Evidence-based Guidelines for the use of Stem Cell Therapy

Respiratory Conditions

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Department of Health Research
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DISCLAIMER

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

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 All MoHFW guidelines are subject to regular review and may be updated or withdrawn.

MESSAGE

In this evolving and promising landscape of modern medicine, stem cell therapy stands as one of the most dynamic areas of scientific enquiry. Its potential to revolutionize the treatment of a wide array of conditions, from degenerative diseases to traumatic injuries, has generated immense excitement and hope. Keeping the highest quality of evidence as the foundational base for formulating recommendations is of utmost importance.

The Evidence-based guidelines for the use of stem cell therapy represent a comprehensive synthesis of the best available evidence providing a framework for clinicians, researchers, and policymakers alike. Devised to support the responsible integration of stem cell treatment into clinical practice, these guidelines offer clear and transparent evidence-based recommendations that are based on latest scientific knowledge backed by a rigorous methodology.

As we navigate the complexities of stem cell therapy, it is imperative that we balance innovation with caution. The guidelines aim to address this balance by emphasizing the importance of rigorous clinical trials, ethical considerations, and patient safety. In closing, we commend the contributors for their dedication in creating these evidence-based guidelines for the use of stem cell therapy and look forward to more such guidelines in the future.

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Secretary DHR & DG, ICMR

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DGHS

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ACKNOWLEDGEMENTS

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

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ABBREVIATIONS

ARDS	:	Acute Respiratory Distress Syndrome
CI	:	Confidence Interval
DoIs	:	Declaration of Interests
ESC	:	Embryonic Stem Cell
EtD	:	Evidence to Decision
GDG	:	Guideline Development Group
GDT	:	Guideline Development Tool
GRADE	:	Grading of Recommendations Assessment, Development and Evaluation
ICU	:	Intensive Care Unit
iPSC	:	induced Pluripotent Stem Cell
MSC	:	Mesenchymal Stromal Stem Cell
MA	:	Meta-Analysis
MCID	:	Minimal Clinically Important Difference
MD	:	Mean Difference
NICE	:	National Institute for Care and Health Excellence
PICO	:	Population Intervention, Comparator and Outcome
RCTs	:	Randomized Controlled Trials
RoB-2	:	Risk of Bias- 2
RR	:	Risk Ratio
SAE	:	Serious Adverse Event
SMD	:	Standardized Mean Difference
SR	:	Systematic Review
VFDs	:	Ventilator Free Days
WHO	:	World Health Organization

EXECUTIVE SUMMARY

1. Background & Rationale:

Acute Respiratory Distress Syndrome (ARDS) is a severe pulmonary condition characterized by diffuse lung inflammation and oedema that commonly causes acute respiratory failure. Common causes include pneumonia, non-pulmonary sepsis, aspiration of gastric contents and major trauma. It has persistently high mortality rate with no robust pharmacological treatments. Due to the drastic increase in the ARDS incidence during COVID-19 pandemic, global awareness heightened leading to a surge in the number of clinical trials. Various cell types including embryonic stem cell (ESC), induced pluripotent stem cell (iPSC) and mesenchymal stromal stem cell (MSC) have been investigated for their therapeutic potential in ARDS. These stem cells possess unique regenerative and immunomodulatory properties which promote lung tissue repair and modulate the exaggerated inflammatory response seen in ARDS. Several mechanisms underpin MSC-based treatments in ARDS, including homing to the intrapulmonary injury site, the regulation of immune and inflammatory cells, the paracrine action of cytokines, the secretion of exosomes with benefits, and the attenuation of pulmonary fibrosis. It is quintessential to take an evidence-based approach during the development of such regenerative therapies, with the best quality evidence being sought to determine the true effectiveness & efficacy of such approaches. The overall goal of these guidelines is to provide evidence-based recommendations for the use of stem cell therapy in acute respiratory distress syndrome.

2. Target audience:

The recommendations in this guideline are intended to inform the policy makers, patients and health care professionals especially pulmonologists practicing in tertiary care centers as well as researchers and scientists working in the field of regenerative medicine regarding the efficacy and safety of stem cell therapy in acute respiratory distress syndrome.

3. Guideline Development Methods:

This guideline was developed using standard methodology as described by international agencies like the World Health Organization (WHO) and National Institute for Care and Health Excellence (NICE).[1,2] This involved the creation of a steering group, a guideline development group and systematic review teams. Briefly, the process involved: (i) Identifying priority review questions, (ii) Evidence synthesis by systematic review (SR) & meta-analysis (MA), (iii)Review of evidence profiles and grading the certainty of evidence (iv) Formulation of recommendations using the Evidence to Decision (EtD) framework (v) Drafting the guideline (vi) External review and (vii) Dissemination of guidelines. The GRADE approach (Grading of Recommendations Assessment, Development and Evaluation) was used to assess the certainty of evidence for each review question. The evidence

generated was analyzed by the GDG to make judgments and formulate recommendations based on the EtD Framework in the GRADEpro GDT software. This included assessment of the effects (balance between benefits and harms) of the intervention, values and preferences of the patients, resources required, cost effectiveness, acceptability and feasibility of the intervention and equity considerations. In brief, the GDG members examined the evidence, made judgments on the EtD framework for each disease condition, and formulated the wording of the final recommendations. This was followed by external peer review before the final release of guidelines.

4. Summary of Recommendations:

S. No.	Key Question	Recommendation	Rationale/Justification
1.	In patients with Acute Respiratory Distress Syndrome (ARDS), what is the efficacy and safety of stem cell therapy compared to usual care?	Stem cell therapy is **not recommended** in routine clinical practice for the treatment of ARDS. Strength: Conditional# Certainty of Evidence: Very Low *#It may be used only in the context of rigorously conducted randomized controlled trials.*	There is very low certainty evidence of trivial improvement in pulmonary function and trivial reduction in mortality. There is little to no difference in undesirable effects between stem cell therapy and usual care.

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

I. GUIDELINE DEVELOPMENT PROCESS

1. Introduction:

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

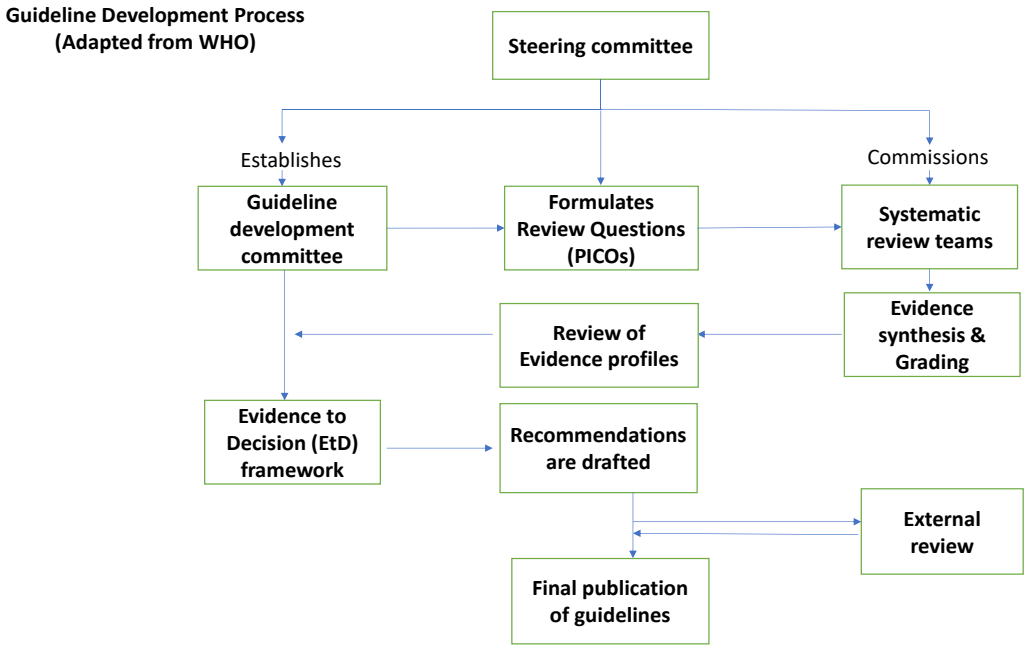

Figure 1: Guideline Development Process –adapted from WHO[1]

2. Rationale/ Scope:

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

therapy despite limited knowledge of its safety and efficacy. Realizing that therapeutic applications need to be based on rational and ethical premises, these guidelines aim to summarize the evidence available on the efficacy and safety of stem cell therapy to guide informed decisions.

The disease condition included for review in the present guidelines is Acute Respiratory Distress Syndrome (ARDS). This was selected based on the directives from the MoHFW and a review of literature on the therapeutic use of stem cell therapy in respiratory disorders. The guidelines aim to provide guidance for the responsible, safe, and effective use of stem cell therapy and highlight the research gaps at which future endeavors need to be targeted.

3. Target audience:

The recommendations in this guideline are intended to inform the policymakers, patients and health care professionals especially pulmonologists practicing tertiary care centers as well as researchers and scientists working in the field of regenerative medicine regarding the safety and efficacy of stem cell therapy in aforementioned respiratory conditions.

4. Contributors:

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

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

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

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

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

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

5. Management of conflict of interests:

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

All the potential GDG members had submitted the duly filled Declaration of Interest (DoIs) form adapted from the WHO.2 These declarations were then reviewed by the steering group and managed appropriately. A summary of the DOIs and how they were managed is provided in Annexure-3.

6. Defining the scope and key questions:

The steering group held a meeting with the potential GDG members to identify the priority disease conditions on which the efficacy and safety of stem cell therapy need to be reviewed. A list of 10 broad disease groups was finalized including a total of 28 conditions. The respiratory disease included only one condition namely acute respiratory distress syndrome (ARDS).

Thereafter, a meeting was held by the GDG to decide on the key review questions relevant for the selected diseases in the PICO format i.e. Population, Intervention, Comparator and Outcome. The outcomes that matter most to the concerned population were carefully selected and specified as critical outcomes for the guideline development. *These questions were formulated without keeping the literature in mind in order to obviate bias. Considering the scarcity of evidence for this experimental intervention, it was decided to keep the PICO question as broad as possible and do a subsequent subgroup analysis for relevant subgroups as needed.*

7. Systematic reviews:

Commissioning of Systematic Reviews: Once the review questions were identified, the ICMR-DHR secretariat floated an Expression of Interest inviting experts in the field from all over the country to conduct systematic reviews and meta-analysis. Out of a total of 130 applications received, 28 teams were selected to conduct SRs and MA. The criteria for evaluation included methodological expertise, subject expertise, quality of systematic reviews published, database access, strength of team and conflict of interests, if any. The systematic reviews were thus commissioned and all the teams were provided with the review questions in PICO format as finalized by the GDG. The ICMR-DHR secretariat and the methodologists provided oversight, including assessment and feedback on each systematic review protocol. The data extraction was checked to ensure uniformity and transparency in the entire process of guideline development.

Literature search strategy: To maintain a uniform methodology, all the systematic review teams were instructed to design literature searches on the following databases: PubMed, Embase, Web of Science, and Cochrane CENTRAL. **Only randomized controlled trials were included in the systematic review.** No grey literature was included. However, hand-searching of references to find relevant review articles was carried out. Non-English articles were excluded only if translation was not possible. Regarding 'Population', for any disease condition, all the grades of severity were included, and subgroup analyses (if mentioned apriori in the protocol) was done wherever needed. All interventions with well characterized stem cells or stem cell-derived products were included.

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

- No evidence of randomization
- More than 30% of randomized patients deviated from allocated intervention post-randomization
- Absence of stem cell characterization (flow cytometry or immuno- phenotyping or culture)

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

Data extraction methods: Data extraction was conducted by the systematic review teams and reviewed by the ICMR-DHR secretariat and the methodologists. The level of manipulation done to develop stem cell and stem cell derived products was interpreted by DHR secretariat into less than or more than minimal manipulation as defined by CDSCO (Annexure 1) and information provided in the trial itself. The teams were advised to use plot digitizer wherever feasible, if values were not available in text. Imputations and assumptions were best to be avoided. All methodological queries were resolved with the help of guideline methodologists and the teams were also advised to refer to the *Cochrane Handbook for Systematic Reviews of Interventions* to resolve any methodological queries.[3] While doing meta-analysis, the use of standardized mean difference (SMD) was discouraged, as it is easier to compare mean difference (MD) with the minimal clinically important difference (MCID).

Risk of Bias Assessment: Risk of bias for each study outcome was assessed using the Revised Cochrane Risk of Bias-2 (RoB-2) tool.[4] For assessment, the following terms of reference were agreed upon by the GDG and provided to all the systematic review teams:

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

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

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

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

9. Grading of the certainty of the evidence:

The GRADE approach was used to access the certainty of evidence using the GRADEpro GDT software (https://www.gradepro.org/). At baseline, RCTs start with high certainty of evidence and this certainty can be downgraded based on pre-defined criteria like the risk of bias, inconsistency, imprecision, indirectness, and publication bias. Publication bias was evaluated only if the number of studies for a particular meta-analysis were more than 10. If the studies were less than 10, it was considered inevaluable. The systematic review teams completed their reviews and shared the evidence profiles with the guideline secretariat. The secretariat then reviewed the evidence profiles

with the help of guideline methodologists and any discrepancies in the review were resolved through discussion with the systematic review teams. The table below highlights the significance of the certainty of evidence as per the GRADE approach.[5]

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

10. Drafting of recommendations using Evidence to Decision (EtD) frameworks:

The Guideline secretariat prepared the draft EtD frameworks. The EtD Framework available on the GRADEpro GDT software was used to draft recommendations. It consists of a set of criteria that determine the strength and direction of a recommendation to bring about transparency in the formulation of recommendations. These criteria include the certainty of evidence, the balance between benefits and harms, the acceptability and feasibility of the intervention, patient values and preferences, equity considerations, resource use and cost effectiveness. Prior to drafting recommendations, all the GDG members were apprised of this framework and every criterion was explained in detail. The secretariat presented these frameworks along with a review of evidence profile and forest plots provided by the systematic review teams to the GDG.

11. Formulation of recommendations:

The GDG members were asked to make judgments on each of the domain of the EtD framework based on the evidence presented to them. Judgments on the desirable and undesirable effects were based on the findings of the systematic reviews and meta-analysis. Review of literature/research evidence as well as the experience of the GDG members was used to inform the discussions pertaining to patient values and preferences, resource use and cost effectiveness, acceptability, feasibility of the intervention along with equity considerations. Wherever research evidence was unavailable, the opinion of the GDG was recorded in additional considerations. The entire body of evidence was put into the GRADE EtD framework for drafting the final recommendation for each review question.

Thorough discussion and deliberation was held on each of the domains with an aim to reach consensus on each judgment. Based on the voting for judgments for each domain, final voting was done to determine the strength and direction of the recommendation. The final recommendation for

each disease condition was made by consensus, defined as an agreement by 75% or more of the GDG members. Consensus was reached for all recommendations in this guideline and there were no strong disagreements. The GDG also identified caveats in the existing evidence and prioritized areas for future research.

12. Strength of recommendations:

The strength of a recommendation is the extent to which the GDG is confident in the balance between the desirable and undesirable effects of the intervention, across the range of patients for whom the recommendations are intended. When a GDG was very certain about this balance (for example the desirable effects clearly outweighing the undesirable effects), a strong recommendation in favor of an intervention or against the intervention was issued and vice versa. However, when the GDG was uncertain about this balance, a conditional recommendation was issued. Owing to the experimental nature of the stem cell therapy, a separate column of *"may be used only in the context of rigorously conducted randomized controlled trials"* was added by the GDG in the Evidence to Decision framework of these guidelines.[6]

13. Document preparation and peer review:

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

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II. RECOMMENDATIONS

1. ACUTE RESPIRATORY DISTRESS SYNDROME

A. BACKGROUND:

Acute respiratory distress syndrome (ARDS) is a life-threatening respiratory condition characterized by hypoxemia, and stiff lungs, which often requires invasive mechanical ventilation. An Indian study reported the incidence of ARDS among mechanically ventilated patients to be 11.4% with sepsis being the most common (34.6%) risk factor.[1] Other common risk factors of ARDS include severe pneumonia, trauma, aspiration of gastric contents etc. Despite decades of clinical studies, pharmacological treatments such as glucocorticoids, pulmonary surfactants, inhaled nitric oxide, antioxidants, protease inhibitors and anti-inflammatory drugs, have demonstrated limited efficacy in the management of ARDS. The mortality rate associated with ARDS was reported as 39.3% from a systematic review and meta-analysis (SRMA) of studies from 2009-2019 and survivors frequently experience long-term complications and reduced quality of life.[2]

B. RECOMMENDATIONS:

Stem cell therapy is **not recommended** in routine clinical practice for the treatment of Acute Respiratory Distress Syndrome.

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

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

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

Rationale/Justification:
This recommendation has been made as there is very low certainty evidence of trivial improvement in pulmonary function and trivial reduction in mortality in patients with ARDS. There is little to no difference in undesirable effects between stem cell therapy and usual care. 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 and limited period of follow-up.

C. SUMMARY OF EVIDENCE:

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

Included Studies: A total of 5044 studies were identified (PubMed=1060, Embase=2676, Web of Science=1187, Cochrane Library=121) for initial screening. 1032 duplicate records were removed and a total of 4012 articles were screened by their titles, followed by abstracts. 3981 articles were excluded based on the inclusion criteria of the review, leaving only 31 studies for full text screening. Out of these, 16 studies did not meet the eligibility criteria and were excluded due to varying reasons leading to 15 studies[3-17] that were included in the review. **All the included studies fall under the category of more than minimal manipulation.**

These 15 studies, involving 418 participants in the intervention group and 345 in the comparator group, were primarily focused on COVID-19 associated ARDS with disease severity ranging from moderate to severe. Only randomized controlled trials were included, where stem cells either mesenchymal or induced pluripotent stem cells were administered in patients with ARDS. Thirteen studies compared the intervention against a placebo, and the predominant study design was phase 1/2 clinical trials, with safety as the primary outcome. Stem cells were primarily sourced from bone marrow or umbilical cord. Most studies had a follow-up duration of 28 days.

Critical outcomes reviewed:

S. No.	Outcomes	What does it measure?
1.	All-cause mortality	Number of deaths due to any cause over a given period of time.
2.	Ventilator free days (VFDs) (Higher is better)	Composite outcome including patient being alive without mechanical ventilation, calculated within a specific timeframe.
3.	ICU-free days (Higher is better)	Patient being alive and out of Intensive Care Unit (ICU) within a specified period.
4.	Duration of hospital stay (Lower is better)	Total number of days for which the patient was hospitalized.
5.	Serious adverse events	-

Risk of Bias Assessment:

1. Risk of bias of each individual study according to the Cochrane risk of bias-2 tool for all-cause mortality:

	Bias arising from the randomization process	Bias due to deviations from intended interventions	Bias due to missing outcome data	Bias in measurement of the outcome	Bias in selection of the reported result	Overall bias
Cécile Pochon	+	+	+	+	-	-
Amy L. Lightner	+	+	+	+	+	+
Bellingan G	+	+	+	+	+	+
Ichikado K	+	+	+	+	-	-
Zarrabi M	+	+	+	+	+	+
Rebelatto	+	+	+	+	+	+
Fathi-Kazerooni	+	+	+	+	-	-
Gorman Ellen A	+	+	+	+	-	-
Zheng G	+	+	-	-	-	-
Aghayan et al	+	+	+	+	+	+
Dilogo IH	+	+	+	+	+	+
Lanzoni G	+	+	+	+	+	+
Matthay et al	+	+	+	+	+	+
Michael E. Bowdish	+	X	+	+	-	X
Monsel A	+	+	+	+	+	+

2. Risk of bias of each individual study according to the Cochrane risk of bias-2 tool for SAE:

	Bias arising from the randomization process	Bias due to deviations from intended interventions	Bias due to missing outcome data	Bias in measurement of the outcome	Bias in selection of the reported result	Overall bias
Cécile Pochon	+	+	+	+	-	-
Amy L. Lightner	+	+	+	+	+	+

Bellingan G	+	+	+	+	+	+
Ichikado K	+	+	+	+	-	-
Gorman Ellen A	+	+	+	+	-	-
Lanzoni G	+	+	+	+	+	+
Michael E. Bowdish	+	X	+	+	-	X
Monsel A	+	+	+	+	+	+

3. Risk of bias of each individual study according to the Cochrane risk of bias-2 tool for ventilator-free days:

	Bias arising from the randomization process	**Bias due to deviations from intended interventions**	**Bias due to missing outcome data**	**Bias in measurement of the outcome**	**Bias in selection of the reported result**	**Overall bias**
Cécile Pochon	+	+	+	+	-	-
Amy L. Lightner	+	+	+	+	+	+
Bellingan G	+	+	+	+	+	+
Ichikado K	+	+	+	+	-	-
Gorman Ellen A	+	+	+	+	-	-
Zheng G	+	+	-	-	-	-
Matthay et al	+	+	+	+	+	+
Monsel A	+	+	+	+	+	+

4. Risk of bias of each individual study according to the Cochrane risk of bias-2 tool for ICU-free days:

	Bias arising from the randomization process	**Bias due to deviations from intended interventions**	**Bias due to missing outcome data**	**Bias in measurement of the outcome**	**Bias in selection of the reported result**	**Overall bias**
Bellingan G	+	+	+	+	+	+
Zheng G	+	+	-	-	-	-
Matthay et al	+	+	+	+	+	+

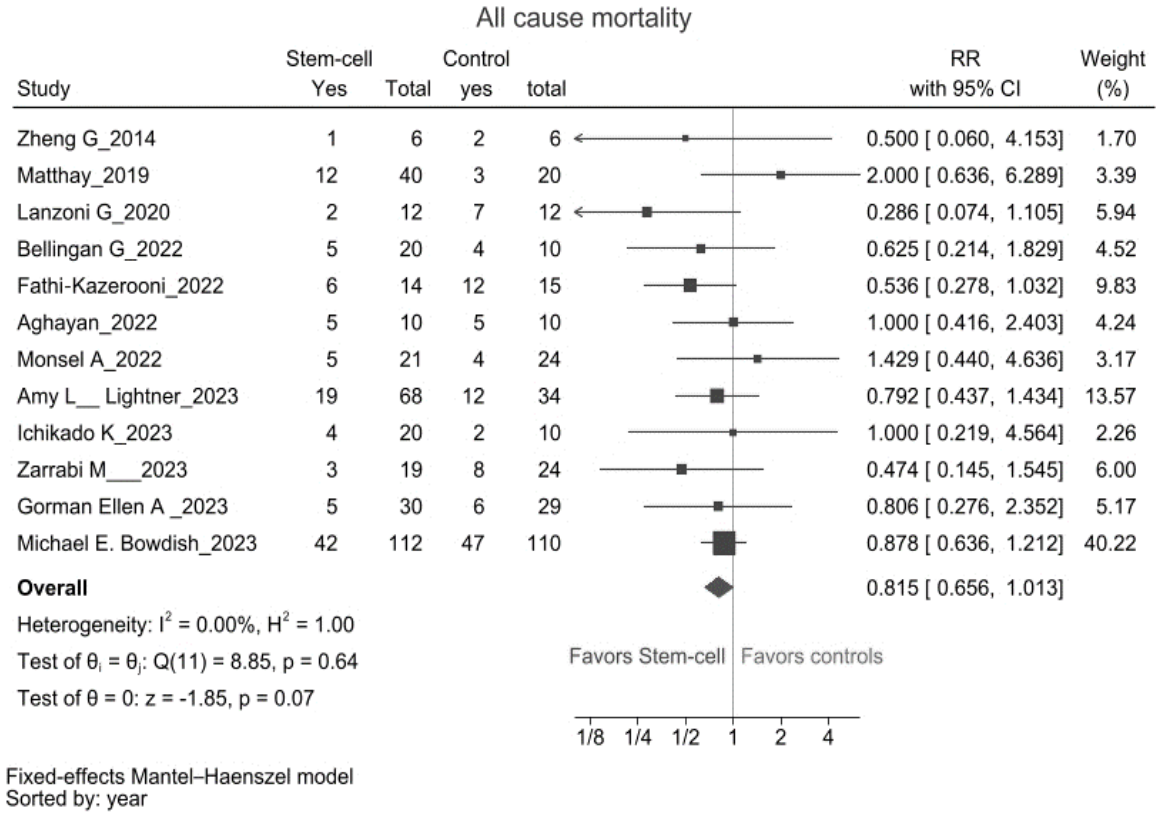
5. Risk of bias of each individual study according to the Cochrane risk of bias-2 tool for duration of hospitalization:

	Bias arising from the randomization process	Bias due to deviations from intended interventions	Bias due to missing outcome data	Bias in measurement of the outcome	Bias in selection of the reported result	Overall bias
Gorman Ellen A	+	+	+	+	-	-
Zheng G	+	+	-	-	-	-
Matthay et al	+	+	+	+	+	+
Michael E. Bowdish	+	X	+	+	-	X

Desirable Effects:

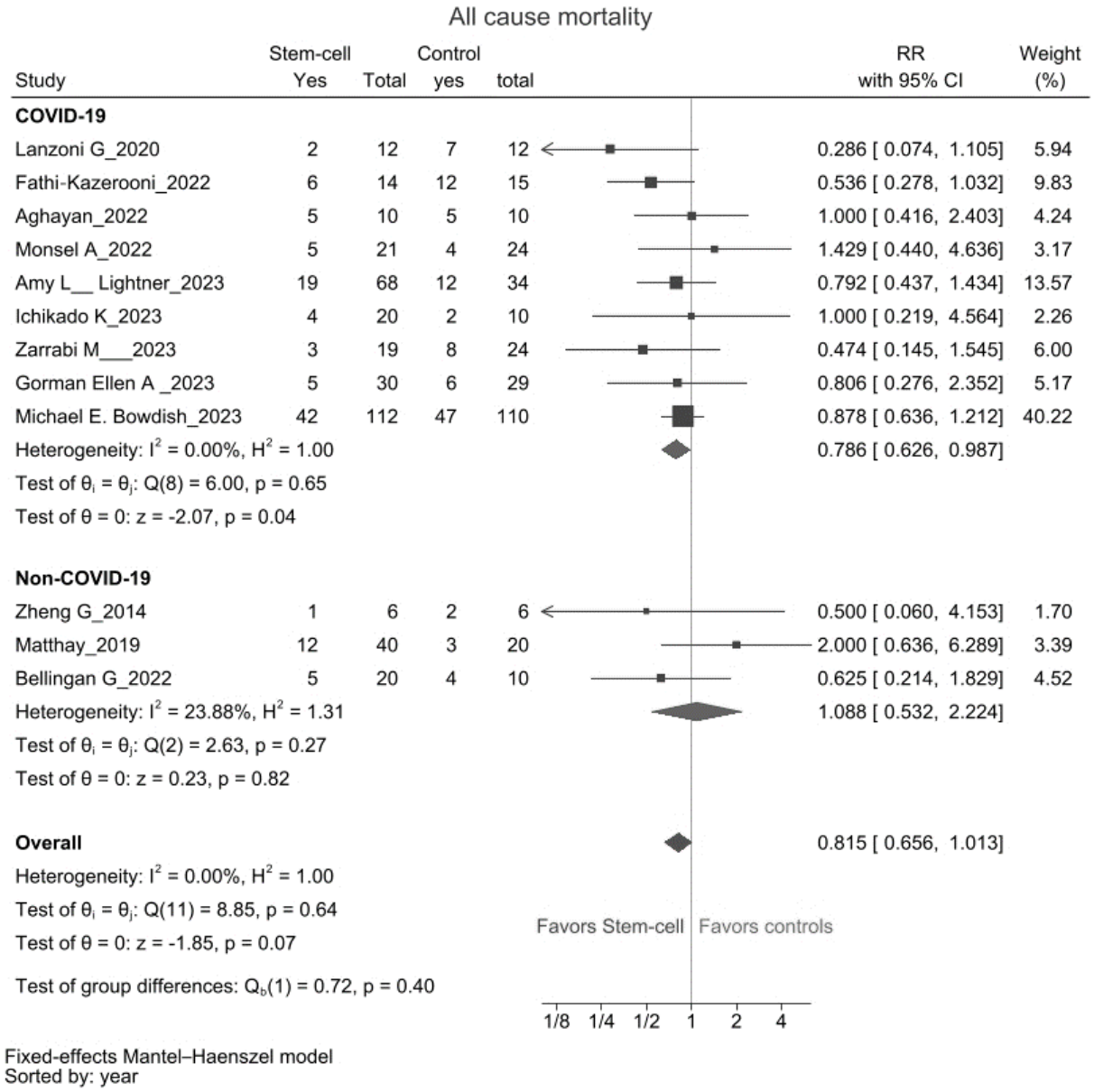
1. All-cause mortality (28 days): 12 trials, with a total of 676 participants, reported all-cause mortality at 28 days. The pooled analysis yielded a risk ratio of 0.815 (95% CI: 0.656 to 1.013) in the stem cell group as compared to the usual care, which was statistically non-significant.

1.1. Effect of stem cell treatment on 28-day all-cause mortality as compared to the usual care in patients with ARDS:

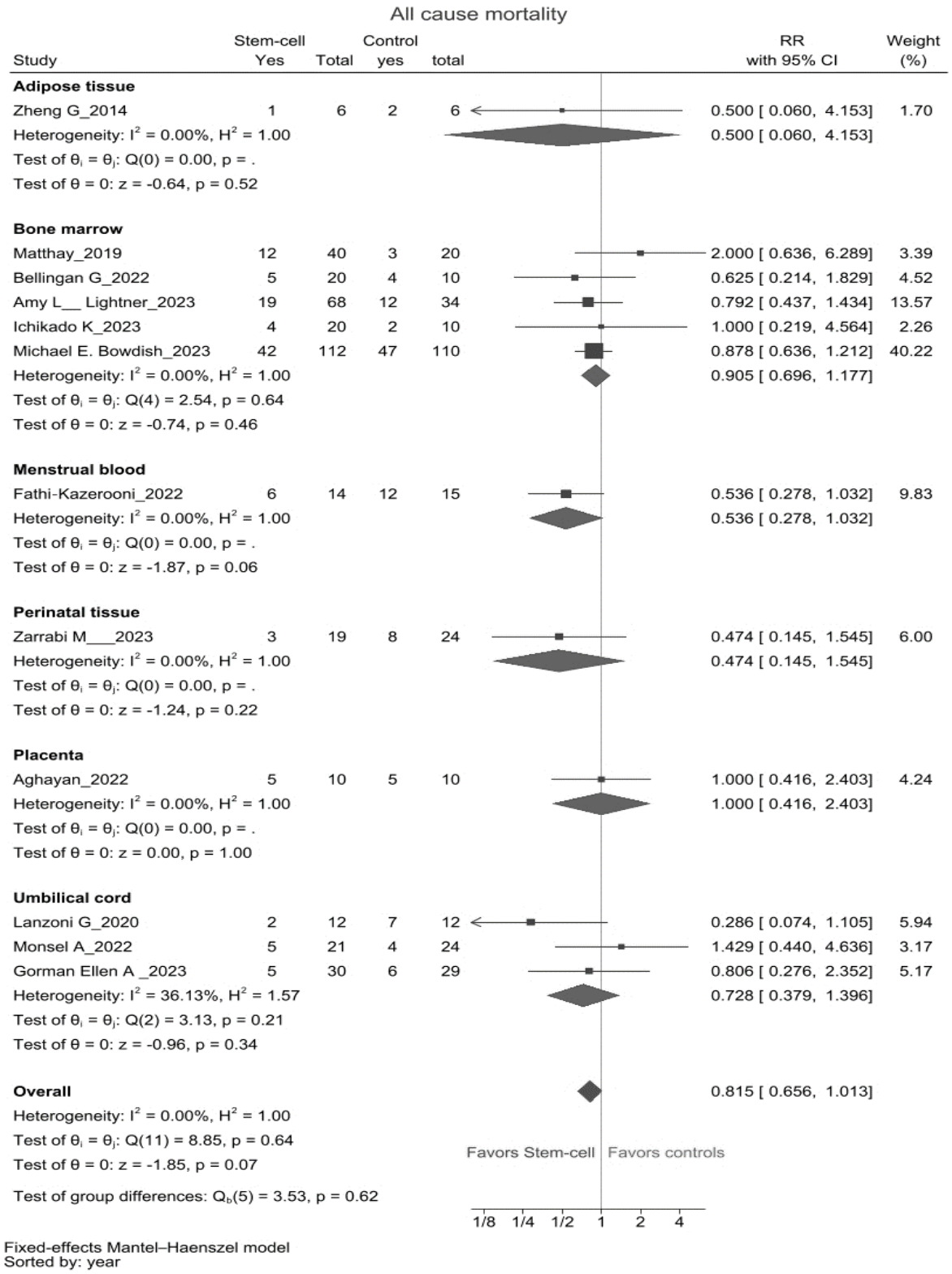


Subgroup analysis:

1.2. Effect of stem cell treatment on 28-day all-cause mortality as compared to the usual care in patients with ARDS based on the aetiology:

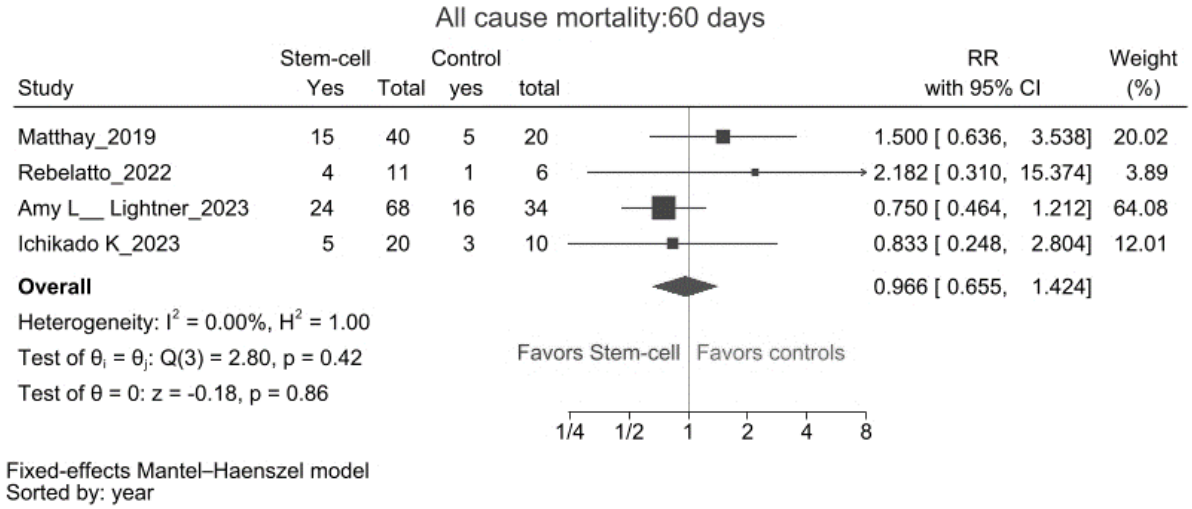


1.3. Effect of stem cell treatment on 28-day all-cause mortality as compared to the usual care in patients with ARDS based on the source of stem cell:



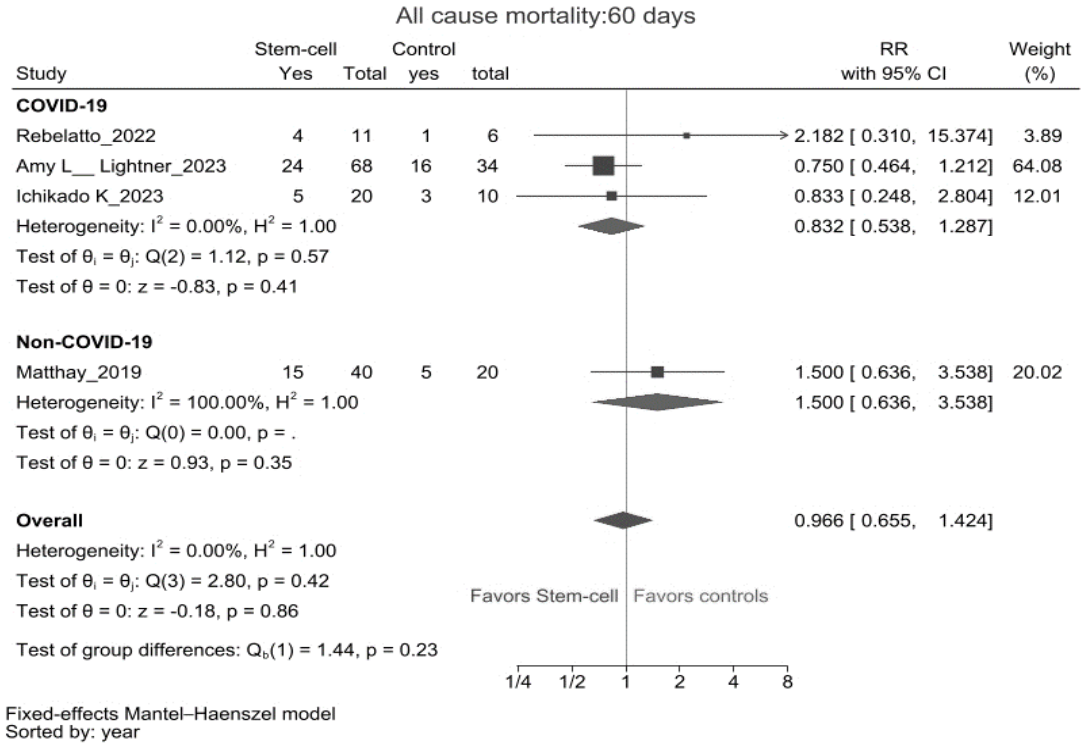
2. All-cause mortality (60 days): 4 trials, with a total of 209 participants, reported all-cause mortality at 60 days. The pooled analysis yielded a risk ratio of 0.966 (95% CI: 0.655 to 1.424) in the stem cell group as compared to the usual care, which was statistically non-significant.

2.1. Effect of stem cell treatment on 60-day all-cause mortality as compared to the usual care in patients with ARDS:

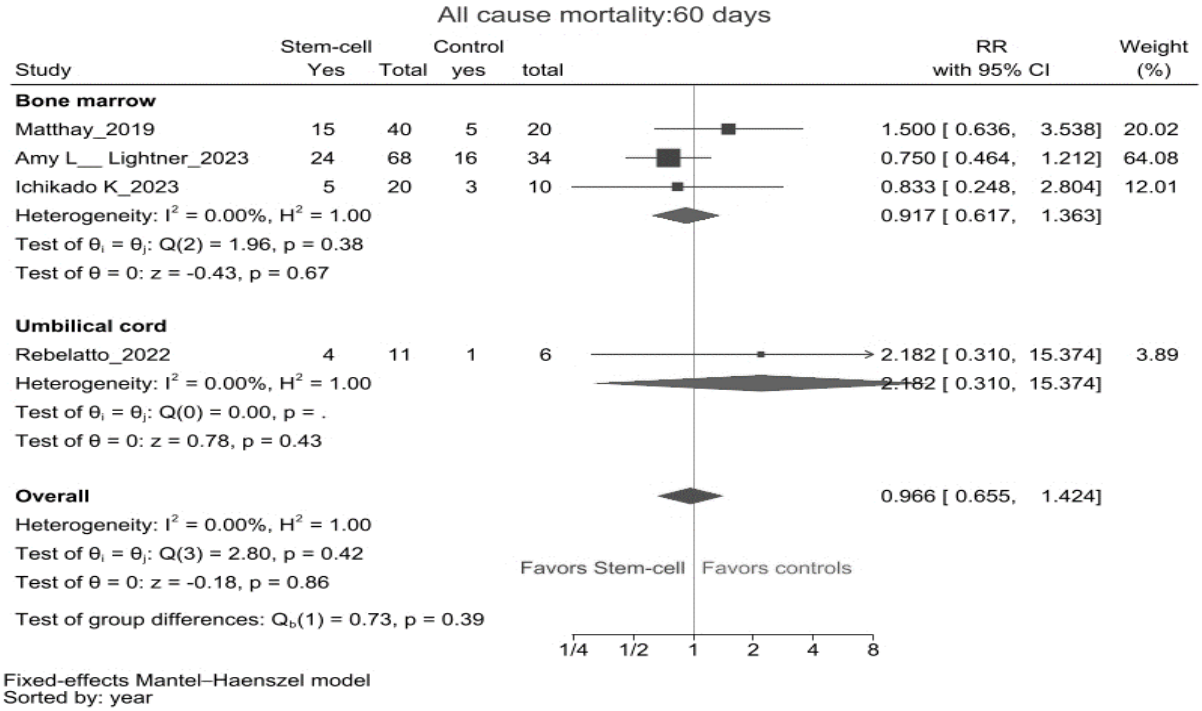


Subgroup Analysis:

2.2. Effect of stem cell treatment on 60-day all-cause mortality as compared to the usual care in patients with ARDS based on the aetiology:

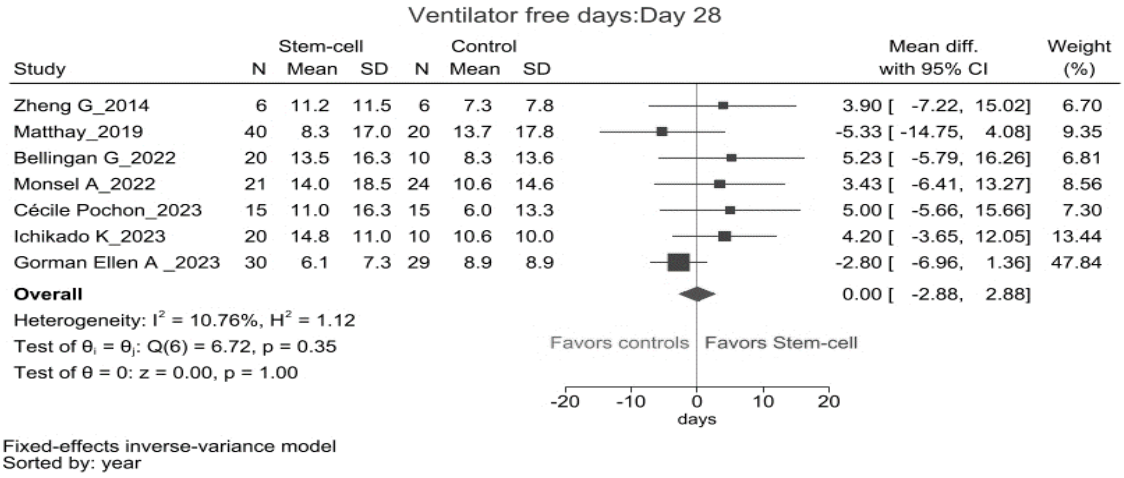


2.3. Effect of stem cell treatment on 60-day all-cause mortality as compared to the usual care in patients with ARDS based on the source of stem cell:



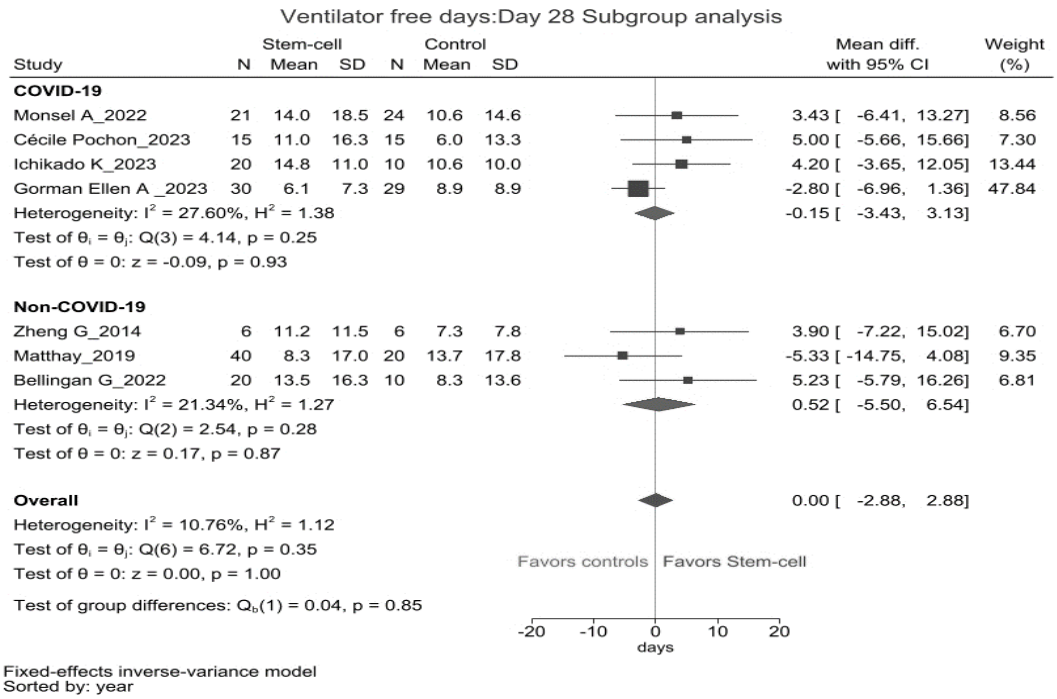
3. Ventilator free days: 7 trials, with a total of 266 participants, reported ventilator free days at 28 days. The pooled analysis yielded a mean difference of 0.00 (95% CI: -2.88 to 2.88) between the stem cell and the usual care arm, which was statistically non-significant.

3.1. Effect of stem cell treatment on the number of ventilator-free days as compared to the usual care in patients with ARDS:

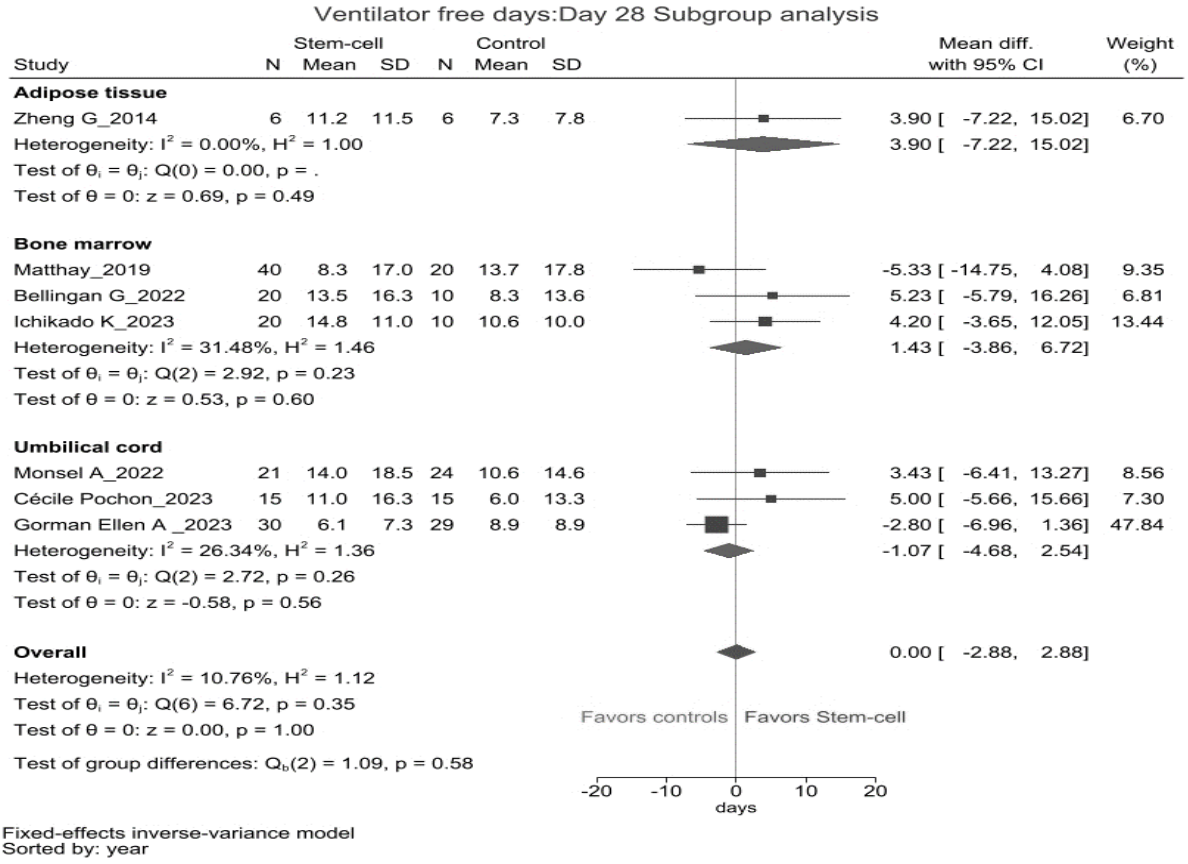


Subgroup Analysis

3.2. Effect of stem cell treatment on the number of ventilator-free days as compared to the usual care in patients with ARDS based on aetiology:

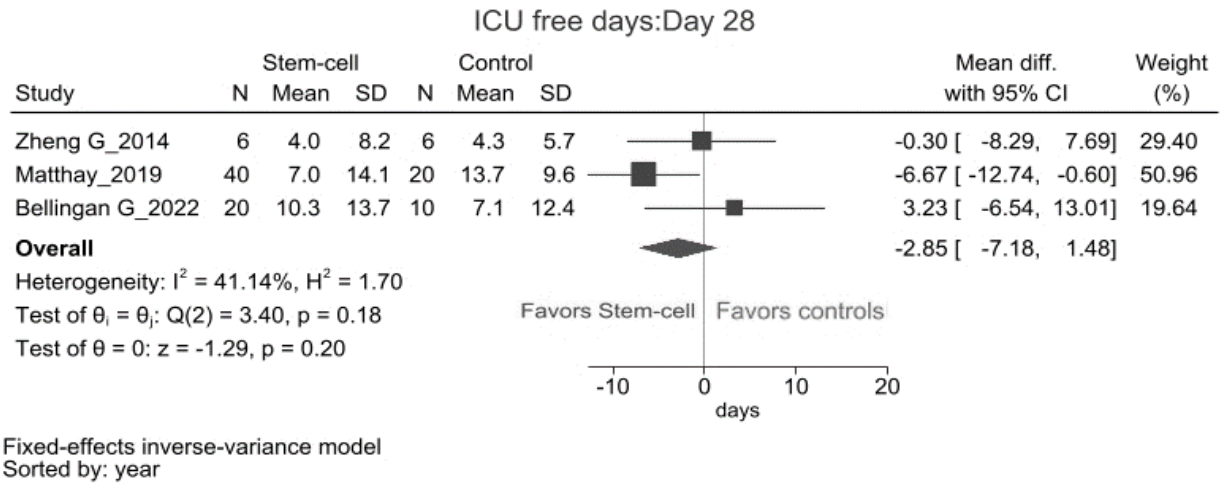


3.3. Effect of stem cell treatment on the number of ventilator-free days as compared to the usual care in patients with ARDS based on source of stem cell:



4. ICU -free days: 3 trials, with a total of 102 participants, reported ICU-free days at 28 days. The pooled analysis yielded a mean difference of -2.85 days (95% CI: -7.18 to 1.48) between the stem cell and the usual care arm, which was statistically non-significant.

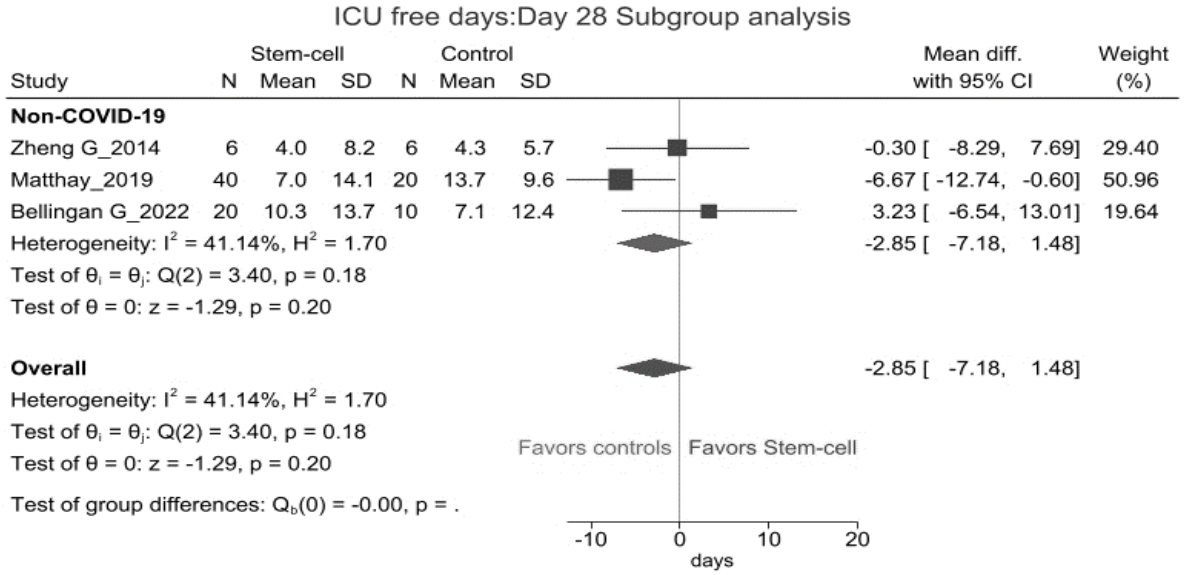
4.1. Effect of stem cell treatment on the number of ICU-free days as compared to the usual care in patients with ARDS:



Fixed-effects inverse-variance model
Sorted by: year

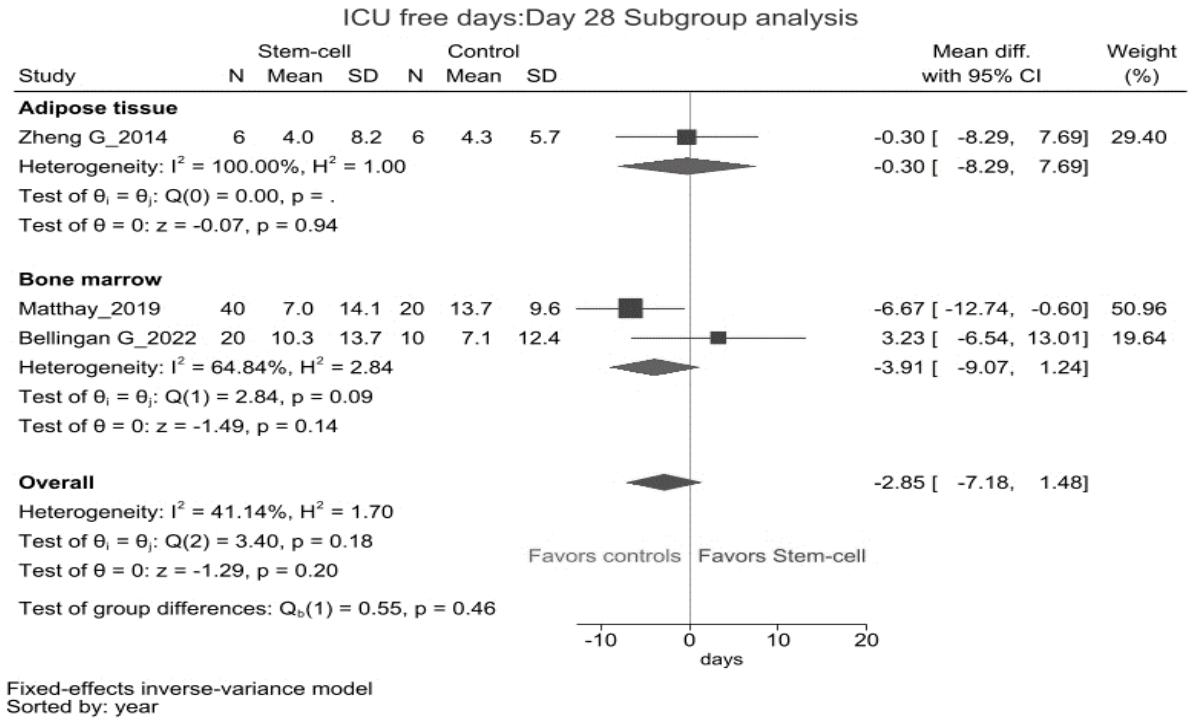
Subgroup analysis

4.2. Effect of stem cell treatment on the number of ICU-free days as compared to the usual care in patients with ARDS based on aetiology:



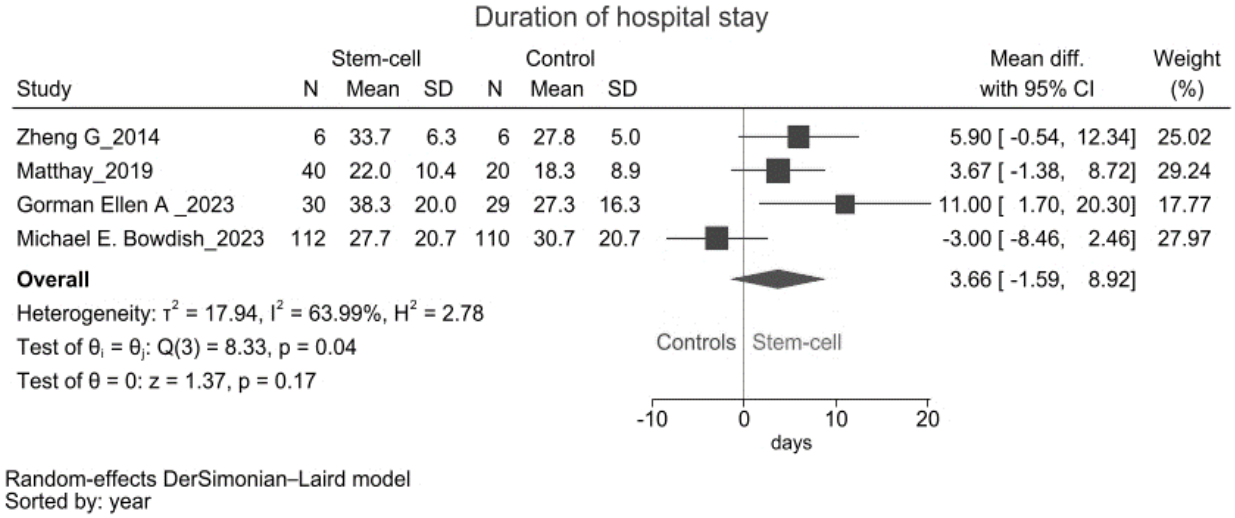
Fixed-effects inverse-variance model
Sorted by: year

4.3. Effect of stem cell treatment on the number of ICU-free days as compared to the usual care in patients with ARDS based on source of stem cell:



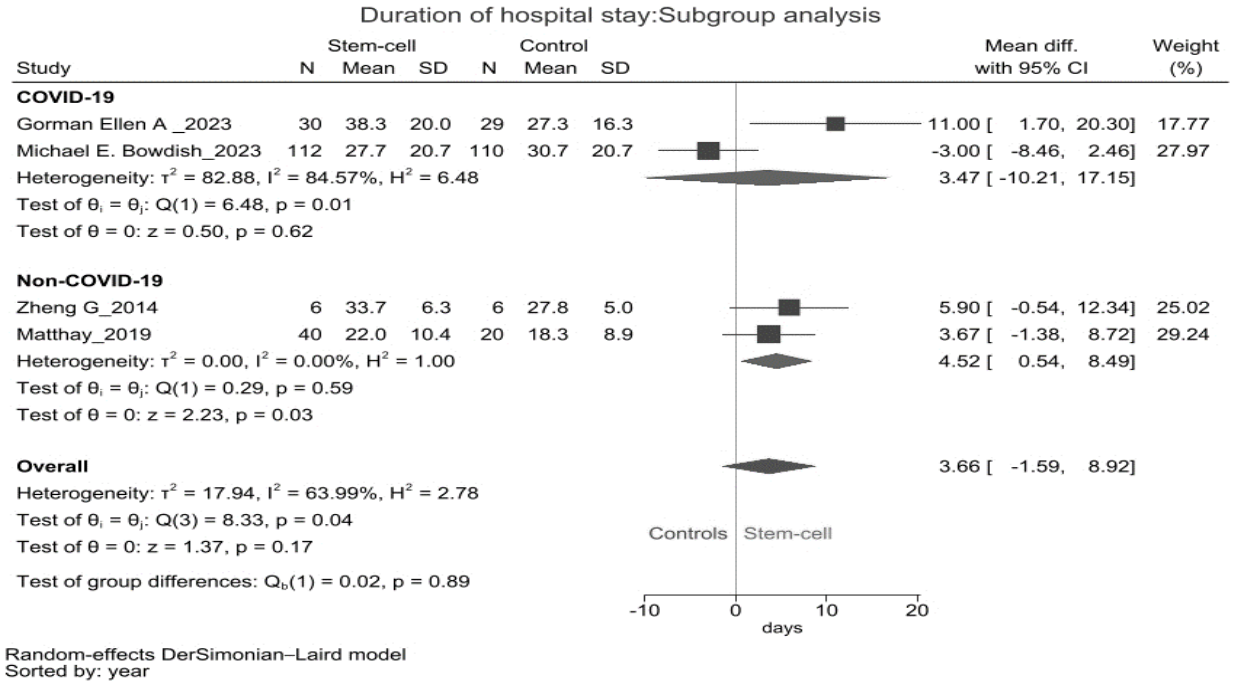
5. Duration of hospitalization: 4 trials, with a total of 353 participants, reported the duration of hospitalization. The pooled analysis yielded mean difference of 3.66 (95% CI: -1.59 to 8.92) between the stem cell and the usual care arm, which was statistically non-significant.

5.1. Effect of stem cell treatment on the duration of hospitalization as compared to the usual care in patients with ARDS:

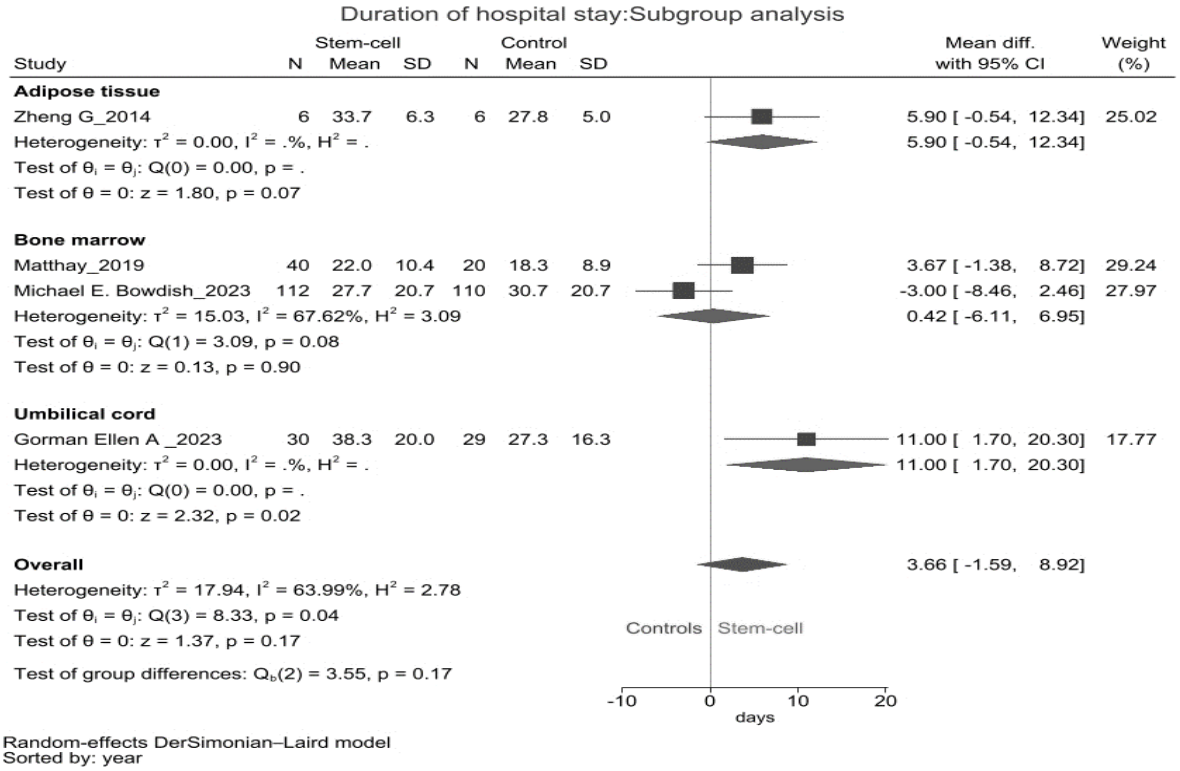


Subgroup analysis

5.2. Effect of stem cell treatment on the duration of hospitalization as compared to the usual care in patients with ARDS based on aetiology:



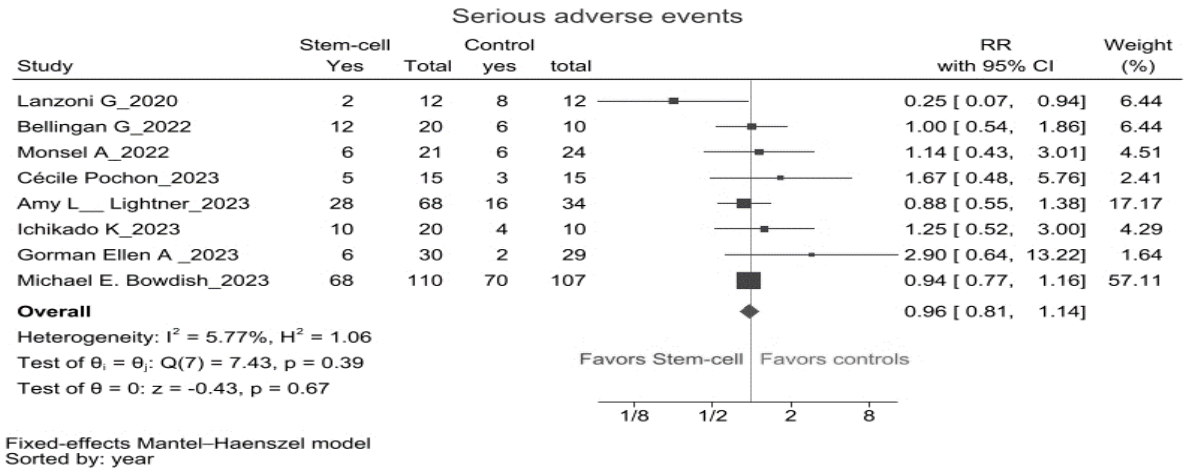
5.3. Effect of stem cell treatment on the duration of hospitalization as compared to the usual care in patients with ARDS based on source of stem cell:



Undesirable effects:

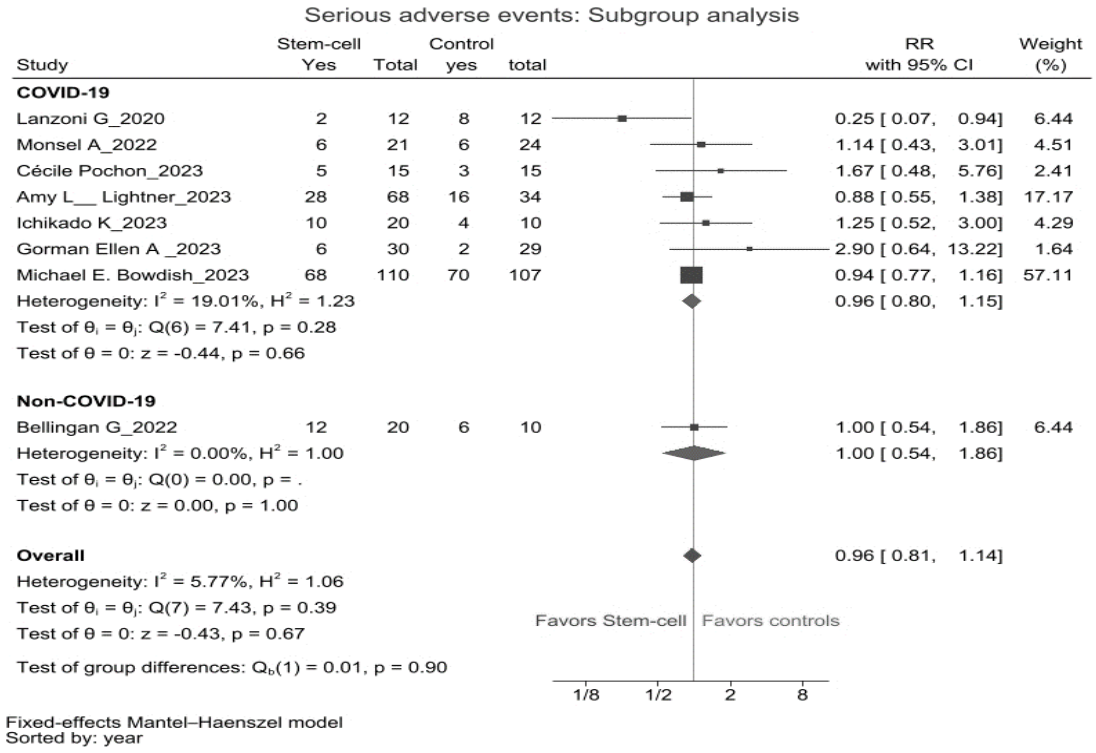
6. Serious Adverse Events (SAEs): 8 trials, with a total of 537 participants, reported the serious adverse event. The pooled analysis yielded a risk ratio of 0.96 (95% CI: 0.81 to 1.14) in the stem cell group as compared to the usual care, which was statistically non- significant.

6.1. Effect of stem cell treatment on the risk of serious adverse events as compared to the usual care in patients with ARDS:

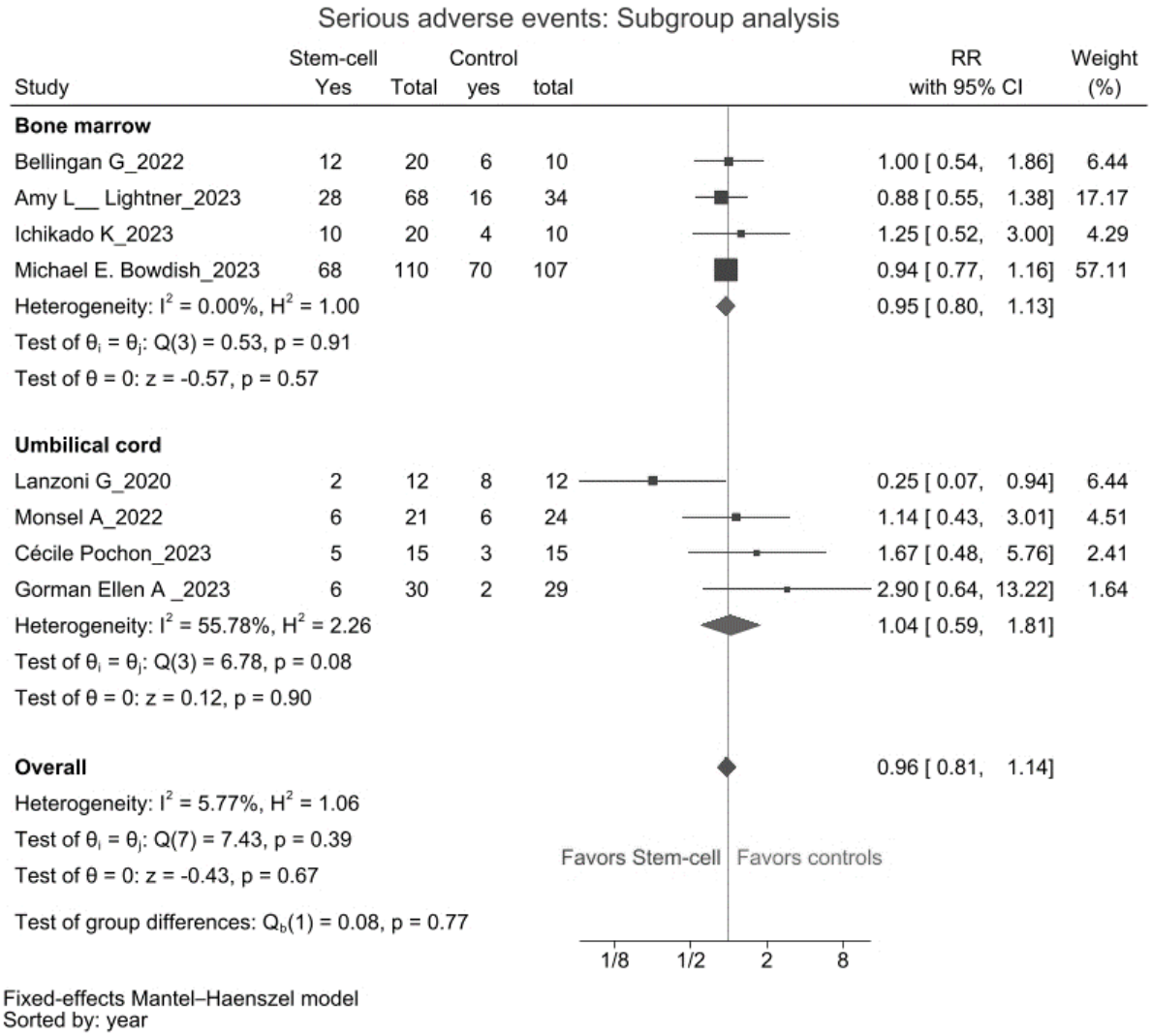


Subgroup analysis

6.2. Effect of stem cell treatment on the risk of serious adverse events as compared to the usual care in patients with ARDS based on aetiology:



6.3. Effect of stem cell treatment on the risk of serious adverse events as compared to the usual care in patients with ARDS based on source of stem cell:



Summary of findings:

Stem cells therapy compared to usual care in ARDS

Patient or population: ARDS
Setting: Hospital
Intervention: Stem cell therapy
Comparison: Usual care

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with usual care	**Risk with stem cell therapy**				
All-cause mortality (28 days)	368 per 1,000	**300 per 1,000** (242 to 373)	**RR 0.815** (0.656 to 1.013)	676 (12 RCTs)	⊕⊕◯◯ Low[a,b]	
Ventilator-free days	The mean ventilator free days in the usual care arm was 9.34 (range: 6.0 to 13.7)	MD **0** (2.88 lower to 2.88 higher)	-	266 (7 RCTs)	⊕◯◯◯ Very low[b,c]	
ICU-free days	The mean ICU free days in the usual care arm was 8.36 (range: 4.3 to 13.7)	MD **2.85 lower** (7.18 lower to 1.48 higher)	-	102 (3 RCTs)	⊕⊕◯◯ Low[b,d]	
Duration of hospitalization	The mean hospitalization days I the usual care arm was 26.02 (range: 18.3 to 30.7)	MD **3.66 higher** (1.59 lower to 8.92 higher)	-	353 (4 RCTs)	⊕◯◯◯ Very low[b,c,e]	
SAE	477 per 1,000	**458 per 1,000** (387 to 544)	**RR 0.96** (0.81 to 1.14)	537 (8 RCTs)	⊕⊕◯◯ Low[a,b]	
All-cause mortality (60 days)	357 per 1,000	**345 per 1,000** (234 to 509)	**RR 0.966** (0.655 to 1.424)	209 (4 RCTs)	⊕⊕⊕◯ Moderate[b]	

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

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

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

Explanations
a. downgraded by one level for risk of bias as 1/3rd – 2/3rd of studies are at high risk of bias
b. downgraded by one level for imprecision as CI crosses the line of null effect
c. downgraded two levels for risk of bias as more than 2/3rd of studies (by wt.) are at high risk of bias
d. downgraded by one level for inconsistency as there is variation in effect estimates (I^2 is 41%)
e. downgraded by one level for inconsistency as there is variation in effect estimates (I^2 is 64%)

Evidence profile:
Stem cell therapy as compared to usual care in ARDS

Certainty assessment							Summary of findings				
							Study event rates (%)			Anticipated absolute effects	
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	With Usual care	With Stem cell therapy	Relative effect (95% CI)	Risk with Usual care	Risk difference with Stem cell therapy
All-cause mortality (28 days)											
676 (12 RCTs)	serious[a]	not serious	not serious	serious[b]	Not detetcted	⊕⊕◯◯ Low[a,b]	112/304 (36.8%)	109/372 (29.3%)	**RR 0.815** (0.656 to 1.013)	112/304 (36.8%)	**68 fewer per 1,000** (from 127 fewer to 5 more)
Ventilator-free days											
266 (7 RCTs)	very serious[c]	not serious	not serious	serious[b]	None	⊕◯◯◯ Very low[b,c]	-	-	-	The mean ventilator free days in the usual care arm was 9.34 (range: 6.0 to 13.7)	MD **0** (2.88 lower to 2.88 higher)
ICU-free days											
102 (3 RCTs)	not serious	serious[d]	not serious	serious[b]	None	⊕⊕◯◯ Low[b,d]	-	-	-	The mean ICU free days in the usual care arm was 8.36 (range: 4.3 to 13.7)	MD **2.85 lower** (7.18 lower to 1.48 higher)
Duration of hospitalization											
353 (4 RCTs)	very serious[c]	serious[e]	not serious	serious[b]	None	⊕◯◯◯ Very low[b,c,e]	-	-	-	The mean hospitalization days I the usual care arm was 26.02 (range: 18.3 to 30.7)	MD **3.66 higher** (1.59 lower to 8.92 higher)

Evidence profile:
Stem cell therapy as compared to usual care in ARDS

Certainty assessment							Summary of findings				
SAE											
537 (8 RCTs)	serious[a]	not serious	not serious	serious[b]	None	⊕⊕◯◯ Low[a,b]	115/241 (47.7%)	137/296 (46.3%)	**RR 0.96** (0.81 to 1.14)	115/241 (47.7%)	**19 fewer per 1,000** (from 91 fewer to 67 more)
All-cause mortality (60 days)											
209 (4 RCTs)	not serious	not serious	not serious	serious[b]	None	⊕⊕⊕◯ Moderate[b]	25/70 (35.7%)	48/139 (34.5%)	**RR 0.966** (0.655 to 1.424)	25/70 (35.7%)	**12 fewer per 1,000** (from 123 fewer to 151 more)

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

Explanations
a. downgraded by one level for risk of bias as 1/3rd – 2/3rd of studies are at high risk of bias
b. downgraded by one level for imprecision as CI crosses the line of null effect
c. downgraded two levels for risk of bias as more than 2/3rd of studies (by wt.) are at high risk of bias
d. downgraded by one level for inconsistency as there is variation in effect estimates (I^2 is 41%)
e. downgraded by one level for inconsistency as there is variation in effect estimates (I^2 is 64%)

D. SUMMARY OF JUDGEMENTS:

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

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

***** This recommendation has been made as there is very low certainty evidence of trivial improvement in pulmonary function and trivial reduction in mortality in patients with ARDS.
** There is little to no difference in undesirable effects between stem cell therapy and usual care.
*** The committee opined that stem cell treatment is associated with large costs.

E. CAVEATS IN EXISTING EVIDENCE:

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

1. Lack of sufficient number of RCTs with low risk of bias.
2. Small number of participants and/or events in included trials
3. Heterogeneity in the type of stem cell therapy used, ranging from bone marrow to mononuclear to umbilical cord to adipose tissue
4. Lack of long term follow up of patients in most studies, thus providing insufficient evidence on the safety of this experimental therapy
5. Lack of cost effectiveness data

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III. PRIORITY AREAS FOR FUTURE RESEARCH

Stem cell therapy is a rapidly growing field with significant potential, but continued research is needed to optimize stem cell types, delivery methods, and clinical outcomes. It is essential to adopt an evidence-based approach in the development of these regenerative therapies, ensuring that the best available evidence is used to evaluate their true effectiveness and safety. Currently, most available evidence is of very low certainty.

Based on the assessment of evidence (clinically important difference, statistical significance and certainty of evidence) for the safety and efficacy of stem cell therapy in the included respiratory conditions, priority areas for future research were identified and are as follows:

- Acute Respiratory Distress Syndrome

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

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IV. ANNEXURES

Annexure 1: Clarification on the 'stem cell derived products' as per directives under section 33P of the Drugs & Cosmetics Act, 1940 as defined under New Drugs and Clinical Trials Rules, 2019

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

For the purpose of this clause:

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

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

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

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

Annexure 2: CONTRIBUTORS

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Annexure 3: DECLARATION OF INTEREST (DoI)

Name	Declaration Interest (s)	Management of conflict(s) of interest
Dr. Sushama Nagarkar, Patient representative from Yash Charitable Trust	Declared that the outcome of the meeting or work may affect the interests of people with whom she has substantial personal/ professional interests.	The steering group observed this as a potential conflict of interest and therefore decided against her inclusion in the GDG.
Dr. Kameshwar Prasad, Fortis Flt Lt Rajan Dhall Hospital, Vasant Kunj, New Delhi	None declared	Not applicable
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Dr. Rakesh Lodha, All India Institute of Medical Sciences, New Delhi	None declared	Not applicable
Dr. Anil Gurtoo, Ex-Professor, Lady Hardinge Medical College (LHMC), New Delhi	None declared	Not applicable
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Dr. Sujata Mohanty, All India Institute of Medical Sciences, New Delhi	She declared that she is a member of the Subject Expert Committees of CDSCO & NMC.	The Steering Group did not see it as a potential CoI.
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Dr Jefferson Daniel J, Christian Medical College, Vellore	None declared	Not applicable

CENTRE FOR EVIDENCE-BASED GUIDELINES

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

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