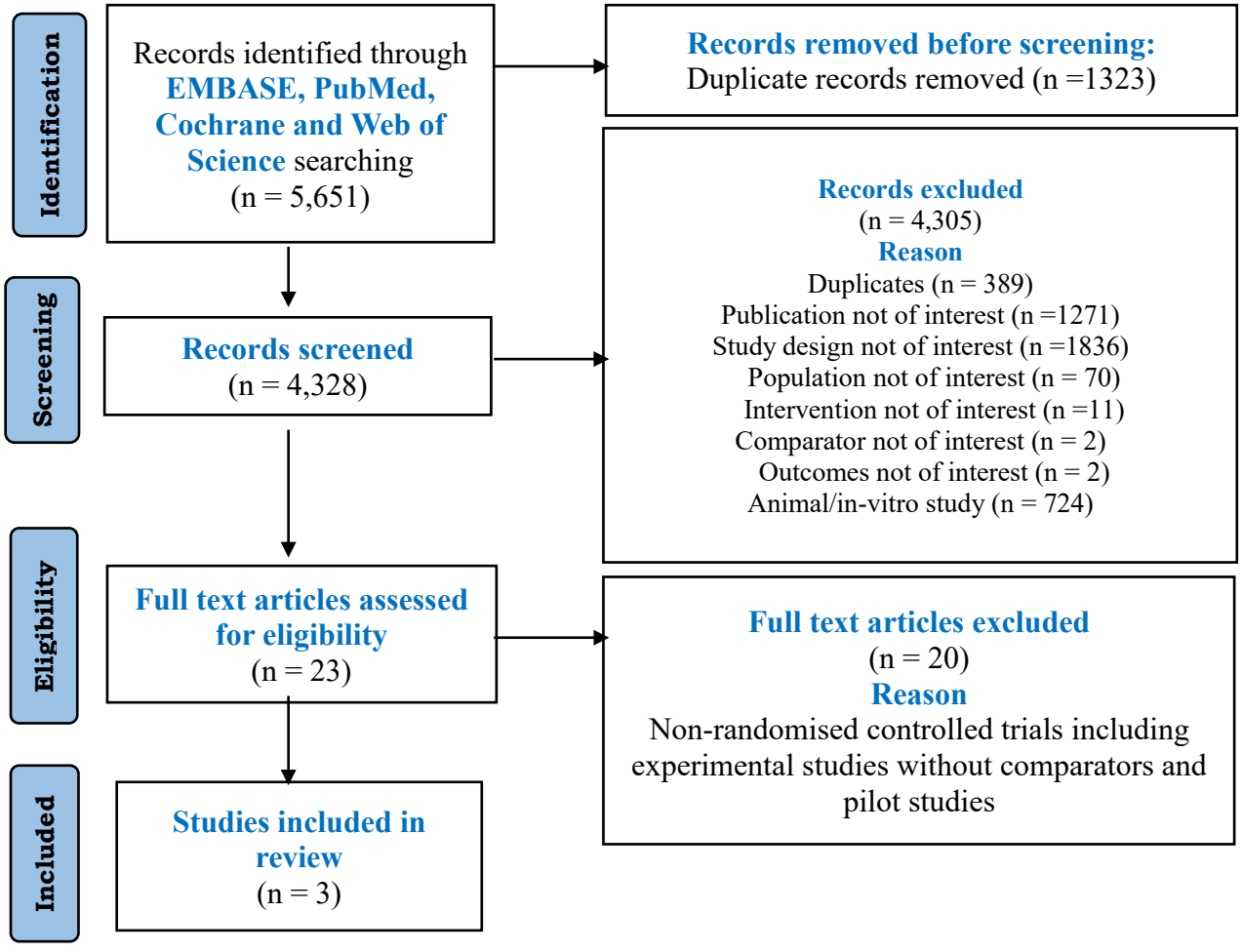
Concept	ID	Search Terms	Hits
PubMed (Performed on 24-09-2023)			
Muscular dystrophy		"Muscular dystrophy" OR "Duchene muscular dystrophy" OR Dystrophinopathy OR "Pseudohypertrophic muscular dystrophy" OR "Becker muscular dystrophy" OR "Emery Dreifuss muscular dystrophy" OR "Facioscapulohumeral Muscular Dystrophy" OR "Limb-girdle muscular dystrophy" OR "Severe childhood autosomal recessive muscular dystrophy" OR "Oculopharyngeal muscular dystrophy" OR "distal muscular dystrophy" OR steinert OR "hereditary progressive muscular dystrophy" OR "ocular muscular dystrophy" OR "congenital muscular dystrophy" OR "myotonic muscular dystrophy" OR "myotonic dystrophy type 1" OR "myotonic dystrophy type 2"	34,210
Stem cell therapy		"Stem cell therapy" OR "Cell therapy" OR "Progenitor cells" OR "Mesenchymal stem cells" OR "Hematopoietic stem cells" OR "Bone marrow mononuclear cells" OR "Induced pluripotent stem cells" OR "cardiosphere derived stem cells" OR "regenerative medicines" OR "stem cell-based therapy" OR "stem cell-derived therapy"	256,215
Muscular dystrophy AND Stem cell therapy	#3	#1 AND #2	875

Embase 24-09-2023			
Muscular Dystrophy (MD)	#1	'muscular dystrophy'/exp OR 'muscular dystrophy' OR 'duchene muscular dystrophy' OR 'dystrophinopathy'/exp OR dystrophinopathy OR 'pseudohypertrophic muscular dystrophy'/exp OR 'pseudohypertrophic muscular dystrophy' OR 'becker muscular dystrophy'/exp OR 'becker muscular dystrophy' OR 'emery dreifuss muscular dystrophy'/exp OR 'emery dreifuss muscular dystrophy' OR 'facioscapulohumeral muscular dystrophy'/exp OR 'facioscapulohumeral muscular dystrophy' OR 'limb-girdle muscular dystrophy'/exp OR 'limb-girdle muscular dystrophy' OR 'severe childhood autosomal recessive muscular dystrophy' OR 'oculopharyngeal muscular dystrophy'/exp OR 'oculopharyngeal muscular dystrophy' OR 'distal muscular dystrophy' OR steinert OR 'hereditary progressive muscular dystrophy' OR 'ocular muscular dystrophy' OR 'congenital muscular dystrophy'/exp OR 'congenital muscular dystrophy' OR 'myotonic muscular dystrophy'/exp OR 'myotonic muscular dystrophy' OR 'myotonic dystrophy type 1'/exp OR 'myotonic dystrophy type 1' OR 'myotonic dystrophy type 2'/exp OR 'myotonic dystrophy type 2'	63,438
Stem cell therapy	#2	'stem cell therapy'/exp OR 'stem cell therapy' OR 'cell therapy'/exp OR 'cell therapy' OR 'progenitor cells' OR 'mesenchymal stem cells'/exp OR 'mesenchymal stem cells' OR 'hematopoietic stem cells'/exp OR 'hematopoietic stem cells' OR 'bone marrow mononuclear cells' OR 'induced pluripotent stem cells'/exp OR 'induced pluripotent stem cells' OR 'cardiosphere derived stem cells' OR 'regenerative medicines' OR 'stem cell-based therapy'/exp OR 'stem cell-based therapy' OR 'stem cell-derived therapy'	530,071
Muscular dystrophy AND Stem cell therapy	#3	#1 AND #2	3,101
Web of Science 25-09-2023			
Muscular dystrophy	#1	ALL=("Muscular dystrophy" OR "Duchene muscular dystrophy" OR Dystrophinopathy OR "Pseudohypertrophic muscular dystrophy" OR "Becker muscular dystrophy" OR "Emery Dreifuss muscular dystrophy" OR "Facioscapulohumeral Muscular Dystrophy" OR "Limb-girdle muscular dystrophy" OR "Severe childhood autosomal recessive muscular dystrophy" OR "Oculopharyngeal	46,972

		muscular dystrophy" OR "distal muscular dystrophy" OR steinert OR "hereditary progressive muscular dystrophy" OR "ocular muscular dystrophy" OR "congenital muscular dystrophy" OR "myotonic muscular dystrophy" OR "myotonic dystrophy type 1" OR "myotonic dystrophy type 2")	
Stem cell therapy	#2	ALL=("Stem cell therapy" OR "Cell therapy" OR "Progenitor cells" OR "Mesenchymal stem cells" OR "Hematopoietic stem cells" OR "Bone marrow mononuclear cells" OR "Induced pluripotent stem cells" OR "cardiosphere derived stem cells" OR "regenerative medicines" OR "stem cell-based therapy" OR "stem cell-derived therapy")	274,521
Muscular dystrophy AND Stem cell therapy	#3	#2 AND #1	1,655
Cochrane Central			
	#1	MeSH descriptor: [Muscular Dystrophies] explode all trees	595
	#2	"Muscular dystrophy"	1197
	#3	"Duchenne muscular dystrophy"	828
	#4	dystrophinopath*	44
	#5	"pseudohypertrophic muscular dystrophy"	2
	#6	"Becker muscular dystrophy"	93
	#7	"emery dreifussmuscular dystrophy"	2
	#8	"facioscapulohumeral muscular dystrophy"	87
	#9	"limb girdle muscular dystrophy"	43
	#10	"oculopharyngeal muscular dystrophy"	10
	#11	"distal muscular dystrophy"	0
	#12	"Steinert disease"	7
	#13	"Hereditary progressive muscular dystrophy"	0
	#14	"Ocular muscular dystrophy"	0
	#15	"Congenital muscular dystrophy"	16
	#16	"Myotonic muscular dystrophy"	4
	#17	"Myotonic dystrophy type1"	0
	#18	"Myotonic dystrophy type 2"	6
	#19	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18	1330
	#20	"Stem cell therapy"	528
	#21	"Progenitor cells"	1645
	#22	"Mesenchymal stem cell"	1206
	#23	"Hematopoietic stem cell"	5406

	#24	"bone marrow derived mononuclear cell"	137
	#25	"induced pluripotent stem cell'	37
	#26	"Cell therapy"	2188
	#27	"Cardiosphere derived stem cells"	4
	#28	"Regenerative medicines"	14
	#29	"Stem cell based therapy"	24
	#30	"Stem cell derived therapy"	0
	#31	#20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30	9549
	#32	#19 AND #31	20

iii. PRISMA flow diagram

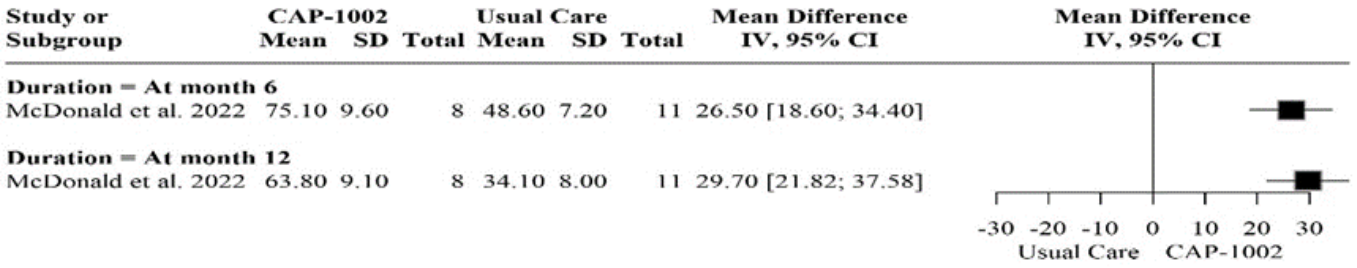


iv. Summary of included studies:

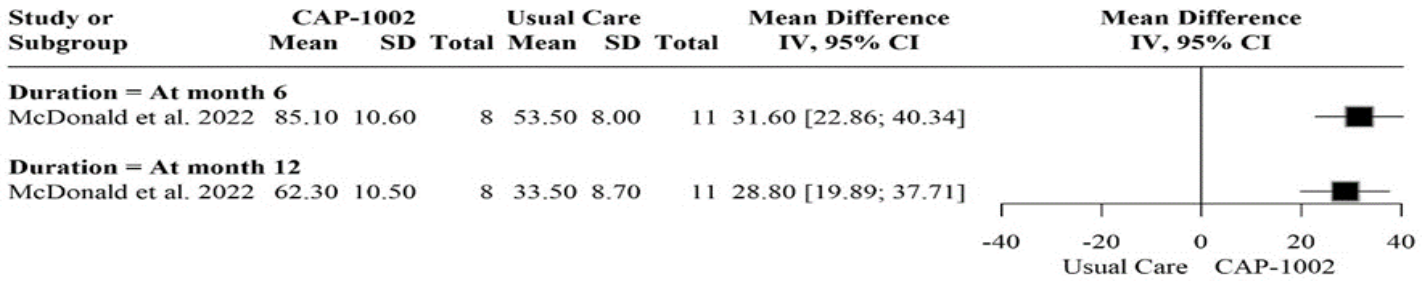
Study	Population	Intervention	Comparison	Outcomes	Comments
McDonald et al. 2022[1]	Male patients with DMD	Allogeneic CDCs-Intravenous CAP-1002	Placebo	• Cardiac assessments • Performance of upper limb • Safety outcomes	
Taylor et al. 2019[2]	Male patients age ≥12 years with genetic diagnosis of DMD	Allogeneic CDCs-Intracoronary CAP-1002	Usual care	• Cardiac assessments • Pulmonary function • Performance of upper limb • Safety outcomes	
Torrente et al. 2007[3]	Patients diagnosed with DMD	Muscle-Derived CD133+ Stem Cells-Intramuscular)	Sham control-Intramuscular saline	• Muscle strength effects	

v. Additional Forest plots:

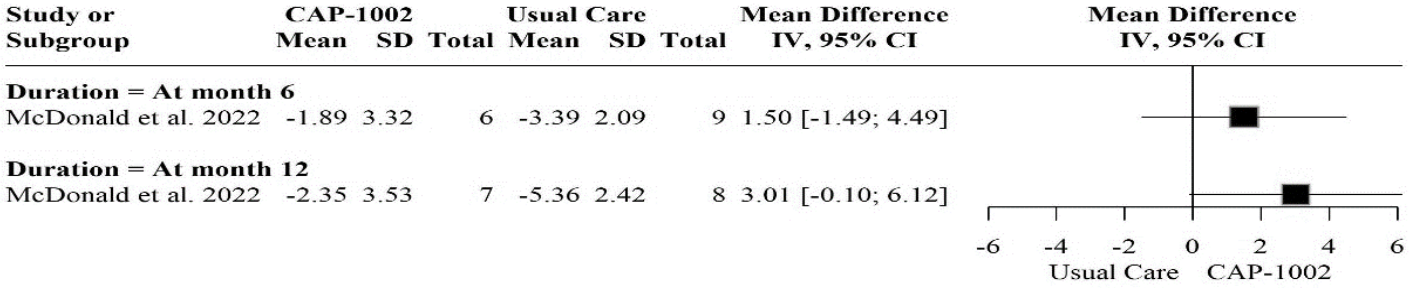
1. PUL 1.2 combined total Dimension (given in LS-Mean [SE]): Evidence from HOPE-2 trial reporting the PUL 1.2 combined total Dimension yielded a mean difference of 26.50 (95% CI: 18.60 to 34.40) at the end of six months and 29.70 (95%CI: 21.82 to 37.58) at the end of 12 months between the stem cell transplantation arm and usual care arm. The differences were statistically significant at both time points.



2. PUL 2.0 combined total dimension (given in LS-Mean [SE]): Evidence from HOPE-2 trial reporting the PUL 2.0 combined total Dimension yielded a mean difference of 31.60 (95% CI: 22.86 to 40.34) at the end of six months and 28.80 (95% CI: 19.89 to 37.71) at the end of 12 months between the stem cell transplantation arm and usual care arm. The differences were statistically significant at both time points.

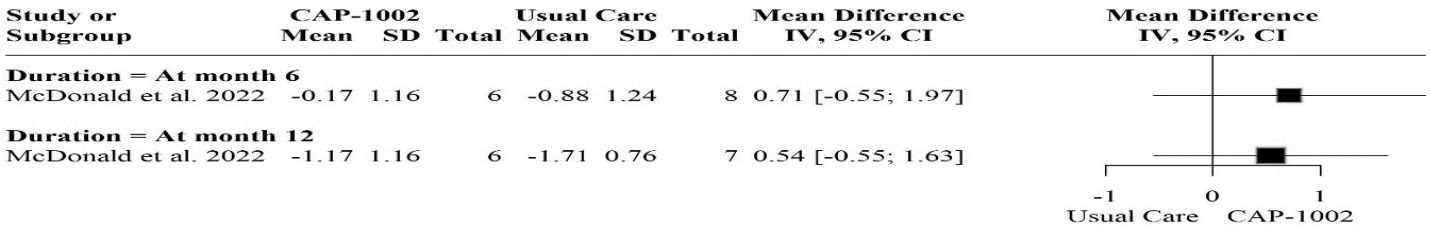


3. PUL 1.2 mid- level Dimension (Given in mean Change from Baseline [SD]):
Evidence from the HOPE-2 trial reporting the PUL 1.2 mid-level Dimension yielded a mean difference of 1.50 (95% CI: -1.49 to 4.49) at the end of six months and 3.0 (95% CI: -0.1 to 6.12) at the end of 12 months between the stem cell transplantation arm and usual care arm. The difference was statistically non-significant.



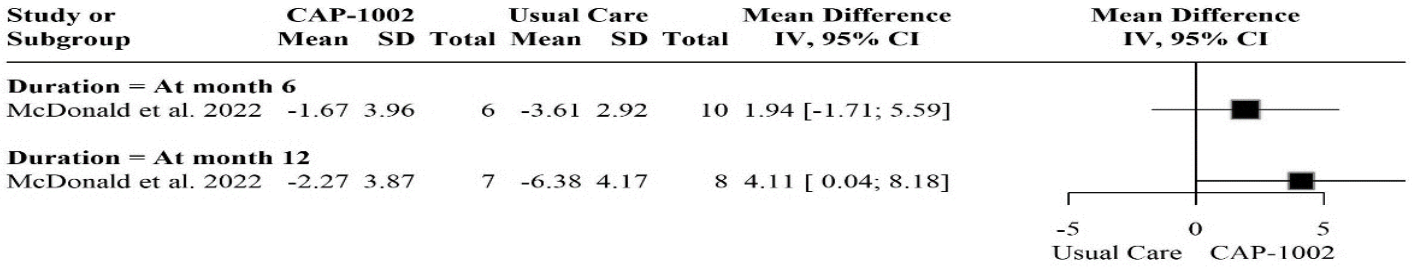
4. PUL 2.0 mid-level Dimension (Given in mean Change from Baseline [SD]):

Evidence from the HOPE-2 trial reporting the PUL 2.0mid-level Dimension yielded a mean difference of 0.71 (95% CI: -0.55 to 1.97) at the end of six months and 0.54 (95%CI: -0.55 to 1.63) at the end of 12 months between the stem cell transplantation arm and usual care arm. The differences were statistically non- significant at both time points.

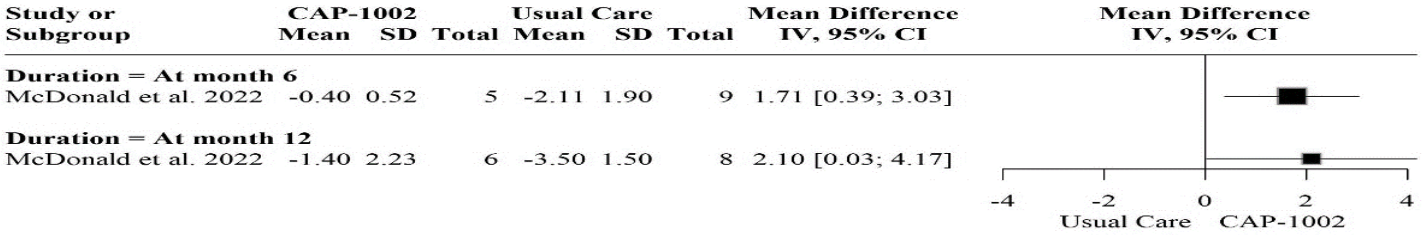


5. PUL 1.2 combined Total Dimension (Given in mean Change from Baseline [SD]):

Evidence from the HOPE-2 trial reporting the PUL 1.2 combined total Dimension yielded a mean difference of 1.94 (95% CI: -1.71 to 5.59) at the end of six months and 4.11 (95% CI: 0.04 to 8.18) at the end of 12 months between the stem cell transplantation arm and usual care arm. The difference was statistically non- significant at 6 months whereas, it was significant at 12-month time point.



6. PUL 2.0 combined Total Dimension (Given in mean Change from Baseline [SD]):
Evidence from the HOPE-2 trial reporting the PUL 2.0 combined total Dimension yielded a mean difference of 1.7 (95% CI:0.4 to 3.0) at the end of six months and 2.10 (95% CI: 0.03 to 4.17) at the end of 12 months between the stem cell transplantation arm and usual care arm. The differences were statistically significant at both time points.



vi. Evidence to decision framework

QUESTION

Should Stem Cell Therapy vs standard therapy be used for Muscular dystrophy?	
POPULATION:	Patients with Muscular dystrophy
INTERVENTION:	Stem Cell Therapy
COMPARISON:	Usual Care
MAIN OUTCOMES:	Improvement in muscle strength, functional abilities and serious adverse events
SETTING:	Hospital/ Tertiary care
PERSPECTIVE:	Population
BACKGROUND:	Muscular dystrophy (MD) refers to a group of genetic diseases that cause progressive weakness and degeneration of skeletal muscles. These disorders (of which there are more than 30) vary in age of onset, severity, and the pattern of the affected muscles. All forms of MD grow worse over time as muscles progressively degenerate and weaken. Many people with MD eventually lose the ability to walk.

CONFLICT OF INTERESTS:	None

ASSESSMENT

Problem Is the problem a priority?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	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.[4] Amongst various muscular dystrophies, Duchenne Muscular Dystrophy (DMD) is the most common.	
Desirable Effects How substantial are the desirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	
●Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	**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. **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. **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

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know	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%).	

Study ID	SAE	No. of patients (Intervention)	No. of patients (comparator)
McDonald et al. 2022[1]	Hypersensitivity (acute allergic reaction during second dose of CAP-1002)	1	0
Taylor et al. 2019[2]	Fever and confusion	1	0
	Ventricular fibrillation	1	0
	Urinary tract infection	1	0
	Femur fracture	0	1

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Very low ○ Low ○ Moderate ○ High ○ No included studies	The certainty of evidence is very low to small number of studies with low sample size and imprecise results.	

Values Is there important uncertainty about or variability in how much people value the main outcomes?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability	Main outcome is improvement in muscle strength and functional ability which is likely to be highly valued by most patients, parents and caregivers.[5]	
Balance of effects Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Favors the comparison ○Probably favors the comparison ●Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	It is less clear if benefits of stem cell intervention outweigh the harms, based on limited evidence.	
Resources required How large are the resource requirements (costs)?		

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	No direct evidence of the resources required in stem cell transplantation in patients with MD has been identified. On a global scale, the most frequently reported range for single treatment is $10,000 to $20,000. However, the cost is influenced by several factors such as type, quality, source of stem cells, the condition to be treated, and the location of the treatment facility.[6]	
Certainty of evidence of required resources What is the certainty of the evidence of resource requirements (costs)?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Very low ○ Low ● Moderate ○ High ○ No included studies	No research evidence was identified.	The GDG members were fairly certain about the large resources required for providing stem cell treatment.
Cost effectiveness Does the cost-effectiveness of the intervention favor the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**

○ Favors the comparison ● Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ No included studies	No research evidence for stem cell therapy was identified.	The intervention was not found to be effective and hence the committee deferred to comment on cost effectiveness.
Equity What would be the impact on health equity?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Reduced ● Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	No research evidence was identified	
Acceptability Is the intervention acceptable to key stakeholders?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**

○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	Study by Crossnohere et al in 2022 has reported that both caregivers and patients were willing to accept risk in exchange for a treatment that would potentially slow the disease. The findings of this study provide insight into risk tolerance in Duchenne muscular dystrophy, which can be used to inform regulatory benefit-risk determinations and inform conversations about treatment decision making with DMD patients in clinical settings.[7]	
Feasibility Is the intervention feasible to implement?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	No research evidence was identified.	Feasible to implement in tertiary care centers.

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	**Trivial**	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Trivial	**Small**	Moderate	Large		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies

VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	**Does not favor either the intervention or the comparison**	Probably favors the intervention	Favors the interventio n	Varies	Don't know
RESOURCES REQUIRED	**Large costs**	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	**Moderate**	High			No included studies
COST EFFECTIVENESS	Favors the comparison	**Probably favors the comparison**	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the interventio n	Varies	No included studies
EQUITY	Reduced	**Probably reduced**	Probably no impact	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	**Conditional recommendation against the intervention**	**Use only in the context of rigorously conducted clinical trials**	**Conditional recommendation for either the intervention or the comparison**	**Conditional recommendation for the intervention**	**Strong recommendation for the intervention**
○	○	●	○	○	○

CONCLUSIONS

Recommendation

Stem Cell Therapy is **not recommended*** in routine practice for the treatment of muscular dystrophy**. 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.

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.

vii. Data extraction

Data Extraction Methods:

Two reviewers independently screened the titles and abstracts to determine, whether the study pertained to stem cell therapy in Muscular Dystrophy and possibly eligible. If so, the main text and supplementary material were evaluated on whether it met the inclusion criterion. Discrepancy or conflicts were resolved by consensus or arbitration of a third reviewer.

Data mining was done using a pre-defined criterion. Similarly, two independent reviewers were involved to extract the following information from individual study: title, author information, country, blinding, year of publication, type of Muscular Dystrophy, follow-up period, baseline characteristics of patients (age, ambulatory status), intervention details (type of stem cell, delivery route), adverse events, reported outcomes, additional information that was addressed or has considerable relevance for this study. At this phase, conflicts were resolved by consensus or arbitration of a third reviewer.

Data Extraction Sheet:

Study	**McDonald et al. 2022[1]**
Study type	Phase II, double-blinded, multi-centric, RCT
Number of participants; (N)	20

Countries and setting	USA, Multicentric
Duration of study Follow up (post intervention):	12 months
Method of assessment of disease condition:	• Clinical and phenotypic manifestations • Genetically confirmed
Subgroup analysis within study	NR
Inclusion criteria:	• Male patients ≥ 10 years old • Diagnosis of DMD based on clinical and phenotypic manifestations consistent with DMD with confirmatory genetic testing performed at a certified laboratory • Performance of Upper Limb motor function scale (PUL 1·2 /PUL 2·0 entry item score of 2–5) • If ambulatory, 10-meter walk/run velocity < 1 meter/second (equivalent to time > 10 seconds) • Receiving standard of care therapy at an experienced, multidisciplinary DMD centre • Treatment with a glucocorticoid for ≥ 12 months prior to randomisation (with stable dose for ≥ 6 months prior to randomisation)
Exclusion criteria:	• Left ventricular (LV) ejection fraction < 35% • Elbow-flexion contractures >30° in both extremities • Ambulant if ≥ 18 years of age; percent predicted forced vital capacity < 35% • Treatment with an approved exon-skipping therapy if on changing or stable dose for less than 24 months prior to randomization
Recruitment/selection of patients:	• Randomly assigned at a 1:1 ratio to either CAP-1002 or placebo • Using stratified permuted blocks via an interactive web-based response system • Randomization was stratified by site and PUL entry item score • Clinicians, caregivers, patients, and clinical operations personnel remained fully masked before, during, and after the interim analysis
Intervention: Source and type of stem cells	• The obtained myocardial tissue from two human donor hearts was cultured to create Cardiosphere-derived cells (CDCs).
Intervention: Method of their characterization	• 12 lots of CDCs were formulated as CAP-1002 and cryopreserved. • Identity and purity were confirmed by high (99·6% plus or minus 0·2%) CD105 and low (0·4% plus or minus 0·3%) CD45 expression.

Intervention: Route of administration	• Intravenously once every 3 months for a total of four infusions
Intervention: Dose	• CAP-1002 ($1{\cdot}5\times10^8$ CDCs) and placebo (the same formulation minus CDCs) frozen concentrates were supplied in a total volume of 20 mL of cryogenic cell preservation solution.
Intervention: Dose - If the trial has taken multiple doses, then which dose values has been used for MA	• Intravenously ($1{\cdot}5\times10^8$ CDCs) once every 3 months for a total of four infusions.
Efficacy outcomes reported with time points	**Cardiac Assessments (at 12 months):** LVEF; LVESV; LVEDV; indexed LV ES volume and LV ED volume; inferior, anterior, lateral and septal Systolic wall thickening; inferior, anterior, lateral and septal ES wall thickness average; inferior, anterior, lateral, septal and Global Circumferential strain; Global statistical test of cardiac measures and; CK-MB/ total CK **Mean difference in percentile ranked change at 12 months; Least square mean, (95% CI), p-value:** LVEF (%) • At month 6: 23.0 (SE=11.8); p =0.07 • At month 12: 45.7 (95% CI: 19.1 to 72.2), SE=12.5, p = <0.01 LVESV (ml) : 45.9 (11.8 to 79.9), p = 0.012 LVEDV (ml) : -0.6 (-41.7 to 40.5), p = 0.98 LV ES volume, indexed (ml/m^2) : 53.1 (13.6 to 92.6), p = 0.013 LV ED volume, indexed (ml/m^2) : 47.8 (5.4 to 90.1), p = 0.031 Systolic wall thickening inferior (%) : 14.6 (-16.2 to 45.5), p = 0.33 Systolic wall thickening anterior (%) : 0.2 (-25.3 to 25.7), p = 0.96 Systolic wall thickening lateral (%) : 21.7 (-25.2 to 68.7), p = 0.35 Systolic wall thickening septal (%) : 0.9 (-40.5 to 42.3), p = 0.96 ES wall thickness average, septal (mm) : 6.6 (-28.1 to 41.4), p =0.69 ES wall thickness average, lateral (mm) : 20.0 (-15.1 to 55.2), p = 0.23 ES wall thickness average, inferior (mm) : 31.5 (-7.0 to 70.0), p = 0.11 ES wall thickness average, anterior (mm) : 30.7 (-11.5 to 72.8), p = 0.17

	ED wall thickness average, septal (mm) : 5.5 (-39.4 to 50.4), p = 0.78 ED wall thickness average, lateral (mm) : 16.9 (-32.1 to 65.9), p = 0.47 ED wall thickness average, inferior (mm) : 19.5 (-21.5 to 60.5), p = 0.33 ED wall thickness average, anterior (mm) : 36.2 (-0.6 to 73.0), p = 0.05 Circumferential strain, septal LV (%) : 22.8 (-10.1 to 55.7), p = 0.16 Circumferential strain, lateral LV (%) : 17.8 (-22.8 to 58.5), p = 0.35 Circumferential strain, inferior LV (%) : 35.0 (-0.8 to 70.9), p = 0.06 Circumferential strain, anterior LV (%) : 3.1 (-27.6 to 33.7), p = 0.82 Global circumferential strain (%) : 2.6 (-47.4 to 52.7), p = 0.94 Global statistical test of cardiac measures : 24.5 (9.0 to 40.0), p = 0.007 CK-MB/ total CK : 29.1 (4.0 to 54.2), p = 0.025 **Performance of upper limb (at 12 months):** PUL 1.2 outcomes at Mid-level, High-level, Combined mid-level and distal-level, Distal-level, Total score **Mean difference in percentile ranked change at 12 months; Least square mean, (95% CI), p-value:** Mid-level PUL 1.2 : • At month 6, 27.6 (SE=13.3); p =0.05 • At month 12, 36.2 (95% CI: 7.9 to 64.5), SE= 13.8, p = 0.01 High-level (Shoulder level) PUL 1.2 : 27.4 (-6.8 to 61.6), p = 0.11 Combined mid-level and distal-level PUL 1.2 : 38.1 (11.1 to 65.1), p = 0.01 Distal-level PUL 1.2 : 5.2 (-17.2 to 27.7), p = 0.64 Total PUL 1.2 : 29.7 (5.7 to 53.7), p = 0.02 Global statistical test of PUL measures : 24.4 (6.8 to 42.1), p = 0.01 PUL 2.0 outcomes at Mid-level, High-level, Combined mid-level and distal-level, Distal-level, Total score **Mean difference in percentile ranked change at 12 months; Least square mean, (95% CI), p-value:** Mid-level PUL 2.0 : 29.6 (-1.1 to 60.4), p = 0.06

	High-level PUL 2.0 : 8.6 (-14.0 to 31.2), p = 0.44 Combined mid-level and distal-level PUL 2.0 : 28.4 (-0.7 to 57.6), p = 0.06 Distal-level PUL 2.0 : -7.1 (-31.5 to 17.4), p = 0.56 Total PUL 2.0 : 28.8 (1.5 to 56.1), p = 0.04
Safety outcomes reported with time points-Serious adverse events	**Safety Outcomes (during the 12 months study period)** • Hypersensitivity (acute allergic reaction during second dose of CAP-1002): 1 vs 0 patients

Safety outcomes reported with time points-Other adverse events	**Other adverse events (during the 12 months study period)**
	• Hypersensitivity reaction: 3 vs 0 patients; including five events in CAP-1002 like tachycardia, pyrexia, allergic reaction, throat irritation and tightness
	• Treatment-emergent adverse events related to investigational product or administration procedure: 3 vs 2 patients; including the following events
	  • Dizziness (1 vs 0 patients),
	  • Dysgeusia (1 vs 2 patients),
	  • Oropharyngeal pain (1 vs 0 patients),
	  • Flushing (0 vs 1 patients)

Funding	This study was sponsored by Capricor Therapeutics with involvement in study design. (The funder had no role in data collection, data interpretation and data analysis).
ROB2 Assessment: Specify separately for each domain	Randomization process: Low Deviations from the intended interventions: Low Missing outcome data: Low Measurement of the outcome: Low Selection of the reported result: Low
Study	**Taylor et al. 2019[2]**
Study type	Phase I/II, open label, multicentric, RCT
Number of participants; (N)	25
Countries and setting	USA, multicentric
Duration of study Follow up (post intervention):	12 months

Method of assessment of disease condition:	Genetically confirmed
Subgroup analysis within study	NR
Inclusion criteria:	• Male patients ≥12 years who were genetic diagnosis of DMD and cardiomyopathy with fibrosis in ≥4 left ventricular (LV) segments (based on the American Heart Association 16 segment model). • Patients could not have an LV ejection fraction (LVEF) ≤35%, were required to be receiving evidence-based medical care for >3 months and systemic glucocorticoids for >6 months prior to screening and be candidates for cardiac catheterization.
Exclusion criteria:	• If they were receiving IV inotropic or vasoactive medications, • Could not undergo MRI, • Had preexisting antibodies against all available CAP-1002 master cell banks (MCBs), • Planned surgery in the next 12 months, • Had implanted or had an indication for an LV assist device (LVAD), • Had moderate to severe valvular disease, • Had an active infection or systemic allergic reaction or autoimmune disease, • Had a history of cardiac tumor or prior stem cell therapy, • Had a known hypersensitivity to bovine products or dimethyl sulfoxide, • Had abused drugs or alcohol, • Were currently or recently participating in a related clinical study, • Had HIV infection, chronic viral hepatitis, abnormal liver function, abnormal hematology, or uncontrolled diabetes.
Recruitment/selection of patients:	• Randomly assigned at a 1:1 ratio to either CAP-1002 plus usual care or usual care alone • Using a dominant-biased coin design within each of 5 blocks of 6 patients each. • Care providers were not masked to group assignment • Cardiac MRI analyses were performed by a core laboratory blinded to treatment assignment and outcomes
Intervention: Source and type of stem cells	• Myocardial tissue from human donor hearts, cardiosphere-derived cells (CDCs) [cardiac progenitor cell population]

Intervention: Method of their characterization	• The obtained myocardial tissue from human donor hearts was dissected, explants and cultured • Explant-derived cells were collected to comprise master cell banks (MCB), cardiospheres were formed in non adherent culture, cardiosphere-derived cells (CDCs) were expanded over several passages, and CAP-1002 doses were formulated and cryopreserved for storage prior to use.
Intervention: Route of administration	• Global intracoronary infusion (each major coronary artery) with a Terumo (Tokyo, Japan) Finecross MG catheter.
Intervention: Dose	• A single maximum dose of 25 M cells was delivered to each major coronary artery for an intended total dose of 75 M cells per patient. A 12.5 M cell dose was administered to any unusually small coronary artery, at the discretion of the site investigator.
Intervention: Dose - If the trial has taken multiple doses, then which dose values has been used for MA	NA
Efficacy outcomes reported with time points	**Cardiac Assessments (at 6 and 12 months):** **Mean change from baseline at month 6:** Cap-1002 (n=13) vs Usual care (n=11) **Myocardial Scar**: -1.11 (1.63) vs -0.53 (2.86) **LVEF:** 1.07 (3.38) vs 0.74 (5.50) **LVESV:** -0.79 (5.87) vs 0.60 (8.80) **LVEDV:** 0.14 (8.54) vs 3.44 (14.31) **Mean change from baseline at month 12:** Cap-1002 (n=13) vs Usual care (n=11) **Myocardial Scar**: -1.35 (1.78) vs -0.09 (5.47) **LVEF:** -0.35 (2.70) vs 0.62 (4.40) **LVESV:** 4.51(8.00) vs 1.29 (7.13) **LVEDV:** 6.16 (11.66) vs 3.21(12.31) **Pulmonary function (at 6 and 12 months):** **Mean change from baseline at month 6:** CAP-1002 (n=13) VS Usual care (n=11) FEV1 (L): 2.09 (15.01) vs 3.18 (16.23) FEV1 (%p): -2.01(15.23) vs -0.62 (19.16) FVC (L): 3.48 (18.77) vs 1.45 (15.18) FVC %p: -1.08 (17.87) vs -2.55 (19.96)

	FEV1/FVC (%): -1.09 (3.99) vs 1.97(8.79) FEV1/FVC %p: -0.79 (4.00) vs 2.33 (9.49) FEF_{25-75}% (L/s): 8.02 (39.50) vs 7.61 (42.23) FEF_{25-75}%p: 5.83 (41.89) vs 3.71 (41.25) PEF (L/s): 3.52 (26.04) vs 0.90 (13.50) PEF %p: -0.42 (28.44) vs -2.63 (15.05) FET (s) [2]: 35.53 (63.00) vs 5.29 (46.59) **Mean change from baseline at month 12:** CAP-1002 (n=13) VS Usual care (n=11) FEV1 (L): -0.09 (14.68) vs 7.91 (16.32) FEV1 (%p): -6.31(16.69) vs -0.37(23.23) FVC (L): 0.46 (14.96) vs 1.56 (11.26) FVC %p: -6.13 (17.40) vs -6.68 (17.70) FEV1/FVC (%): -0.30 (3.24) vs 5.92(7.94) FEV1/FVC %p: -0.32 (3.38) vs 6.53 (7.60) FEF_{25-75}% (L/s): 8.76 (43.89) vs 18.97 (31.31) FEF_{25-75}%p: 5.07 (48.29) vs 12.53 (35.01) PEF (L/s): 4.63 (30.82) vs 2.55 (11.63) PEF %p: 1.93 (35.21) vs -5.80 (12.69) FET (s) [2]: 30.10 (95.42) vs 11.34 (28.23) **Performance of upper limb (at 6 and 12 months):** **Mean change from baseline at month 6:** CAP-1002 (n=13) VS Usual care (n=11) Shoulder: -17.36 (16.71) vs 8.45 (33.17) Middle: 3.11 (32.76) vs -6.60 (20.74) Distal: -3.19 (19.81) vs 0.96 (4.53) Middle+ Distal: 0.90 (8.70) vs -3.90 (9.53) Overall: -5.62 (6.47) vs 0.65 (3.65) **Mean change from baseline at month 12:** CAP-1002 (n=13) VS Usual care (n=11) Shoulder: -27.78 (4.81) vs -14.71 (20.10) Middle: 18.15 (44.41) vs -6.05 (8.57) Distal: 5.03 (11.22) vs 1.57 (4.59) Middle+ Distal: 7.00 (17.61) vs -2.53 (5.05) Overall: -5.79 (0.48) vs -3.05 (6.13)

	Quality of life (at 6 and 12 months): **Patient reported PODCI:** **Mean change from baseline at month 6:** CAP-1002 (n=13) VS Usual care (n=11) Upper Extremity and Physical Function: -52.56 (242.52) vs -80.35 (265.76) Transfer and Basic Mobility:10.47 (19.00) vs -0.70 (36.49) Sports/Physical Functioning: 5.95 (32.80) vs 9.75 (61.05) Pain/Comfort: 4.32 (24.40) vs 13.97 (33.31) Happiness: -107.12 (182.80) vs 146.89 (501.07) Global Function: 27.51 (48.99) vs -23.30 (111.80) **Mean change from baseline at month 12:** CAP-1002 (n=13) VS Usual care (n=11) Upper Extremity and Physical Function: -53.63 (174.74) vs 28.69 (97.64) Transfer and Basic Mobility: -3.45 (48.60) vs 10.44 (57.72) Sports/Physical Functioning: -6.31 (60.05) vs 1.32 (70.25) Pain/Comfort: -2.41 (38.51) vs 16.62 (60.39) Happiness: 32.06 (100.06) vs 72.32 (400.75) Global Function: 16.99 (64.18) vs -0.04 (91.80) **Parent reported PODCI:** **Mean change from baseline at month 6:** CAP-1002 (n=13) VS Usual care (n=11) Upper Extremity and Physical Function: -133.53 (462.45) vs -18.71 (144.71) Transfer and Basic Mobility: -6.34 (23.77) vs -11.32 (42.72) Sports/Physical Functioning: -26.69 (132.32) vs -8.28 (33.61) Pain/Comfort: 5.28 (15.97) vs 14.81 (37.01) Happiness: 9.28 (21.99) vs -5.03 Global Function: 1.05 (61.81) vs -39.61 (58.69) **Mean change from baseline at month 12:** CAP-1002 (n=13) VS Usual care (n=11) Upper Extremity and Physical Function: -107.56 (389.88) vs -3.32 (119.24) Transfer and Basic Mobility: -4.88 (52.21) vs -14.28 (60.98) Sports/Physical Functioning: -24.39 (103.42) vs -40.68 (77.75) Pain/Comfort: -1.06 (50.67) vs 5.66 (32.07) Happiness: 16.82 (23.95) vs -19.53 (17.83) Global Function: 3.15 (61.44) vs 3.83 (111.99) **Patient reported PedsQL**

	Mean change from baseline at month 6: CAP-1002 (n=13) VS Usual care (n=11) Daily Activities: 32.61 (90.71) vs -2.58 (11.98) Treatment Barriers: 11.14 (62.36) vs -1.22 (24.69) Worry: 12.09 (39.52) vs -19.73 (24.98) Communication: 22.05 (48.80) vs -22.19 (37.85) Total summary: 14.88 (52.71) vs -12.85 (14.03) **Mean change from baseline at month 12:** CAP-1002 (n=13) VS Usual care (n=11) Daily Activities: 12.59 (55.06) vs -1.50 (19.68) Treatment Barriers: 18.44 (51.88) vs -2.52 (20.78) Worry: 18.70 (82.01) vs -24.45 (20.50) Communication: 36.84 (82.67) vs -24.45 (24.46) Total summary: 19.14 (66.62) vs -14.11 (13.56) **Parent reported PedsQL** **Mean change from baseline at month 6:** CAP-1002 (n=13) VS Usual care (n=11) Daily Activities: -1.03 (49.85) vs 5.33 (34.34) Treatment Barriers: 1.59 (48.85) vs 6.77 (25.40) Worry: 22.29 (18.35) vs -1.24 (25.31) Communication: -2.91 (18.35) vs 10.47 (54.03) Total summary: 2.66 (34.39) vs 0.65 (17.95) **Mean change from baseline at month 12:** CAP-1002 (n=13) VS Usual care (n=11) Daily Activities: -1.41 (44.43) vs -8.70 (35.78) Treatment Barriers: -2.93 (44.03) vs 3.37 (19.60) Worry: 27.32 (71.73) vs -1.39 (54.50) Communication: 4.48 (25.20) vs 1.10 (31.28) Total summary: 4.85 (39.12) vs -7.89 (9.27)
Safety outcomes reported with time points-Serious adverse events	**Serious AEs: 3 vs 1 patient** including five events • Fever and confusion (1 vs 0 patient) • Ventricular fibrillation (1 vs 0 patient) • Urinary tract infection (1 vs 0 patient) • Femur fracture (0 vs 1 patient)

Safety outcomes reported with time points-Other adverse events	**Non-serious AEs: 14 vs 4 patients** Cardiac: • Atrial fibrillation: 5 vs 1 patients • Atrioventricular block, 2nd degree: 1 vs 0 patient • Supraventricular tachycardia: 1 vs 1 patient • Bradycardia: 2 vs 0 patients • Ventricular tachycardia: 2 vs 0 patients Orthopedic: • Femur fracture: 1 vs 0 patient • Tibia fracture: 1 vs 1 patient • Fibula fracture: 0 vs 1 patient • Radius fracture: 1 vs 0 patient
Funding	• Capricor, Inc. • California Institute for Regenerative Medicine (The public funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The Article Processing Charge was funded by Capricor Therapeutics, Inc.)
ROB2 Assessment: Specify separately for each domain	Randomization process: Low Deviations from the intended interventions: Low Missing outcome data: Low Measurement of the outcome: Low Selection of the reported result: Low
Study	**Torrente et al. 2007[3]**
Study type	Phase I, double-blind RCT
Number of participants; (N)	8
Countries and setting	Italy, single centric
Duration of study Follow up (post intervention):	7 months
Method of assessment of disease condition:	• Clinical evaluation with observation of proximal muscle weakness (Gowers sign positive), pseudohypertrophy of the calves, lordotic and wide-based gait and stance; • Increase of the levels of muscular enzymes creatin kinase;

	• Muscle biopsy and dystrophin analyses (IF, WB, and molecular analysis) consistent with DMD
Subgroup analysis within study	Not reported
Inclusion criteria:	• Age at least 4 years old • Diagnosis of Duchenne muscular dystrophy confirmed by: a) clinical evaluation with observation of proximal muscle weakness (Gowers sign positive), pseudohypertrophy of the calves, lordotic and wide-based gait and stance; b) increase of the levels of muscular enzymes creatin kinase; c) muscle biopsy and dystrophin analyses (IF, WB, and molecular analysis) consistent with DMD) • Preserved ability to ambulate at the time of the selection • Adequate muscle strength and muscle bulk at the tibialis anterior
Exclusion criteria:	• Patients not ambulant at the moment of the inclusion • Onset symptoms before the age of 2–3 years old • Severe cardiac and respiratory dysfunction • Deficient immune system and/or autoimmune disease • Presence of additional diseases (i.e., family history of epilepsy, cerebral palsy) • Mental retardation (Intelligence Quotient through the Wechsler Intelligence scale above 70) • Steroid therapy in the previous 6 months • Psychological/psychiatric disorders
Recruitment/selection of patients:	• Eligible patients were assigned to either stem cell (A case) or saline solution alone (B case) by using to a statistical series based on random sampling numbers drawn up by Professor Bresolin. • Allocation was concealed using sealed envelope • Blinding was achieved according to the "double-dummy technique."
Intervention: Source and type of stem cells	• Autologous Muscle-derived cells CD133+ from the tibialis anterior muscle of all included patients
Intervention: Method of their characterization	• Muscle-derived cells were plated in serum-free conditions. • The microbiological and viral analysis of the supernatant of 24 and 48-h muscle cell culture were negative and excluded the presence of contaminant agents in all specimens. • After 48 h of culture, the CD133+ cells were enriched from cultured dystrophic muscle-

	derived cells using a magnetic cell sorting (MACS) (median purity 88%; range 76–98%)
Intervention: Route of administration	• Intramuscular transplantation
Intervention: Dose	• A total of 2 x 10^4 cells (stem cell group A) or with saline solution (sham group B).
Intervention: Dose - If the trial has taken multiple doses, then which dose values has been used for MA	• Three parallel injections (intramuscular transplantation) were done at 1 mm of inter distance in the middle of the left abductor digiti minimi (ADM) muscle either with 2 x 10^4 cells (stem cell group A) or with saline solution (sham group B).
Efficacy outcomes reported with time points	Muscle Strength Effects (Maximal Isometric Voluntary Contraction) at 2, 4, and 6 months Mean Change SD Baseline value: Left ADM: 154 ± 13.97 g Right ADM: 139.7 ± 14.41 g Not significant
Safety outcomes reported with time points-Serious adverse events	Not reported
Safety outcomes reported with time points-Other adverse events	Local or systemic side effects
Funding	Supported by the Association Francaisecontre les Myopathies, the Italian Ministry of Health, the Fondazione IRCCS Ospedale Maggiore Policlinico of Milan, the Associazione La Nostra Famiglia Fondo DMD Gli Amici di Emanuele, and by the Centro Dino Ferrari, Department of Neurological Science, University of Milan, Italy.
ROB2 Assessment: Specify separately for each domain	Randomization process: Low Deviations from the intended interventions: Low Missing outcome data: Low Measurement of the outcome: Low Selection of the reported result: Low

viii. List of Excluded Studies:

Author, Year	Title	Reason
Sharma et al. 2012	Administration of autologous bone marrow-derived mononuclear cells in children with incurable neurological disorders and injury is safe and improves their quality of life.	No comparator
Périé et al. 2014	Autologous myoblast transplantation for oculopharyngeal muscular dystrophy: A phase I/IIa clinical study.	No comparator
Law et al. 1993	Cell transplantation as an experimental treatment for Duchenne muscular dystrophy.	No comparator
Sharma et al. 2013	A clinical study shows safety and efficacy of autologous bone marrow mononuclear cell therapy to improve quality of life in muscular dystrophy patients.	No comparator
Klimczak et al. 2020	Co-Transplantation of Bone Marrow-MSCs and Myogenic Stem/Progenitor Cells from Adult Donors Improves Muscle Function of Patients with Duchenne Muscular Dystrophy.	No comparator
Duzhar et al. 2021	Duchenne muscular dystrophy: treatment with fetal progenitor cell transplant.	No comparator
Heydemann et al. 2023	Dystrophin Expressing Chimeric (DEC) Cell Therapy for Duchenne Muscular Dystrophy: A First-in-Human Study with Minimum 6 Months Follow-up.	No comparator
Skuk et al. 2006	Dystrophin expression in muscles of Duchenne muscular dystrophy patients after high-density injections of normal myogenic cells.	No comparator
Dai et al. 2018	Efficacy of stem cell therapy in ambulatory and nonambulatory children with Duchenne muscular dystrophy - Phase I-II.	No comparator
Law et al. 1992	Feasibility, safety, and efficacy of myoblast transfer therapy on Duchenne muscular dystrophy boys.	No comparator
Yang et al. 2009	[Functional improvement of patients with progressive muscular dystrophy by bone marrow and umbilical cord blood mesenchymal stem cell transplantations].	No comparator
Cossu et al. 2015	Intra-arterial transplantation of HLA-matched donor mesoangioblasts in Duchenne muscular dystrophy.	No comparator
Miller et al. 1997	Myoblast implantation in Duchenne muscular dystrophy: The San Francisco study.	No comparator
Neumeyer et al. 1998	Pilot study of myoblast transfer in the treatment of Becker muscular dystrophy.	No comparator
Tremblay et al. 1993	Results of a triple blind clinical study of myoblast transplantations without immunosuppressive treatment in young boys with Duchenne muscular dystrophy.	No comparator
Sharma et al. 2015	The role of cell transplantation in modifying the course of limb girdle muscular dystrophy: a longitudinal 5-year study.	Non-randomized clinical Trial

Siemionow et al. 2023	Safety and Efficacy of DT-DEC01 Therapy in Duchenne Muscular Dystrophy Patients: A 12 - Month Follow-Up Study After Systemic Intraosseous Administration.	No comparator
Li et al. 2015	Transplantation of human umbilical cord-derived mesenchymal stems cells for the treatment of Becker muscular dystrophy in affected pedigree members.	No comparator
Yang et al. 2009	Treatment of Duchenne muscular dystrophy using bone marrow and cord blood mesenchymal stem cell transplantation.	No comparator
Świątkowska-Flis et al. 2021	The use of umbilical cord-derived mesenchymal stem cells in patients with muscular dystrophies: Results from compassionate use in real-life settings.	No comparator

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4. BRONCHOPULMONARY DYSPLASIA (BPD)

i. **Key question in PICO format**

ii. **Search strategy**

iii. **PRISMA flow diagram**

iv. **Summary of included studies**

v. **Evidence to decision framework**

vi. **Data extraction**

vii. **List of excluded studies**

i. Key question in PICO format:

1. In patients, preterm neonates (of ≤ 28 week gestation) at high risk of BPD, what the efficacy and safety of stem cell therapy is as compared to the standard care for prevention of BPD?

2. In patients, premature infants with established moderate and severe Bronchopulmonary Dysplasia, what is the efficacy and safety of stem cell therapy as compared to the standard care for treatment of BPD?

Population: Newborn preterm and Bronchopulmonary dysplasia
Intervention: Stem cell therapy
Comparator: Placebo and/or standard care
Critical Outcomes:

For Q 1: Preterm neonates at high risk of BPD

- Incidence of BPD
- Mortality by one year of age.
- Composite outcome of death and moderate to severe BPD
- Adverse neurodevelopmental outcome
- Tumor formation
- Growth at one year

For Q 2: Infants with established moderate and severe BPD

- Mortality by one year
- Need for invasive ventilation or ventilator-free days at 40 weeks postmenstrual age
- Adverse neurodevelopmental outcome at 18-24 months
- Serious adverse events- mortality, tumor formation
- Growth at one year

ii. Search strategy:

Inclusion criteria: Only randomized controlled trials (RCTs) done in premature infants (born <37 weeks of gestation) at risk of evolving BPD or studies in which stem cells were used for the treatment of established BPD or deteriorating respiratory condition were included. Studies published in both English and non-English literatures were eligible.
Exclusion criteria: Non-randomized, pre-clinical/ experimental research studies in animals; systematic reviews, meta-analysis, opinion, and editorials; unpublished RCT

Time frame (T): From the inception of the searched databases until September 23rd, 2023.

1. **Information Sources:**
   The literature search was restricted to 4 databases: PubMed, Embase, Web of Science, and Cochrane CENTRAL. Only peer-reviewed and published articles were included, and no grey literature was included. However, hand-searching of reference lists of review articles and clinical studies was done.

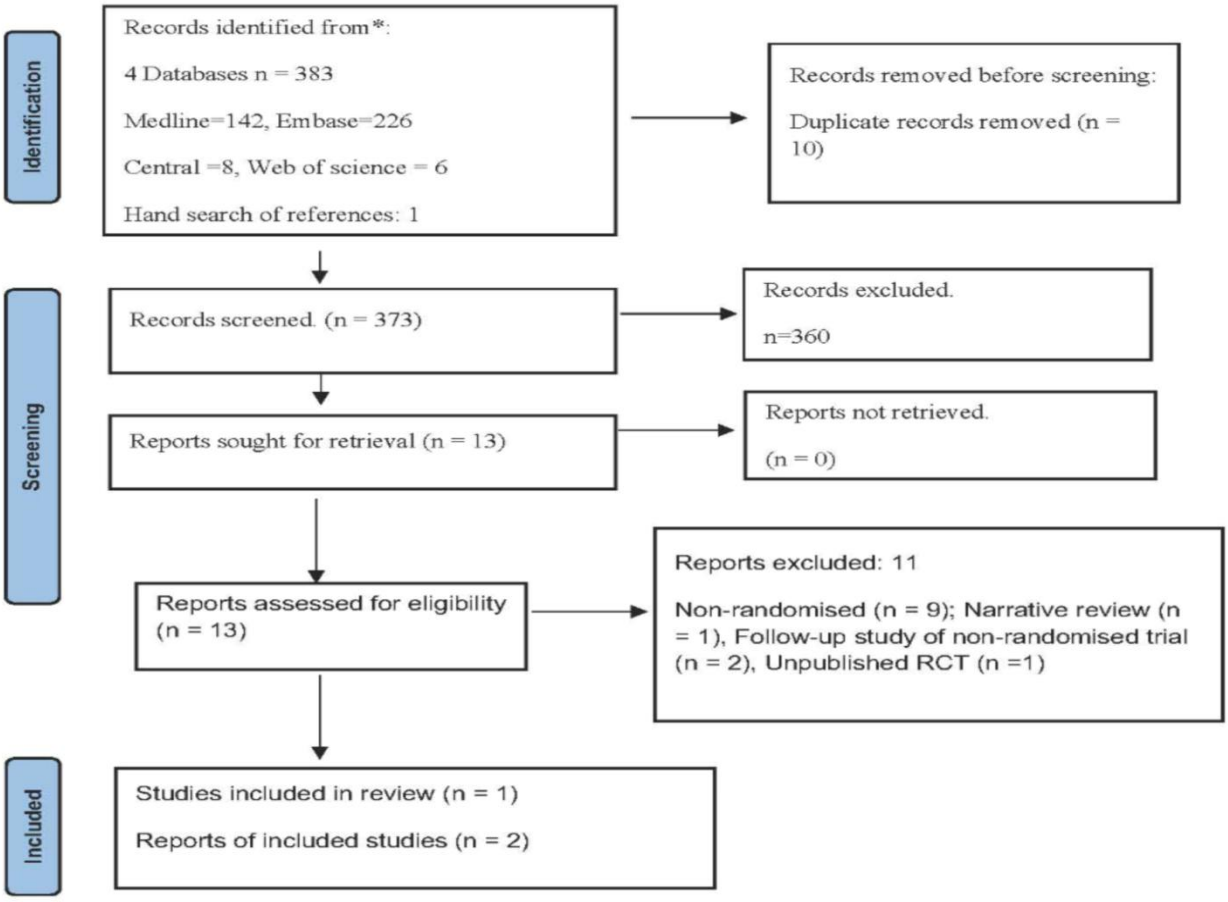
2. **Search Strategy:** Using MESH terms

Database(s): Ovid MEDLINE(R) ALL 1946 to September 23rd, 2023. The search strategy and outcomes of the search are mentioned in Appendix I.
There were no language barriers and Google Translate (California, U.S.A.) was used to translate non-English literature. Rayyan – QCRI software (Doha, Qatar) was used for the literature search.

#	Searches	Results
1	exp stem cell transplantation/	99561
2	exp Cord Blood Stem Cell Transplantation/	3690
3	exp Hematopoietic Stem Cell Transplantation/	57329
4	exp peripheral blood stem cell transplantation/	3870
5	exp mesenchymal stem cell transplantation/	14885
6	exp Mesenchymal Stem Cells/	50958
7	exp Stromal Vascular Fraction/	132
8	(mesenchy* adj3 transplantation*).ab,ti.	1717
9	(stem adj3 transplantation*).ab,ti.	55180
10	(stoma* adj3 transplantation*).ab,ti.	41
11	(cell adj3 transplantation*).ab,ti.	71010
12	(mesenchy* adj3 therap*).ab,ti.	2677
13	(stem adj3 therap*).ab,ti.	18152
14	stoma*adj3 therap*.ab,ti.	0
15	(cell adj3 therap*).ab,ti.	66260
16	(cell adj3 treatment*).ab,ti.	39957
17	(stoma* adj3 treatment*).ab,ti.	2052
18	(stem adj3 treatment*).ab,ti.	4093
19	(mesenchy* adj3 treatment*).ab,ti.	870
20	(bone marrow adj4 aspirat*).ab,kw,ti.	8584
21	((stromal adj4 fraction*) or "svf").ab,kw,ti.	2645
22	(stem cell adj4 enrichment*).ab,kw,ti.	269
23	or/1-22	262316
24	(Broncho* adj4 Dysplasia).ab,ti.	8995
25	(pulmonar* adj4 Dysplasia).ab,ti.	831
26	(lung* adj4 Dysplasia).ab,ti.	642
27	(bronchio* adj4 Dysplasia).ab,ti.	40

28	Bronchopulmonary Dysplasia/dt, th[Drug Therapy, Therapy]	1651
29	or/24-28	9798
30	23and29	229
31	infant,lowbirthweight/	20319
32	infant,smallforgestationalage/	8665
33	infant,verylowbirthweight/	9960
34	infant,premature/	61876
35	infant,extremelypremature/	3959
36	Rfi!l,b.ti-	29
37	Rrsaturn.b.ti-	138401
38	"Lowbirthweight*'.'...ab,li.	32306
39	(!m'.iorvlbworlt!llilab,ti.	10466
40	"Lowbirthweight*'.'...ab,ti	8598
41	"lnfanr'.'...ab,ti.	461814
42	Smallgestationalruie.Ji.	108
43	6.a.Qji	10682
44	Extremelyiirmsili!C!lb.tL	1501
45	or/31-44	610916
46	30and45	141

iii. PRISMA flow diagram



iv. Summary of included studies:

Study (Year)	Design	Participants (Sample size)	Intervention (n=33) (Age, Dose)	Comparison (n=33)	Outcome (Critical and Important) C= Control; I= Intervention
1. In Preterm neonates at high risk of Bronchopulmonary Dysplasia, what is the efficacy and safety of stem cell therapy as compared to usual care?					
Ahn et al. 2021[1]	**RCT**	N= 66 Gestation: 23 to 28 weeks; Birth weight: 500 to 1250 g **Inclusion:** Invasive ventilator support, enhanced ventilator settings within 24 hours before study enrollment. **Exclusion:** Severe congenital anomalies, lung hypoplasia, severe septic shock, or severe (grade ≥ 3) intraventricular hemorrhage (I.V.H.)	Age at MSC transplantation (postnatal days) :11.4 ± 2.4; Standardized human UCB-derived MSCs at passage 6; Intratracheal route, 1×10^7 cells/kg in 2 cc/kg of normal saline	An equal volume of normal saline. Usual care	**Critical:** Incidence of BPD (any severity): I=30/33(91%); C=32/33 (97%); Moderate to severe BPD – I = 13/33 (39.4%); C = 17/33 (51.5%); Mortality by one year of age- I = 3/33 (9.1%); C = 1/33 (3.0%); Composite outcome of death and moderate to severe BPD – I = 16/33 (48.5%); C = 18/33 (54.5%); Adverse neurodevelopmental outcome- I = 3/28 (10.71%); C = 22/31 (70.96%); Tumor formation- Not reported **Important:** Growth at one year – Not reported
2. In Infants with moderate and severe Bronchopulmonary Dysplasia, what is the efficacy and safety of stem cell therapy as compared to usual care					
No RCT available	-	-	-	-	-

GA: Gestational Age

iv. Evidence to decision framework

QUESTION 1 (Prevention of bronchopulmonary dysplasia)

Should stem cell therapy vs. routine care for prevention of bronchopulmonary dysplasia be used for BPD?	
POPULATION:	BPD high risk preterm neonates
INTERVENTION:	Stem cell therapy
COMPARISON:	Usual care
MAIN OUTCOMES:	Bronchopulmonary dysplasia, any severity, at 36 weeks PMA; Moderate to severe bronchopulmonary dysplasia; Composite outcome of mortality or moderate to severe BPD at 36 weeks PMA; Mortality at discharge; Cerebral palsy at 5 years; Blindness at 5 years; Deafness at 5 years; Motor delay at 5 years; Mental delay at 5 years; Social delay at 5 years.
SETTING:	Hospital/ Tertiary care
PERSPECTIVE:	Population
BACKGROUND:	Bronchopulmonary dysplasia (BPD) is a chronic respiratory condition that impacts premature infants who need mechanical ventilation and oxygen therapy.[2] A study by Bhunwal et al reported an incidence of 11.2% in preterm neonates (<33 week gestation) with respiratory distress with a higher incidence in infants <1 kg and <28 weeks gestation.[3]
CONFLICT OF INTERESTS:	None

ASSESSMENT

Problem Is the problem a priority?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	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.[2] It increases the duration of respiratory support, duration of hospital stays and also increases the risk of neurodevelopmental impairment.	

Desirable Effects How substantial are the desirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Trivial ○ Small ○ Moderate ○ Large ○ Varies ● Don't know	**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 to 1.14) 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. **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. **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. **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. **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.	

Undesirable Effects How substantial are the undesirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Trivial ○ Small ○ Moderate ○ Large ○ Varies ● Don't know	No serious adverse events related to MSCs were observed until six months after transplantation. We found no evidence on the possible undesirable effects of stem cell therapy such as tumor formation.	
Certainty of evidence What is the overall certainty of the evidence of effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
● Very low ○ Low ○ Moderate ○ High ○ No included studies	The certainty of evidence for all critical outcomes was very low.	
Values Is there important uncertainty about or variability in how much people value the main outcomes?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**

○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability	BPD is a major morbidity in preterm neonates, that increases the risk of neurodevelopmental impairment, respiratory morbidity, long term sequelae, growth delay.	
Balance of effects Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Favors the comparison ● Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	We found limited data on desirable effects, and no data on undesirable effects.	
Resources required How large are the resource requirements (costs)?		

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	Though autologous umbilical cord MSCs are readily available, retrieval, storage, culture and characterisation of stem cells would incur significant costs.	
Certainty of evidence of required resources What is the certainty of the evidence of resource requirements (costs)?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Very low ○ Low ● Moderate ○ High ○ No included studies	No direct evidence was identified.	The GDG was fairly confident that the required resources for stem cell therapy are large.
Cost effectiveness Does the cost-effectiveness of the intervention favor the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**

○ Favors the comparison ○ Probably favors the comparison ● Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ No included studies	No data	
Equity What would be the impact on health equity?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Reduced ● Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	No data	Stem cells retrieval, culture and characterisation needs special resources and expertise, that may not be available in resource-limited settings.
Acceptability Is the intervention acceptable to key stakeholders?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**

○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	No data	
Feasibility Is the intervention feasible to implement?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	No research evidence was identified regarding feasibility on the use of stem cell therapy in Bronchopulmonary Dysplasia.	

SUMMARY OF JUDGEMENTS (Prevention of bronchopulmonary dysplasia)

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	Moderate	Large		Varies	**Don't know**
UNDESIRABLE EFFECTS	Trivial	Small	Moderate	Large		Varies	**Don't know**
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			

BALANCE OF EFFECTS	Favors the comparison	**Probably favors the comparison**	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**Don't know**
RESOURCES REQUIRED	**Large costs**	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	**Moderate**	High			No included studies
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	**Does not favor either the intervention or the comparison**	Probably favors the intervention	Favors the intervention	Varies	No included studies
EQUITY	Reduced	**Probably reduced**	Probably no impact	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

QUESTION 2 (Treatment of established moderate and severe BPD)

Should stem cell therapy vs. routine care for infants with established moderate and severe BPD be used?	
POPULATION:	Premature infants with established moderate and severe BPD
INTERVENTION:	Stem cell therapy
COMPARISON:	Usual care
MAIN OUTCOMES:	Mortality by one year, Need for invasive ventilation or ventilator-free days at 40 weeks postmenstrual age, Adverse neurodevelopmental outcome at 18-24 months, Serious adverse events- mortality, tumor formation, Growth at one year
SETTING:	Hospital/ Tertiary care
PERSPECTIVE:	Population

BACKGROUND:	Bronchopulmonary dysplasia (BPD) is a chronic respiratory condition that impacts premature infants who need mechanical ventilation and oxygen therapy.[2] A study by Bhunwal et al reported an incidence of 11.2% in preterm neonates (<33 week gestation) with respiratory distress with a higher incidence in infants <1 kg and <28 weeks gestation.[3]
CONFLICT OF INTERESTS:	None

ASSESSMENT

Problem Is the problem a priority?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	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.[2] It increases the duration of respiratory support, duration of hospital stays and also increases the risk of neurodevelopmental impairment.	
Desirable Effects How substantial are the desirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Trivial ○ Small ○ Moderate ○ Large ○ Varies ● Don't know	No research evidence identified.	

Undesirable Effects How substantial are the undesirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Trivial ○ Small ○ Moderate ○ Large ○ Varies ● Don't know	No research evidence identified.	
Certainty of evidence What is the overall certainty of the evidence of effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Very low ○ Low ○ Moderate ○ High ● No included studies		
Values Is there important uncertainty about or variability in how much people value the main outcomes?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**

○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability	BPD is a major morbidity in preterm neonates, that increases the risk of neurodevelopmental impairment, respiratory morbidity, long term sequelae, growth delay.	
Balance of effects Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● Don't know	No evidence identified as no included studies.	
Resources required How large are the resource requirements (costs)?		

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	Though autologous umbilical cord MSCs are readily available, retrieval, storage, culture and characterisation of stem cells would incur significant costs.	
Certainty of evidence of required resources What is the certainty of the evidence of resource requirements (costs)?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Very low ○ Low ● Moderate ○ High ○ No included studies	No direct evidence was identified.	The GDG was fairly confident that the required resources for stem cell therapy are large.
Cost effectiveness Does the cost-effectiveness of the intervention favor the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**

○ Favors the comparison ● Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ No included studies	No data	
Equity What would be the impact on health equity?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Reduced ● Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	No data	Stem cells retrieval, culture and characterisation needs special resources and expertise, that may not be available in resource-limited settings.
Acceptability Is the intervention acceptable to key stakeholders?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**

○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	No data	
Feasibility Is the intervention feasible to implement?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	No research evidence was identified regarding feasibility on the use of stem cell therapy in Bronchopulmonary Dysplasia.	

SUMMARY OF JUDGEMENTS (Treatment of established moderate and severe BPD)

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	Moderate	Large		Varies	**Don't know**
UNDESIRABLE EFFECTS	Trivial	Small	Moderate	Large		Varies	**Don't know**
CERTAINTY OF EVIDENCE	Very low	Low	Moderate	High			**No included studies**
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			

BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**Don't know**
RESOURCES REQUIRED	**Large costs**	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	**Moderate**	High			No included studies
COST EFFECTIVENESS	Favors the comparison	**Probably favors the comparison**	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	No included studies
EQUITY	Reduced	**Probably reduced**	Probably no impact	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	**Conditional recommendation against the intervention**	**Use only in the context of rigorously conducted RCTs**	**Conditional recommendation for either the intervention or the comparison**	**Conditional recommendation for the intervention**	**Strong recommendation for the intervention**
○	○	●	○	○	○

CONCLUSIONS

Recommendation

Stem Cell Therapy is **not recommended** in routine practice for the treatment or prevention of bronchopulmonary dysplasia. It may be used only in the context of rigorously conducted randomized controlled trials.

Justification

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

v. Data extraction

Data Extraction Sheet:

Study	**Ahn et al. 2021[1]**
Study type	Phase II clinical trial was a randomized, double-blind, placebo- controlled two-center trial
Number of participants; (N)	66
Countries and setting	Neonatal intensive care units (NICUs) of Samsung Medical Center (SMC) and Asan Medical Center (AMC), Seoul, Korea
Duration of study Follow up (post intervention):	5 March 2013 and 23 March 2015
Method of assessment of disease condition:	Preterm infants with a gestational age of 23 to 28 weeks, weighing 500 to 1250 g at birth, and who were on continuous invasive ventilator support because of respiratory deterioration. Respiratory deterioration was defined as clinical signs of respiratory distress.
Subgroup analysis within study	
Inclusion criteria:	Preterm infants with a gestational age of 23 to 28 weeks, weighing 500 to 1250 g at birth, and who were on continuous invasive ventilator support because of respiratory deterioration.
Exclusion criteria:	Severe congenital anomalies, lung hypoplasia, severe septic shock, or severe (grade ≥ 3) intraventricular hemorrhage (IVH).

Recruitment/selection of patients:	Blocked randomization stratified according to gestational weeks.
Intervention: Source and type of stem cells	Standardized human UCB-derived MSCs at passage 6 (Pneumostem, Medipost Co, Seoul, Korea)
Intervention: Method of their characterization	Pneumostem, Medipost Co, Seoul, Korea
Intervention: Route of administration	Intratracheally via a gavage tube in two fractions into the left and right lungs.
Intervention: Dose	Total dose of 1 × 10^7 cells/kg in 2 cc/kg of normal saline
Intervention: Dose - If the trial has taken multiple doses, then which dose values has been used for MA	NA

Efficacy outcomes reported with time points

	The risk with routine care for prevention of bronchopulmonary dysplasia	**Anticipated absolute effects* (95% CI)** Risk with Stem cell therapy	**Relative effect (95% CI)**	**No of participants (studies)**	**Certainty of the evidence (GRADE)**	**Comment**
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 R.C.T.)	⊕⊕◯◯ Low[a]	
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 R.C.T.)	⊕⊕◯◯ Low[a]	
Composite outcome of mortality or moderate to 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 R.C.T.)	⊕⊕◯◯ Low[a]	
Mortality at discharge	30 per 1,000	85 per 1,000 (10 to 732)	RR 2.81 (0.33 to 24.16)	66 (1 R.C.T.)	⊕⊕◯◯ Low[a]	
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 R.C.T.)	⊕⊕◯◯ Low[a]	

Blindness at 5 years	0 per 1,000	0 per 1,000 (0 to 0)	not estimable	59 (1 R.C.T.)	⊕⊕◯◯ Low[a]	
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 R.C.T.)	⊕⊕◯◯ Low[a]	
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 R.C.T.)	⊕◯◯◯ Very Low[a,b]	
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 R.C.T.)	⊕◯◯◯ Very Low[a, b]	
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 R.C.T.)	⊕◯◯◯ Very Low[a, b]	

Safety outcomes reported with time points-Serious adverse events	No serious adverse events related to MSCs were observed until 6 months after transplantation.
Safety outcomes reported with time points-Other adverse events	No newly developed abnormal mass lesions were found on chest radiography and no significant abnormal results requiring correction were presented in laboratory tests [including complete blood count, glucose, aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, alkaline phosphatase, total protein, albumin, blood urea nitrogen, creatinine, and C-reactive protein] which were checked at 6 months after transplantation in all infants.
Funding	This study was supported by MEDIPOST (PHO0133531); the Future Medicine 2030 project of the Samsung Medical Center (#SMX1230441) and the Korea Drug Development Fund funded by the Ministry of Science and ICT, Ministry of Trade, Industry, and Energy and Ministry of Health and Welfare (HN22C0414, Republic of Korea). The funder had no role in data collection, data interpretation and data analysis.
ROB2 Assessment: Specify separately for each domain	Randomization process: Low Deviations from the intended interventions: Low Missing outcome data: Low Measurement of the outcome: Low Selection of the reported result: Low

viii. List of excluded studies:

Study	Exclusion reason
Zhuxiao et al. 2023[2]	Not an RCT
Xia et al. 2022[4]	Not an RCT
Boehme et al. 2022[5]	Not an RCT
Powell SB et al. 2019[6]	Not an RCT
Lim R et al. 2018[7]	Not an RCT
Ahn SY et al. 2017[1]	Follow- up study of open label, dose escalation phase I clinical trial
Rudnicki J et al. 2015[8]	Not an RCT; not related to use of stem cells in BPD
Chang YS et al. 2014[9]	Not an RCT
NCT01632475-2019[10]	Follow-up study of phase I trial
NCT03857841-2021[11]	Stopped early due to a business decision. Unpublished
NCT03645525[12]	Incomplete study – data not available as recruiting.

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10. Follow-Up Study of Safety and Efficacy of Pneumostem® in Premature Infants With Bronchopulmonary Dysplasia.ClinicalTrials.gov identifier: NCT01632475. Updated 2019-04-09. Accessed 2023-04-10. https://clinicaltrials.gov/study/NCT01632475?tab=table
11. A Safety Study of IV Stem Cell-derived Extracellular Vesicles (UNEX-42) in Preterm Neonates at High Risk for BPD. ClinicalTrials.gov identifier: NCT03857841. Updated: 2021-10-12. Accessed 2023-04-10.
12. https://clinicaltrials.gov/study/NCT0385784.

5. SPINAL MUSCULAR ATROPHY

i. **Key question in PICO format**

ii. **Search strategy**

iii. **PRISMA flow diagram**

iv. **Summary of included studies**

v. **Evidence to decision framework**

vi. **Data extraction**

vii. **List of excluded studies**

i. Key question in PICO format:

In patients with spinal muscular atrophy (SPA), what is the efficacy and safety of stem cell therapy as compared to usual care?

Population: Patient with spinal muscular atrophy
Intervention: Stem cell therapy
Comparator: Control/Usual care
Critical Outcomes: Primary Outcome Measures (Motor Function): Assessed using standardized measures such as HINE, Ballard Score, Respiratory parameters (FVC, FEV1), EMG study

Mortality: Tracked to assess the survival rate of patients

Adverse Events: Documented and categorized based on severity and frequency

ii. Search strategy (October 2023):

A comprehensive and systematic search was conducted to identify relevant studies on the efficacy and safety of stem cell therapy for the treatment of patients with Spinal Muscular Atrophy. The search was performed without language or publication date restrictions.

Category	Search Terms
Population (P)	"Muscular Atrophy, Spinal"[mesh] OR "Spinal Muscular Atroph*" OR "Adult-Onset Spinal Muscular Atrophy" OR "Amyotrophy, Neurogenic Scapuloperoneal, New England Type" OR "Bulbospinal Neuronopathy" OR "Distal Spinal Muscular Atrophy" OR "Hereditary Motor Neuronopathy" OR "Muscular Atrophy, Adult Spinal" OR "Myelopathic Muscular Atrophy" OR "Myelopathic Muscular Atrophy, Progressive" OR "Oculopharyngeal Spinal Muscular Atrophy" OR "Progressive Muscular Atrophy" OR "Progressive Myelopathic Muscular Atrophy" OR "Progressive Proximal Myelopathic Muscular Atrophy" OR "Proximal Myelopathic Muscular Atrophy, Progressive" OR "Scapuloperoneal Form of Spinal Muscular Atrophy" OR "Scapuloperoneal Spinal Muscular Atrophy" OR "Spinal Amyotrophy" OR "Spinal Muscular Atrophy, Distal" OR "Spinal Muscular Atrophy, Oculopharyngeal" OR "Spinal Muscular Atrophy, Scapuloperoneal" OR "Spinal Muscular Atrophy, Scapuloperoneal Form"
Intervention (I)	"Stem Cel*" OR "Fetal Stem Cells" OR "Hematopoietic Stem Cells" OR "Multipotent Stem Cells" OR "Myoblasts" OR "Neoplastic Stem Cells" OR "Neural Stem Cells" OR "Oogonial Stem Cells" OR "Pluripotent Stem Cells" OR "Side-Population Cells" OR "Totipotent Stem Cells"
Comparison (C)	"Standard care" OR "placebo" OR "conventional treatment" OR "control" OR “treatment” OR “therapy” OR “care” OR “procedure” OR “routine” OR “intervention”

The final search strategy will be created by combining the Population, Intervention and comparator components using the AND Boolean operator.

Results:
Study selection: Comprehensive research was done in Medline/PubMed, Cochrane Central, Web of Science, and Embase using the defined search term. Only 2 articles were included in the study as given in Prisma diagram.

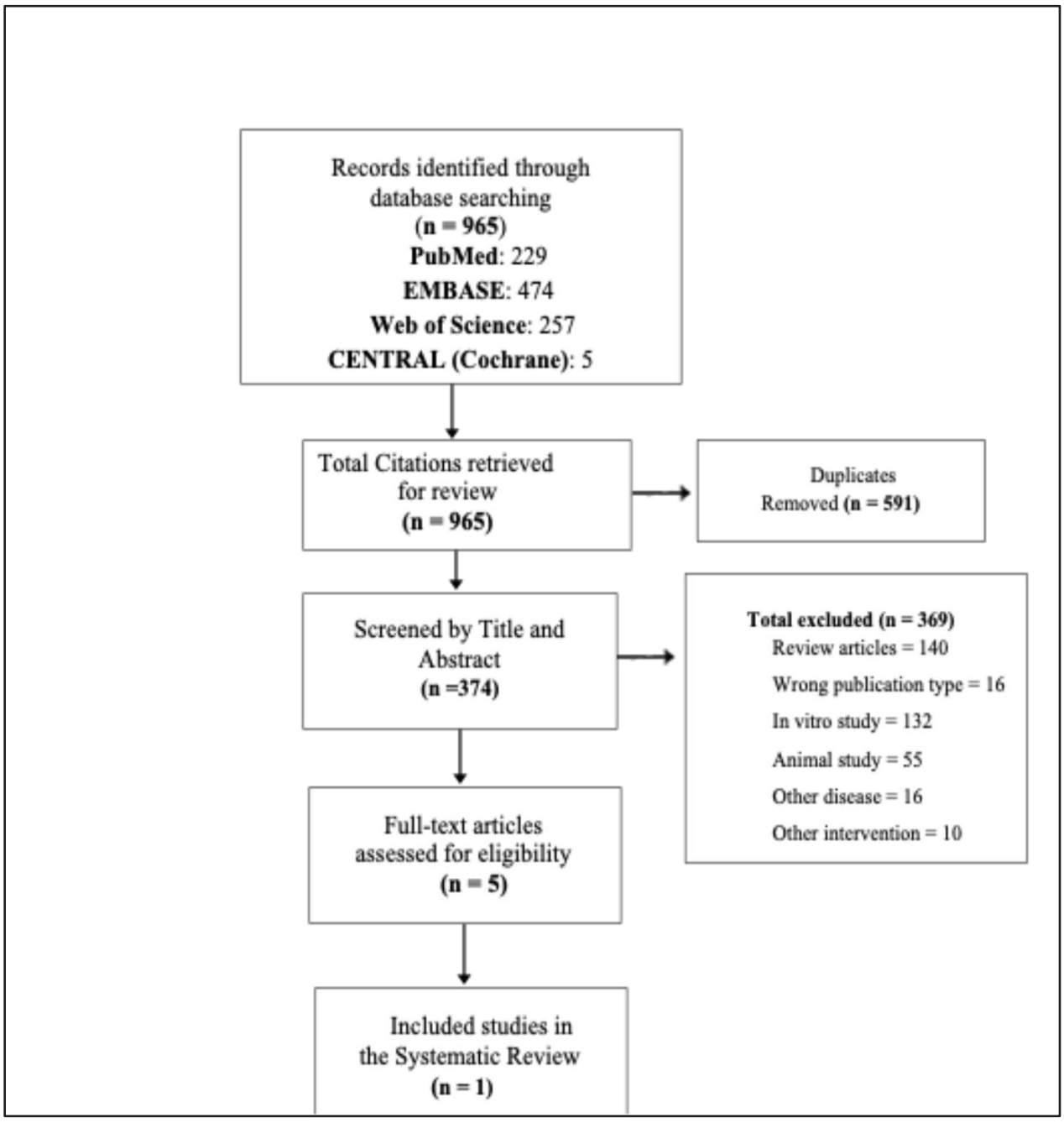
Inclusion criteria:

- Study design: Randomized controlled trials
- Participants: Patients of any age and gender clinically diagnosed with spinal muscular atrophy.
- Interventions: Studies evaluating transplantation or infusion of any stem cell type as Adult Stem Cells, Fetal Stem Cells, Hematopoietic Stem Cells, Multipotent Stem Cells, Myoblasts, Neoplastic Stem Cells, Neural Stem Cells, Oogonial Stem Cells, Pluripotent Stem Cells, Side-Population Cells, and Totipotent Stem Cells injected through intracerebral, intrathecal, intravenous, intranasal or any other route.
- Comparators: Placebo, no intervention, standard care, or pharmacological therapy.
- Outcomes: Primary outcomes are motor function, quality of life, mortality by 2 years, need for respiratory support, and adverse events. Secondary outcomes include feeding issues etc.

Exclusion criteria:

- Study design: Reviews, case reports, case series, editorials, letters, commentaries, and animal studies
- Participants: Studies involving patients with diseases other than spinal muscular atrophy will be excluded. Limits will be applied for humans only.
- Interventions: Studies investigating stem cell therapies along with additional interventions like gene therapy, biomaterials etc. Studies just analyze extracted stem cell products like exosomes and secretomes.
- Outcomes: Studies not reporting outcomes of interest.
- Others: Abstracts, protocols, unpublished data, ongoing trials without results.

iii. PRISMA flow Diagram:



iv. Summary of included studies:

Study	Type of study	Population	Intervention	Outcome	Result
Mohseni et al.[1]	Phase 1 clinical trial in patients with SMA1 who received side population adipose-derived mesenchymal stem cells - SPADMSCs	Ten patients with genetically confirmed smn1 deletion of exon 7 and 8 and two copy number of smn2. The patients included were under 12 months of age, with hypotonia, weakness, paradoxical respiration, and need for respiratory support. They were randomly divided into equal groups of intervention and control.	The SPADMSC cells were administered via intrathecal route in the lumbar L4-L5 area. Patients received three intrathecal doses of 10^6, 2×10^6 and 5×10^6 cells/kg every 15 days.	The primary outcome measures were safety and tolerability of SPADMSCs. The secondary outcome measures were the mean changes in HINE and Ballard scores and EDX studies.	The treatment was safe and well tolerated, without any adverse effect. One of the patients in the intervention group was alive after 24 months of study. Clinical scores, need for supportive ventilation, and number of hospitalizations were not meaningful parameters in the response of patients in the intervention and control groups. All five patients in the intervention group showed significant improvement in the motor amplitude response of the tibial nerve.

Related studies

Only one study could be included in the review. However, a case series was found regarding the stem cell therapy. In the study, three children with spinal muscular atrophytype 1 underwent multiple intrathecal and intravenous infusions of mesenchymal stem cells. Their pretreatment, treatment, and posttreatment physical function were quantitated by the Children's Hospital of Philadelphia. Infant Test of Neuromuscular Disorders scale was used for two patients and documented by video for all three. Test for neuromuscular disorders in infants had a value of 3 before treatment; 10 and 16 during treatment. After discontinuation of treatment, the value was 0 and 10 at seven and twelve months, respectively. No adverse effects have been noted for at least 44 and 49 months from onset of treatment, respectively. This data represents quantifiable improvements in physical function for any treatment of spinal muscular atrophy. Although the benefits were lost when the therapy was withdrawn, this may be an initial step in establishing mesenchymal stem cells as a safe and effective treatment of spinal muscular atrophy.[3]

v. **Evidence to decision framework:**

QUESTION

Should stem cell therapy vs. standard care be used for treating spinal muscular atrophy?	
POPULATION:	Spinal muscular atrophy patients
INTERVENTION:	Stem cell therapy
COMPARISON:	Standard care
MAIN OUTCOMES:	Safety and tolerability of the allogeneic side population adipose-derived mesenchymal stem cells; Survival at 24 months follow up; Life expectancy; Ballard Score; NCV: Median nerve; NCV: Ulnar nerve; NCV: Tibial Nerve; NCV: Peroneal nerve.
SETTING:	Hospital/ Tertiary care
PERSPECTIVE:	Population
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.[4]
CONFLICT OF INTERESTS:	None

ASSESSMENT

Problem Is the problem a priority?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes	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.[4]	

● Yes ○ Varies ○ Don't know		
Desirable Effects How substantial are the desirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Trivial ○ Small ○ Moderate ○ Large ○ Varies ● Don't know	**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. **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. **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. **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		

How substantial are the undesirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Trivial ○ Small ○ Moderate ○ Large ○ Varies ● Don't know	The treatment was safe and well tolerated, without any adverse effect.	
Certainty of evidence What is the overall certainty of the evidence of effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
● Very low ○ Low ○ Moderate ○ High ○ No included studies	The certainty of evidence is very low due to high risk of bias, inconsistent and imprecise results.	
Values Is there important uncertainty about or variability in how much people value the main outcomes?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability	Patients, parents and caregivers valued improved motor and breathing function, disease stabilization, independence and ability to perform basic personal tasks.	

○ No important uncertainty or variability		
Balance of effects Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Favors the comparison ○ Probably favors the comparison ● Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	It is less clear if benefits of stem cell intervention outweigh the harms, based on the limited evidence.	
Resources required How large are the resource requirements (costs)?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
● Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	No direct evidence of the resources required in stem cell transplantation in patients with SMA has been identified. On a global scale, the most frequently reported range for single treatment is $10,000 to $20,000. However, the cost is influenced by several factors such as type, quality, and source of stem cells, the condition to be treated, and the location of the treatment facility.[5]	
Certainty of evidence of required resources		

What is the certainty of the evidence of resource requirements (costs)?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Very low ○ Low ● Moderate ○ High ○ No included studies		The GDG was fairly certain that stem cell therapy requires large resources.
Cost effectiveness Does the cost-effectiveness of the intervention favor the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Favors the comparison ● Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ No included studies	No research evidence was identified.	The intervention was not found to be effective and hence the committee deferred to comment on cost effectiveness.
Equity What would be the impact on health equity?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**

○ Reduced ● Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	No research evidence was identified.	As stem cell therapy is an expensive treatment offered only at tertiary centres, it is likely to reduce equity.
Acceptability Is the intervention acceptable to key stakeholders?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	No research evidence was identified	
Feasibility Is the intervention feasible to implement?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	No research evidence was identified	

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	Moderate	Large		Varies	**Don't know**
UNDESIRABLE EFFECTS	Trivial	Small	Moderate	Large		Varies	**Don't know**
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	**Does not favor either the intervention or the comparison**	Probably favors the intervention	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	**Large costs**	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	**Moderate**	High			No included studies
COST EFFECTIVENESS	Favors the comparison	**Probably favors the comparison**	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	No included studies
EQUITY	Reduced	**Probably reduced**	Probably no impact	Probably increased	Increased	Varies	Don't know

	JUDGEMENT						
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	**Use only in the context of rigorously conducted clinical trials**	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	○	●	○	○	○

CONCLUSIONS

Recommendation

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 recommendation is not applicable to gene therapy.

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.

vi. Data extraction:

Data Extraction Methods:

Abstract Screening: Two independent reviewers conducted the initial screening of titles and abstracts to identify potentially relevant studies using the Rayyan platform.[6] Any discrepancies between the reviewers were resolved through discussion or consultation with a third reviewer. Studies that did not met the inclusion criteria were excluded at this stage.

Handsearching and reference searches: Handsearching of the included studies or already published relevant review articles was done. Bibliography of papers that matched the eligibility criteria was searched manually to identify any further relevant references, which was subjected to the same screening and selection process.

Full-Text Review: The full text of the selected abstracts were retrieved and assessed for eligibility by the same two independent reviewers. Any disagreements were resolved through the discussion or consultation with a third reviewer. Data extraction was done in Microsoft Excel. Zotero[7] was used to keep track of references and identify duplicates.

Quality Assessment: The quality of the included studies was assessed using appropriate tools based on the study design - Cochrane Risk of Bias Tool for RCTs. Two independent reviewers conducted the quality assessment, and any disagreements were resolved by a third reviewer.

Data Extraction Sheet:

Study	**Mohseni et al. 2022[1]**
Study type	Phase I clinical trial was a randomized, double-blind, placebo- controlled two-center trial
Number of participants; (N)	10 infants (5 in intervention, 5 in control)
Countries and setting	Neonatal intensive care units (NICUs) of Samsung Medical Center (SMC) and Asan Medical Center (AMC), Seoul, Korea
Duration of study Follow up (post intervention):	5 March 2013 and 23 March 2015
Method of assessment of disease condition:	Preterm infants with a gestational age of 23 to 28 weeks, weighing 500 to 1250 g at birth, and who were on continuous invasive ventilator support because of respiratory deterioration. Respiratory deterioration was defined as clinical signs of respiratory distress.
Subgroup analysis within study	-
Inclusion criteria:	Ten patients with genetically confirmed smn1 deletion of exon 7 and 8; and two copy number of SMN2. The patients included were under 12 months of age, with hypotonia, weakness, paradoxical respiration, and need for respiratory support. They were randomly divided into equal groups of intervention and control.

Exclusion criteria:	-
Recruitment/selection of patients:	Blocked randomization stratified according to gestational weeks.
Intervention: Source and type of stem cells	Side population adipose-derived mesenchymal stem cells (SPADMSCs)
Intervention: Method of their characterization	The SPADMSC cells were administered via intrathecal route in the lumbar L4- L5 area. Patients received three intrathecal doses.
Intervention: Route of administration	Intratracheally
Intervention: Dose	Doses of 10^6, 2×10^6 and 5×10^6 cells/kg every 15 days.
Intervention: Dose - If the trial has taken multiple doses, then which dose values has been used for SMA	NA
Efficacy outcomes reported with time points	Survival, Life expectancy, Ballard Score, Nerve Conduction Velocity studies
Safety outcomes reported with time points-Serious adverse events	The treatment was safe and well tolerated, without any adverse effect. One of the patients in the intervention group was alive after 24 months of study. Clinical scores, need for supportive ventilation, and number of hospitalizations were not meaningful parameters in the response of patients in the intervention and control groups. All five patients in the intervention group showed significant improvement in the motor amplitude response of the tibial nerve.
Safety outcomes reported with time points-Other adverse events	The primary outcome measures were safety and tolerability of SPADMSCs. The secondary outcome measures were the mean changes in HINE and Ballard scores and EDX studies.
Funding	94-01-87-28524/Tehran University of Medical Sciences and Health Services The funder had no role in data collection, data interpretation and data analysis.
ROB2 Assessment: Specify separately for each domain	Randomization process: High Deviations from the intended interventions: Low Missing outcome data: Low Measurement of the outcome: some concerns Selection of the reported result: Low

vii. List of excluded studies:

1. Sych N, Klunnyk M, Matiyashchuk I, Demchuk M, Ivankova O, Sinelnyk A, Sorochynska K, &Skalozub M. (2017). Feasibility of combined treatment for type III spinal muscular atrophy: A pilot study. *Journal of Neurorestorology, 5*(0), 167-173.
2. Villanova M, Bach J. R. (2015). Allogeneic mesenchymal stem cell therapy outcomes for three patients with spinal muscular atrophy type 1. American Journal of Physical Medicine & Rehabilitation, 94(5), 410-415.
3. Zaharieva I. T, Scot M, Aragon-Gawinska K, Ridout D, Doreste B, Servais L, Muntoni F, Zhou H. Y. (2022). Response of plasma microRNAs to nusinersen treatment in patients with SMA. Annals of Clinical and Translational Neurology, 9(7), 1011-1026.
4. Mendell J. R, Al-Zaidy S, Shell R, Arnold W. D, Rodino-Klapac , Prior T. W, Lowes L. P, Alfano L. N, Berry K, Church K, Kissel J. T, Nagendran S, L'Italien J, Sproule D. M, Wells C, Burghes A. H. M, Foust K. D, Meyer K, Likhite S, Kaspar B. K. (2018). AVXS-101 phase 1 gene replacement therapy clinical trial in spinal muscular atrophy type 1 (SMA1): 24-month event-free survival and achievement of developmental milestones. Human Gene Therapy, 29(12), A22-A22.
5. Lorenzi M, Jansen J. P, White C, Maru B, Sproule D, Feltner D, Droege M, Dabbous O. (2018). Indirect treatment comparison of AVXS-101 to nusinersen for the treatment of type 1 spinal muscular atrophy (SMA1). Human Gene Therapy, 29(12), A143-A143.
6. Deutsch L, Osredkar D, Plavec J, Stres B. (2021). Spinal muscular atrophy after nusinersen therapy: Improved physiology in pediatric patients with no significant change in urine, serum, and liquor 1h-NMR metabolomes in comparison to an age-matched, healthy cohort. Metabolites, 11(4)

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1. 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.
2. RoB 2: A revised Cochrane risk-of-bias tool for randomized trials | Cochrane Bias [Internet]. [cited 2023 Dec 11]. Available from: https://methods.cochrane.org/bias/resources/rob-2-revised-cochrane-risk-bias-tool-randomized-trials.
3. Villanova M, Bach J. Allogeneic Mesenchymal Stem Cell Therapy Outcomes for Three Patients with Spinal Muscular Atrophy Type 1. Am J Phys Med Rehabil. 2015 May; 94(5):410–5.
4. Verhaart IEC, Robertson A, Wilson, IJ, Aartsma-Rus A, Cameron S, Jones CC, Cook SF, Lochmüller H. Prevalence, Incidence and Carrier Frequency of 5q-Linked Spinal Muscular Atrophy—A Literature Review. Orphanet J. Rare Dis. 2017, 12, 124.
5. https://www.startstemcells.com/stem-cell-therapy-cost.htmlRayyan - AI Powered Tool for Systematic Literature Reviews [Internet]. 2021 [cited 2023 Mar 9]. Available from: https://www.rayyan.ai/.
6. Zotero | Your personal research assistant [Internet]. [cited 2023 Oct 20]. Available from: https://www.zotero.org/.

6.HYPOXIC ISCHEMIC ENCEPHALOPATHY

i. **Key question in PICO format**

ii. **Search strategy**

iii. **PRISMA flow diagram**

iv. **Summary of included studies**

v. **Evidence to decision framework**

vi. **Data extraction**

vii. **List of excluded studies**

i. Key question in PICO format:

In patients with moderate and severe Hypoxic Ischemic Encephalopathy (HIE), what is the efficacy and safety of stem cell therapy as compared to usual care?

Population: Neonates with Hypoxic Ischemic Encephalopathy Subgroup: Term and preterm
Intervention: Any stem cell and product derived from stem cells or their derivatives
Comparator: Usual Care/ Conventional Care
Critical Outcomes: Mortality by one-year age
Adverse neurodevelopmental outcomes at 18-24 months
Serious adverse events- mortality, tumor formation

ii. Search strategy (October 2023):

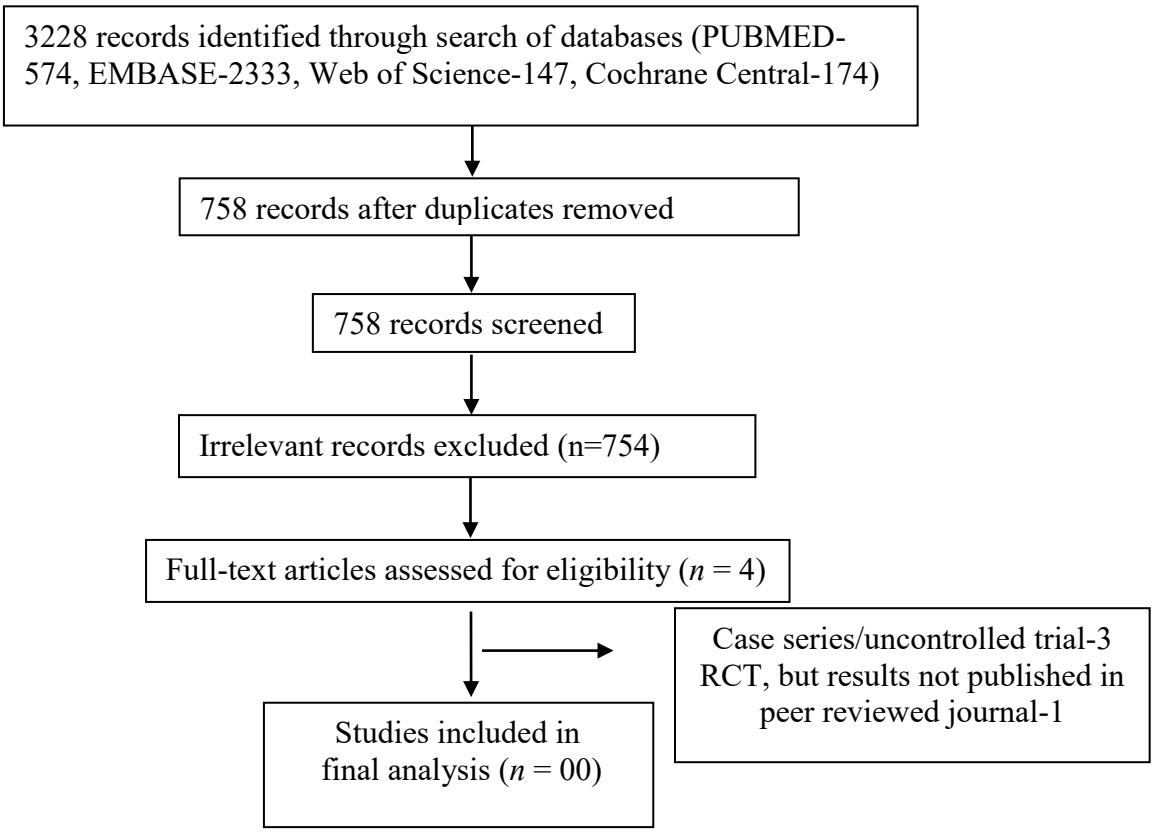
The terminologies (MeSH terms or entry terms) used was divided into three basic groups: study population (newborn, neonate, infant), terms describing or related to hypoxic ischemic encephalopathy (asphyxia, asphyxia neonatorum, hypoxia, ischemia, brain injury), and terms describing or related to stem cell products (stem cell, regenerative cell, mesenchymal cell, cord blood cell, mononuclear cell). Using these MeSH terms or entry terms and suitable Boolean operators, specific search strategies were developed for each search engine. The electronic search was later supplemented by a manual search of the references of the included articles, to identify additional articles. Truncation was used for terms like "stem cell" and "hypoxia" to widen the search and include all relevant keywords. The Boolean function "OR" was used to find articles which use different spellings for ischemia. The only filter applied was to include human studies and randomized controlled trials. No limitation to the date of publishing was applied and articles up to September 2023 were included. All the articles were reviewed by two independent authors.

PubMed Search strategy

We used the advanced search syntax provided by the platform.
(infant, newborn[MeSH] OR newborn*[TIAB] OR "new born"[TIAB] OR "new borns"[TIAB] OR "newly born"[TIAB] OR baby*[TIAB] OR babies*[TIAB] OR premature[TIAB] OR prematurity[TIAB] OR preterm[TIAB] OR "pre term"[TIAB] OR "low birth weight"[TIAB] OR "low birthweight"[TIAB] OR VLBW[TIAB] OR LBW[TIAB] OR infan*[TIAB] OR neonat*[TIAB]) AND ((randomised controlled trial [pt] OR controlled clinical trial [pt] OR randomised [tiab] OR placebo [tiab] OR drug therapy [sh] OR randomly [tiab] OR trial [tiab] OR groups [tiab]) NOT (animals [mh] NOT humans [mh])) AND (("Stem Cells"[Mesh] OR "Stem Cell Transplantation"[Mesh] OR "Stromal Cells"[Mesh] OR "stem cell"[tiab] OR "stem cells"[tiab] OR "mesenchymal cell" OR "mesenchymal cells" OR "mononuclear cell" OR "mononuclear cells" OR "progenitor cell" OR "progenitor cells" OR "cord blood cell" OR "cord blood cells" OR "regenerative cell" OR "regenerative cells" OR "stromal cell" OR "stromal cells") AND (brain injury OR neuro-protect* OR neuro-restorative OR neuroprotect* OR "Asphyxia Neonatorum"[MeSH] OR "Hypoxia-Ischemia, Brain"[MeSH] OR Asphyxia* OR Hypoxia OR Hypoxic OR Hypoxemia OR Hypoxaemia OR Ischemia OR Ischaemia OR ischaemic OR Ischaemic OR anoxia)).
This strategy searched for the specified terms using MeSH (Medical Subject Headings) terms in PubMed/MEDLINE. We adjusted the MeSH Terms as needed based on the controlled vocabulary of PubMed/MEDLINE. Similar search strategies were developed for other search engines.

Study selection: Comprehensive research was done inMedline/PubMed, EMBASE, Cochrane and other search engines followed by duplicates removal and screening of articles as given in Prisma diagram. No completed RCTs, which were peer-reviewed and published for inclusion, were identified.

iii. PRISMA flow diagram:



iv. Summary of included studies:

No studies were found eligible as per the inclusion criteria finalized by the GDG.

v. Evidence to decision Framework:

QUESTION

Should SCT vs. control be used for Hypoxic-ischaemic encephalopathy (HIE)?	
POPULATION:	Patients with Hypoxic-ischaemic encephalopathy (HIE)
INTERVENTION:	Stem Cell Therapy
COMPARISON:	Usual Care
MAIN OUTCOMES:	Critical: Mortality by one year age, Adverse neurodevelopmental outcomes at 18-24 months, Serious adverse events-mortality, tumor formation Important: Growth of infants
SETTING:	Hospital/ Tertiary care
PERSPECTIVE:	Population
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.
CONFLICT OF INTERESTS:	None

ASSESSMENT

Problem Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Annually, 1.15 million infants experience HIE, with 96% of cases occurring in low- and middle-income nations. Approximately 25% of neonates with HIE do not survive, and about 35% face persistent neurodevelopmental challenges.	
Desirable Effects How substantial are the desirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○Trivial ○Small ○ Moderate ○ Large ○ Varies ●Don't know	No evidence identified as no studies were included.	
Undesirable Effects How substantial are the undesirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Trivial ○ Small ○ Moderate ○ Large ○ Varies ● Don't know	No evidence identified as no studies were included.	

Certainty of evidence What is the overall certainty of the evidence of effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Very low ○ Low ○ Moderate ○ High ● No included studies	No research evidence identified.	
Values Is there important uncertainty about or variability in how much people value the main outcomes?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability	Various measures which are highly valued by most patients, parents and caregivers is identification of blood biomarkers which help in indication of HIE and various measures to improve oxygen supply to brain.	
Balance of effects Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**

○ Favors the comparison ○ Probably favors the comparison ○Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ●Don't know	No evidence identified as no included studies.	
Resources required How large are the resource requirements (costs)?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
● Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	No direct evidence of the resources required in stem cell transplantation in patients with HIE has been identified. On a global scale, the most frequently reported range for single treatment is $10,000 to $20,000. However, the cost is influenced by several factors such as type, quality, and source of stem cells, the condition to be treated, and the location of the treatment facility.[1]	
Certainty of evidence of required resources What is the certainty of the evidence of resource requirements (costs)?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**

○ Very low ○ Low ● Moderate ○ High ○No included studies	No research evidence was identified.	The GDG members were fairly certain that stem cell therapy requires large resources.
Cost effectiveness Does the cost-effectiveness of the intervention favor the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Favors the comparison ● Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ No included studies	No research evidence was identified.	
Equity What would be the impact on health equity?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**

○ Reduced ● Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	No research evidence was identified	

Acceptability Is the intervention acceptable to key stakeholders?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ●Probably yes ○ Yes ○ Varies ○ Don't know	No research evidence was identified.	

Feasibility Is the intervention feasible to implement?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ●Probably yes ○ Yes ○ Varies ○ Don't know	No research evidence was identified.	

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	**Trivial**	Small	Moderate	Large		Varies	**Don't know**
UNDESIRABLE EFFECTS	Trivial	**Small**	Moderate	Large		Varies	**Don't know**
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			**No included studies**
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	**Probably favors the comparison**	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the interventio n	Varies	**Don't know**
RESOURCES REQUIRED	**Large costs**	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	**Very low**	Low	**Moderate**	High			No included studies
COST EFFECTIVENESS	Favors the comparison	**Probably favors the comparison**	**Does not favor either the intervention or the comparison**	Probably favors the intervention	Favors the interventio n	Varies	No included studies
EQUITY	Reduced	**Probably reduced**	Probably no impact	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Use only in the context of rigorously conducted RCTs	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	○	●	○	○	○

CONCLUSIONS

Recommendation

Stem Cell Therapy is **not recommended** in routine practice for the treatment of HIE. It may be used only in the context of rigorously conducted randomized controlled trials.

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.

vi. Data extraction:

Data Extraction Methods:

A predesigned, standardized, well-structured proforma was developed for data extraction. Two investigators independently reviewed the eligible articles and extracted data from their full text. The extracted data included as much information available from the following:- administrative details: study author(s), published or unpublished, year of publication, year in which the study was conducted, presence of vested interest, details of other relevant papers cited; details of the study: study design, type, duration, and completeness of follow-up (e.g., greater than 80%), country and location of the study, informed consent, ethics approval; details of participants: sex, birth weight, gestational age, number of participants; details of interventions: initiation, dose, and duration of MSCs administration, co-intervention such as cooling; details of outcomes as mentioned above under types of outcome measures. The disagreements were resolved by discussion.

Ongoing studies identified by our search, when available, detailing the primary author, research question(s), methods, and outcome measures, together were described with an estimate of the reporting date. In case of queries, or requirement of additional data, study investigators/authors were contacted for further clarifications.

Measures of treatment effect:

Risk ratios (RRs), risk differences (RDs), numbers needed to treat for an additional beneficial outcome (NNTB) or numbers needed to treat for an additional harmful outcome (NNTH) for categorical variables, and mean differences (MDs) for continuous variables were used. Any within-group SEM reported in a trial was replaced by its corresponding SD using the formula $SD = SEM \times \sqrt{n}$, where n is the number of participants. For each statistic, 95% confidence intervals (CIs) was reported.

Unit of analysis issues

RCTs in which the unit of allocation was the individual: neonate or infant were included.

Dealing with missing data

A dropout rate for each study was obtained. In case a significant dropout rate (e.g. greater than 20%) was obtained, study author(s) was contacted and requested for additional data. A sensitivity analysis was performed to evaluate the overall results with and without the inclusion of studies with a significant dropout rate. If a study reported outcomes only for participants completing the trial or only for participants who followed the protocol, the study author(s) were contacted to ask them to provide additional information to facilitate an intention-to-treat analysis; in instances when this was not possible, a complete-case analysis was performed.

vii. List of excluded studies:

The study conducted by Cotten et al.[2] in 2020 in the USA (NCT02612155), a quadruple-blinded Randomized Controlled Trial (RCT) was undertaken, involving the infusion of autologous cord blood. The trial included 17 participants in the intervention group and 18 in the placebo group, with 14 and 15 participants completing the study, respectively.

Regarding efficacy outcomes, there was a notable trend towards a higher number of participants in the intervention group with Bayley III scores ≥85 in all three domains (12/14 vs. 6/15, p=0.06). In terms of safety outcomes, comparable results were observed between the two groups for the number of participants with seizures on follow-up, those requiring gastrostomy tube feeding, those needing anti-seizure medication (ASM) at discharge, and those requiring inhaled nitric oxide (iNO) or extracorporeal membrane oxygenation (ECMO). Notably, one death was reported in each group, with two participants lost to follow-up. Serious Adverse Events (SAEs) occurred in 1/17 in the intervention group compared to 2/18 in the placebo group. Additionally, other adverse events were reported in 1/17 in the intervention group and 3/18 in the placebo group. In the study by Cotten et al[3] conducted in 2014 (a phase 1 open-label study), 23 infants (≥35 weeks of gestation) which met criteria for HIE and hypothermia treatment requirement were included. The study involved administering up to four infusions of 1 to 5×10^7 UCB cells/kg, with the first dose given soon after birth and subsequent doses at 24, 48, and 72 hours postnatally. Hydrocortisone pretreatment was administered, and outcomes included the need for extracorporeal membrane oxygenation and seizure medications at discharge. Cell recipients and concurrent cooled infants had similar hospital outcomes. Thirteen of 18 (74%) cell recipients and 19 of 46 (41%) concurrent cooled infants with known 1-year outcomes survived with scores >85. Vital signs including oxygen saturation were similar before and after infusions in the first 48 postnatal hours.

Cotten et al[4] in 2023 conducted another phase I open-label study involving umbilical cord tissue-derived mesenchymal stromal cells (hCT-MSC) in infants undergoing hypothermia for HIE. Eligible infants (≥35 weeks gestation) were treated with hCT-MSC, with primary safety outcomes focusing on infusion reactions or infections within two weeks. Six infants were enrolled, receiving intravenous doses within 48 hours postnatally, and a second dose at two months for some. The study monitored Apgar scores, positive panel reactive antibody (PRA) screen, and length of stay, with no re-hospitalizations reported. All babies survived, with average to low-average developmental assessment standard scores for ages between 12 and 17 postnatal months. hCT-MSC infusions were well tolerated although 5/6 babies developed low titer anti-HLA antibodies by 1 year of age.

Tsuji et al in 2020[5] in a phase I open-label study, explored intravenous infusion of autologous umbilical cord blood cells in newborns with HIE. For infants born with severe asphyxia following caesarean section, umbilical cord blood (UCB) was collected, volume-reduced, and divided into three doses. $CD34^+$ cell concentrations varied per dose, infused at specific intervals post-birth. At 30 days, all six infants survived without circulatory or respiratory support; at 18 months, four had normal neurofunctional development, while two exhibited delayed developments with CP. The physiological parameters and peripheral blood parameters did not change much between pre- and post-infusion. There were no SAEs that might be related to cell therapy.

Author, year	Methodology	Results	Adverse effects
Cotten et al. 2020[2], USA (NCT02612155)	Quadruple blinded RCT, infusion of autologous cord blood, 17 in intervention vs 18 in placebo group, 14 vs 15 completed	Trend towards more number of participants with Bayley III scores ≥85 in all three domains in intervention group (12/14 vs 6/15, p=0.06). Number of participants with seizures on follow up, requiring gastrostomy tube feeding, required ASM at discharge, required iNO or ECMO were comparable between both groups.	1 death in each group, 2 lost to follow up, SAE 1/17 vs 2/18 (intervention vs placebo), other adverse events 1/17 vs 3/18
Cotten et al. 2014[3], USA (NCT00593242)	Open-labelled uncontrolled trial of 23 neonates with HIE who also received hypothermia, UCB cells (up to 4 doses)	Cell recipients and concurrent cooled infants had similar hospital outcomes. Thirteen of 18 (74%) cell recipients and 19 of 46 (41%) concurrent cooled infants with known 1-year outcomes survived with scores >85.	Vital signs including oxygen saturation were similar before and after infusions in the first 48 postnatal hours.
Cotten et al. 2023[4], USA (NCT03635450)	Open-labelled trial, 6 babies with moderate/severe HIE, randomized to receive either one or two dose of 2 million cells/kg/dose of hCT-MSC given intravenously	All babies survived, with average to low-average developmental assessment standard scores for ages between 12 and 17 postnatal months.	hCT-MSC infusions were well tolerated although 5/6 babies developed low titer anti-HLA antibodies by 1 year of age
Tsuji et al. 2020[4], Japan	Autologous cord blood cell therapy for six neonates at 12-24, 36-48, and 60-72 hours in an open labelled trial	At 30 days of age, the six infants survived without circulatory or respiratory support. At 18 months of age, neurofunctional development was normal without any impairment in four infants and delayed with CP in two infants.	The physiological parameters and peripheral blood parameters did not change much between pre- and post- infusion. There were no SAEs that might be related to cell therapy.

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2. NCT02612155. A multi-site study of autologous cord blood cells for hypoxic ischemic encephalopathy. clinicaltrials.gov/ct2/show/nct02612155
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7. OSTEOGENESIS IMPERFECTA

i. **Key question in PICO format**

ii. **Search strategy**

iii. **PRISMA flow diagram**

iv. **Summary of included studies**

v. **Evidence to decision framework**

i. Key question in PICO format: In patients with Osteogenesis Imperfecta, what is the efficacy and safety of stem cell therapy as compared to usual care?

Problem: Patients with Osteogenesis Imperfecta (fetus/new born and children)
Intervention: Any stem cell and product derived from stem cells or their derivatives
Comparator: Usual standard care / conventional care
Critical Outcome: 1. Incidence/frequency of fracture
2. Growth
3. Serious Adverse Event (including those in the mothers in case of fetal therapy)- mortality, tumor formation
4. Ambulation
Important:
1. Quality of Life
2. Severity of pain

ii. Search strategy (October 2023):
Search terms: osteogenesis imperfect, brittle bone disease, stem cell therapy, mesenchymal stem cells, stromal cells, fetal stem cells, adipose derived stem cells, in utero transplantation, pre-natal transplantation.

PubMed:

("osteogenesis imperfecta"[MeSH Terms] OR ("osteogenesis imperfecta type 2a"[All Fields] OR "osteogenesis imperfecta type 1a"[All Fields] OR "osteogenesis imperfecta type v"[All Fields] OR "Osteogenesis Imperfecta Type VII"[All Fields] OR "osteogenesis imperfecta type 3"[All Fields] OR "osteogenesis imperfecta type ix"[All Fields] OR "osteogenesis imperfecta type 6"[All Fields] OR "osteogenesis imperfecta type 2b"[All Fields] OR "osteogenesis imperfecta type viii"[All Fields] OR "osteogenesis imperfecta type iv"[All Fields] OR "osteogenesis imperfecta levin type"[All Fields] OR "Bruck syndrome 1"[All Fields])) AND ("Cord Blood Stem Cell Transplantation"[MeSH Terms] OR "Stem Cell Research"[MeSH Terms] OR "Hematopoietic Stem Cell Transplantation"[MeSH Terms] OR "Mesenchymal Stem Cell Transplantation"[MeSH Terms] OR "Fetal Stem Cells"[MeSH Terms] OR "Erythroid Precursor Cells"[MeSH Terms])

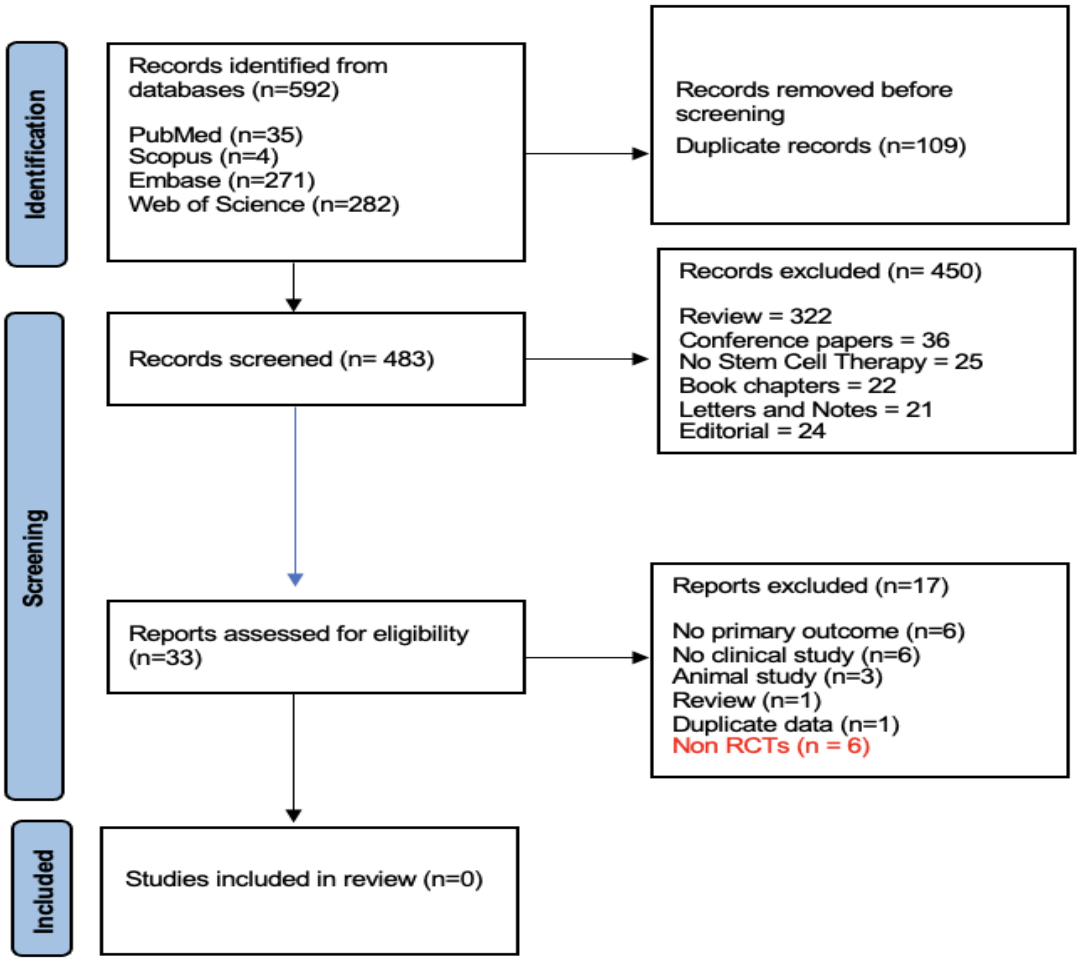
Embase:
('osteogenesis imperfecta'/exp OR 'osteogenesis imperfecta' OR 'osteogenesis imperfecta type1' OR 'osteogenesis imperfecta type 2'/exp OR 'osteogenesis imperfecta type 2' OR 'osteogenesis imperfecta type 3'/exp OR 'osteogenesis imperfecta type 3' OR 'osteogenesis imperfecta type 4' OR 'osteogenesis imperfecta type 5' OR 'osteogenesis imperfecta type 6' OR 'osteogenesis imperfecta type 7' OR 'osteogenesis imperfecta type 9' OR 'osteogenesis imperfecta levine type' OR 'bruck syndrome'/exp OR 'bruck syndrome') AND ('stem cell transplantation'/exp OR 'stem cell transplantation' OR 'erythropoietic stem cell therapy' OR 'hematopoietic stem cell therapy'/exp OR 'hematopoietic stem cell therapy' OR 'mesenchymal stem cell therapy'/exp OR 'mesenchymal stem cell therapy' OR 'foetal stem cell therapy')

Cochrane Library:
("osteogenesis imperfecta" OR "brittle bone disease"):ti,ab,kw AND ("stem-cells" OR "mesenchymal stem-cells" OR "erythropoietic stem-cells" OR "hematopoietic stem-cells" OR "foetal stem-cells"):ti,ab,kw

Scopus:
(TITLE-ABS-KEY (osteogenesis AND imperfecta OR osteogenesis AND imperfecta AND type 1 OR osteogenesis AND imperfecta AND type 2 OR osteogenesis AND imperfecta AND type 3 OR osteogenesis AND imperfecta AND type 4OR osteogenesis AND imperfecta AND type 5 OR osteogenesis AND imperfecta AND type 6 OR osteogenesis AND imperfecta AND type 7 OR osteogenesis AND imperfecta AND type 8 OR osteogenesis AND imperfecta AND type 9) AND TITLE-ABS-KEY (stem AND cell AND therapy OR erythropoietic AND stem AND cell AND therapy OR hematopoietic AND stem AND cell AND therapy OR foetal AND stem AND cell AND therapy OR mesenchymal AND stem AND cells))

Web of Science:
osteogenesis imperfecta OR brittle bone disease OR 'osteogenesis imperfecta type1 OR 'osteogenesis imperfecta type 2 OR 'osteogenesis imperfecta type 3 OR 'osteogenesis imperfecta type 4 OR 'osteogenesis imperfecta type 5 OR 'osteogenesis imperfecta type 6 OR 'osteogenesis imperfecta type 7 OR 'osteogenesis imperfecta type 8 OR 'osteogenesis imperfecta type 9 (Topic) AND stem cell therapy OR mesenchymal stem-cells therapy OR erythropoietic stem-cells therapy OR hematopoietic stem-cells therapy OR foetal stem-cells therapy (Topic)

iii. PRISMA flow diagram:



iv. Summary of included studies:

Six studies were found on the topic. No study could be included in the review as none of the eligible studies were RCTs. Data for few of the non-randomized studies is as shown below:

Study	Study details	Type of Study	Sample size	Intervention	Pre conditioning	Outcomes	Toxicity
Horwitz et al[1]	St. Jude Children's Research Hospital, USA 1999	Case Series	3	Intravenous infusion with unmanipulated stem cell from HLA identical or single-antigen-mismatched siblings	13 m/F Conditioning Regimen: Busalfan (1mg/kg x 16 doses) Ara-C (2g/m^2 x 6 doses) Cyclo (45mg/kg x 2 doses) Total Cell dose: 5.7 x 10^8 cells/Kg 13 m/M Conditioning Regimen: Busalfan (40mg/m^2 x 8 doses) Cyclo (60mg/kg x 2 doses) TBI (180 cGy x 5 doses) Total Cell dose: 6.2 x 10^8 cells/Kg	1. Persistent hemopoietic cells: At 6 months Pt 1 had 21% chimerism while Pt 2&3 had 99% donor cells. 2. Improvement in bone histology: Iliac bone biopsy showed high turnover upto 216 days post transplantation. 3. Increase in total body bone mineral content uto21 – 29 g in 100 days post transplantation. Pt 1: 28.0 g to 49.6 g; Pt 2: 67.0g to 96.8g; 4. Increase in DEXA score. 5. Improvement in growth velocity as compared to age and sex matched normal children. Pt had grown at 50% rate, Pt 2 at 40% and Pt 3 at 0% in the period 6 - 13 months period prior	Pt 2 had sepsis, pulmonary insufficiency, bifrontal hygroma

					32 m/M Busalfan (1mg/kg x 16 doses) Cyclo (50mg/kg x 4 doses) Total Cell dose: 7.5x 10^8 cells/Kg	transfusion but all grew at 100% rates post transfusion (Pt 1 – 8 cm in 7 months, Pt 2 – 6.5 cm in 6 months, Pt 3 – 1.5cm in 12 months) 6. Decreased fracture frequency: Pt 1 had 37 fractures, Pt 2 had 20 while Pt 3 had 3 fractures during the 13 months prior transfusion but they reported respectively 3,2 and 0 fractures in the first 6 months post transfusion.	
Horwitz et al[2]	St. Jude Children's Research Hospital, USA 2001	Case Control Study	Intervention group= 3 Control group = 2	Not detailed	13 m/F Conditioning Regimen: Busalfan (1mg/kg x 16 doses) Ara-C (2g/m^2 X 6 doses) Cyclo (45mg/kg x2 doses) Total Cell dose: 5.7 x 10^8 cells/Kg	1. Increased growth: Prior to transfusion, the cases grew at a median of 5 cms while controls grew at 7.2cms between 6 -13 Mo of age. Post transfusion, the cases grew by median of 7.5 cms while the controls grew by 1.25 cms during the first 6 months.	1. Pt 2 – Sepsis, Transient pulmonary insufficiency, Bifrontal hygroma 2. Pt 3 – Acute Graft versus host disease

					13 m/M Conditioning Regimen: Busalfan(40mg/ m^2x 8 doses) Cyclo (60mg/kg x 2 doses) TBI (180 cGy x 5 doses) Total Cell dose: 6.2 x 10^8 cells/Kg 17 m/M Busalfan (1mg/kg x 16 doses) Cyclo (50mg/kg x4 doses) Total Cell dose: 5.5x 10^8 cells/Kg	2. Increase in total body bone mineral content (TBBMC): All the study subjects had 25-60% of TBBMC as compared to weight matched normal kids prior transfusion. Post transfusion, the cases showed an increase of 45-77% above baseline (21.5 g to 65.3g) while controls had an increase of 25-60% only during first 3 months 3. Reduced Fractures frequency: All the study subjects had a mean of 10(4 -18) fractures in the 6 months prior to transfusion. The cases had a mean of 2(0-3) fractures in the first 6 months and 2(1 – 2) fractures in the next 6 months post transfusion. The controls had a mean of 4(3 – 5) fractures during the same time period.	
Horwitz et al[3]	St. Jude Children's	Case series	6 (3y5m/	Bone Marrow Stromal Cells		1. The median transduction efficiency of	Patient 6 showed

	Research Hospital, USA 2002		M, 4y9m/ M, 2y10m/ M, 3y9mm /F, 3y5m/F , 3y11m/ M)	were injected to patients, after being harvested from appropriate donors and being cultured in laboratory. Each patient received 2 injections of MSCs 8 – 21 days apart. The target dose for 1st infusion was 1X 10^6 cells/Kg of body weight and for the 2nd dose was 5 X 10^6 cells/Kg of body weight.		the MSC being infused was 19% (2 – 25%). 2. The MSCs showed consistent osteogenic differentiation potentials when cultured in osteoinductive media. 3. Skin biopsies and bone marrow aspirates from the patients, taken 4 – 6 weeks after transfusion showed engraftment of the transfused MSCs in their tissues. 4. Five of the six patients did not have detectable antibodies levels against FBS after the two transfusions. 5. Increase in growth velocity: The cases had only 20% of median growth velocity compared to age and sex matched normal children prior transfusionbut it increase to 60 to 94% of the predicted median during first 6 months post transfusion. 6. Patient 6 showed increase in TBBMC from 156 g to 209 g at 3 months	Urticarial Rash 5 min after 2nd transfusion (Resolved spontaneously)

						after MSC therapy	
Le Blanc et al[4]	Karolinska University Hospital Huddinge, Sweden 2005	Case report	1	Intra uterine Fetal infusion of MSC, derived from fetal liver cells, at 32nd week of gestation.		1. The baby was born at 35 weeks of gestation. 2. She had Apgar scores of 9 and 10 at 1 and 5 min, 3. Birth weight of 1,669 g (< 2 SD), length of 40 cm (- 3 SD), and head circumference of 29 cm (- 2.5 SD) 4. She had radiographic features of severe OI 5. She had femur fracture at birth 6. She had clavicle fracture at 6 weeks, rib fracture at 9 months and another femur fracture at 15 months 7. DEXA scan showed 48% bone mineralisation that of age and sex matched controls at 3 months, 56% at 12 months and 76% at 22 months. 8. She had normal psychomotor development 9. Her height was small but growth rate was normal to age and sex matched control at 2 years 10. Her bone biopsy at	None

						9 months of age showed regularly arranged and configured bone trabeculae. Cellularity was 100% in the marrow cavity. 11. Samples taken from her umbilical cord at birth, and skin and bone marrow samples at 9 months showed no trace of donor DNA 12. No antibody against donor MSCs was detected in her blood samples	
Gotherstrom et al[5]	Karolinska Institutet and Karolinska University Hospital, Sweden Yong Loo Lin School of Medicine and National University of Singapore 2014	Case control study	Intervention group = 2 Control = 1 Pt 1: OI type III Pt 2: OI type IV Control: OI type II/III	Human fetal mesenchymal stem cells isolated from the fetal liver cells were transfused to the cases pre natally and post natally		Pt 1: Pre-natal transfusion – 6.5 x10^6 hfMScs at 31 weeks Post natal transfusion – 42x10^6 hfMScs at 8y2m 1. No new fractures Improved growth velocity 2. Improved TBBMC Pt 2: Pre natal transfusion – 40x10^6 hfMScs at 31 wks Post natal transfusion – 88x10^6 hfMScs at 19Mo 11days 1. No new fractures 2. Improved growth velocity	None

						No transfusion done The control died at 5 months of age	
Infante et al[6]	Biocruces Bizkaia Health Research Institute, Cruces University Hospital, Spain 2021	Case series	2 (6y1m/ M, 8y1m/F)	HLA haploidentical Mesenchymal Stem Cell obtained from bone marrow aspirates of healthy siblings was cultured and infused to the affected patients. Each patient received five infusions of $4x10^6$ MSCs/Kg each dose, 5-6 months apart.		1. Reduced fracture frequency. 2. Improvement in bone mineral density (BMD). 3. Improvement of HRQoL parameters	

M - male; F - female; m – months; y – years; Ara-C - cytarabine; Cyclo - cyclophosphamide; TBI - total body irradiation (added because sibling donor was a HLA DRβ1 mismatch)

vi. Evidence to decision Framework:

QUESTION

Should SCT vs. control be used for Osteogenesis Imperfecta?	
POPULATION:	Patients with Osteogenesis Imperfecta
INTERVENTION:	Stem Cell Therapy
COMPARISON:	Usual Care
MAIN OUTCOMES:	Incidence/frequency of fracture, Growth, Serious Adverse Event (including those in the mothers in case of fetal therapy)- mortality, tumor formation, Ambulation
SETTING:	Hospital/ Tertiary care
PERSPECTIVE:	Health System/ Population
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.
CONFLICT OF INTERESTS:	None

ASSESSMENT

Problem Is the problem a priority?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**

○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	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.	
Desirable Effects How substantial are the desirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○Trivial ○Small ○ Moderate ○ Large ○ Varies ●Don't know	No research evidence identified.	
Undesirable Effects How substantial are the undesirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Trivial ○ Small ○ Moderate ○ Large ○ Varies ● Don't know	No research evidence identified.	
Certainty of evidence What is the overall certainty of the evidence of effects?		

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○Very low ○ Low ○ Moderate ○ High ● No included studies	No included studies.	
Values Is there important uncertainty about or variability in how much people value the main outcomes?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability	Main outcome is improvement in muscle strength and functional ability which is likely to be highly valued by most patients, parents and caregivers	
Balance of effects Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**

○ Favors the comparison ○ Probably favors the comparison ○Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ●Don't know	No evidence identified as no included studies.	
Resources required How large are the resource requirements (costs)?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
● Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	No direct evidence of the resources required in stem cell transplantation in patients with OI has been identified. On a global scale, the most frequently reported range for single treatment is $10,000 to $20,000. However, the cost is influenced by several factors such as type, quality, and source of stem cells, the condition to be treated, and the location of the treatment facility.[7]	
Certainty of evidence of required resources What is the certainty of the evidence of resource requirements (costs)?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**

○ Very low ○ Low ● Moderate ○ High ○No included studies		The GDG members were fairly certain that stem cell therapy requires large resources.
Cost effectiveness Does the cost-effectiveness of the intervention favor the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Favors the comparison ● Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ No included studies	No research evidence identified.	
Equity What would be the impact on health equity?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**

○ Reduced ● Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	No research evidence was identified	
Acceptability Is the intervention acceptable to key stakeholders?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ●Probably yes ○ Yes ○ Varies ○ Don't know	No research evidence was identified	
Feasibility Is the intervention feasible to implement?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ●Probably yes ○ Yes ○ Varies ○ Don't know	No research evidence was identified.	

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	**Trivial**	Small	Moderate	Large		Varies	**Don't know**
UNDESIRABLE EFFECTS	Trivial	**Small**	Moderate	Large		Varies	**Don't know**
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			**No included studies**
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	**Probably favors the comparison**	Does not favor either the intervention or the comparison	Probably favors the interventio n	Favors the interventio n	Varies	**Don't know**
RESOURCES REQUIRED	**Large costs**	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	**Very low**	Low	**Moderate**	High			**No included studies**
COST EFFECTIVENESS	Favors the comparison	**Probably favors the comparison**	**Does not favor either the intervention or the comparison**	Probably favors the interventio n	Favors the interventio n	Varies	No included studies
EQUITY	Reduced	**Probably reduced**	Probably no impact	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Use only in the context of rigorously conducted clinical trials	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	○	●	○	○	○

CONCLUSIONS

Recommendation

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.

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.

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