Evidence-based Guidelines for the use of Stem Cell Therapy

Respiratory Conditions Supplement

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Department of Health Research
Directorate General of Health Services

Ministry of Health & Family Welfare
Government of India

CONTENTS

ABBREVIATIONS

ARDS	:	Acute Respiratory Distress Syndrome
BMMSCs	:	Bone Marrow Mesenchymal Stem Cells
EtD	:	Evidence to Decision
EVs	:	Extracellular Vesicles
ICU	:	Intensive Care Unit
GDG	:	Guideline Development Group
MeSH	:	Medical Subject Headings
MDs	:	Mean Differences
MSC	:	Mesenchymal Stem Cell
OI	:	Oxygenation Index
PICO	:	Population Intervention, Comparator and Outcome
PL-MSC	:	Placenta-derived Mesenchymal Stem Cells
PRISMA	:	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QoL	:	Quality of life
RCT	:	Randomized Controlled Trial
RR	:	Risk Ratio
SAEs	:	Serious Adverse Events
SCT	:	Stem Cell Transplantation
SOC	:	Standard of Care
SRMA	:	Systematic Review and Meta-Analysis
UC-MSCs	:	Umbilical Cord Derived Mesenchymal Stem Cell
VFDs	:	Ventilator Free Days

1. Acute Respiratory Distress Syndrome

i. **Key question in PICO format**

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i. Key question in PICO format:

In patients with Acute Respiratory Distress Syndrome, what is the efficacy and safety of stem cell therapy as compared to usual care?

Population: Patients with acute respiratory distress syndrome, all age group
Intervention: Any stem cell and product derived from stem cells or their derivatives
Comparator: Usual Care/Conventional Care
Critical Outcomes: Efficacy: Mortality, Ventilator free days /ICU free days at D28, Duration of hospitalization; Safety: Severe Adverse effects, any tumor formation; Important: Quality of Life, other adverse events

ii. Search Strategy (September 2023):

An electronic search was performed in PubMed, Embase, Web of Science, and Cochrane databases to identify relevant studies. MeSH terms and keywords related to stem cells and ARDS were used to build the search strategy.

Domain	**Pubmed**	Searched on date 26-09-2023
P-ARDS	(acute respiratory distress syndrome) OR (acute respiration distress syndrome) OR ARDS OR (acute lung injury) OR "ALI" OR (adult respiration distress) OR (lung shock) OR (posttraumatic lung failure) OR (respiratory distress syndro*) OR (shock lung)	172,264
I- Stem-cells	(stem cell*) OR "Stem cell treatment" OR "Mesenchymal Stem Cells" OR "Mesenchymal Stromal Cells" OR "MSC" OR "MSCs" OR "Induced pluripotent stem cells" OR "iPSc" OR (progenitor cells) OR (mother cell*) OR (Colony-Forming Unit*) OR (Colony Forming Unit*) OR mesenchymal OR (Bone Marrow Stromal Cell*) OR (Wharton Jelly Cell*) OR (Wharton's Jelly Cell*) OR teratocarcinoma OR (embryonal carcinoma Cell*) OR pluripotent OR multipotent OR totipotent OR (tumor initiating cell*) OR Hematopoietic OR Limbal OR "mESC" OR "mESCs" OR "hESCs" OR (Erythroid Precursor) OR CFU-E OR "CFU E" OR CFU-Es OR (Erythroid Progenitor Cell*) OR Erythropoietic OR (Burst-Forming Units) OR (Burst Forming Units) OR BFU-E OR (BFU E) OR BFU-Es	1,082,105
S-trials	randomi* OR RCT OR non-randomi* OR (non randomi*) OR Placebo OR trial OR (clinical trial) OR feasibility OR safety	3,219,638
	P&I&S	1,060

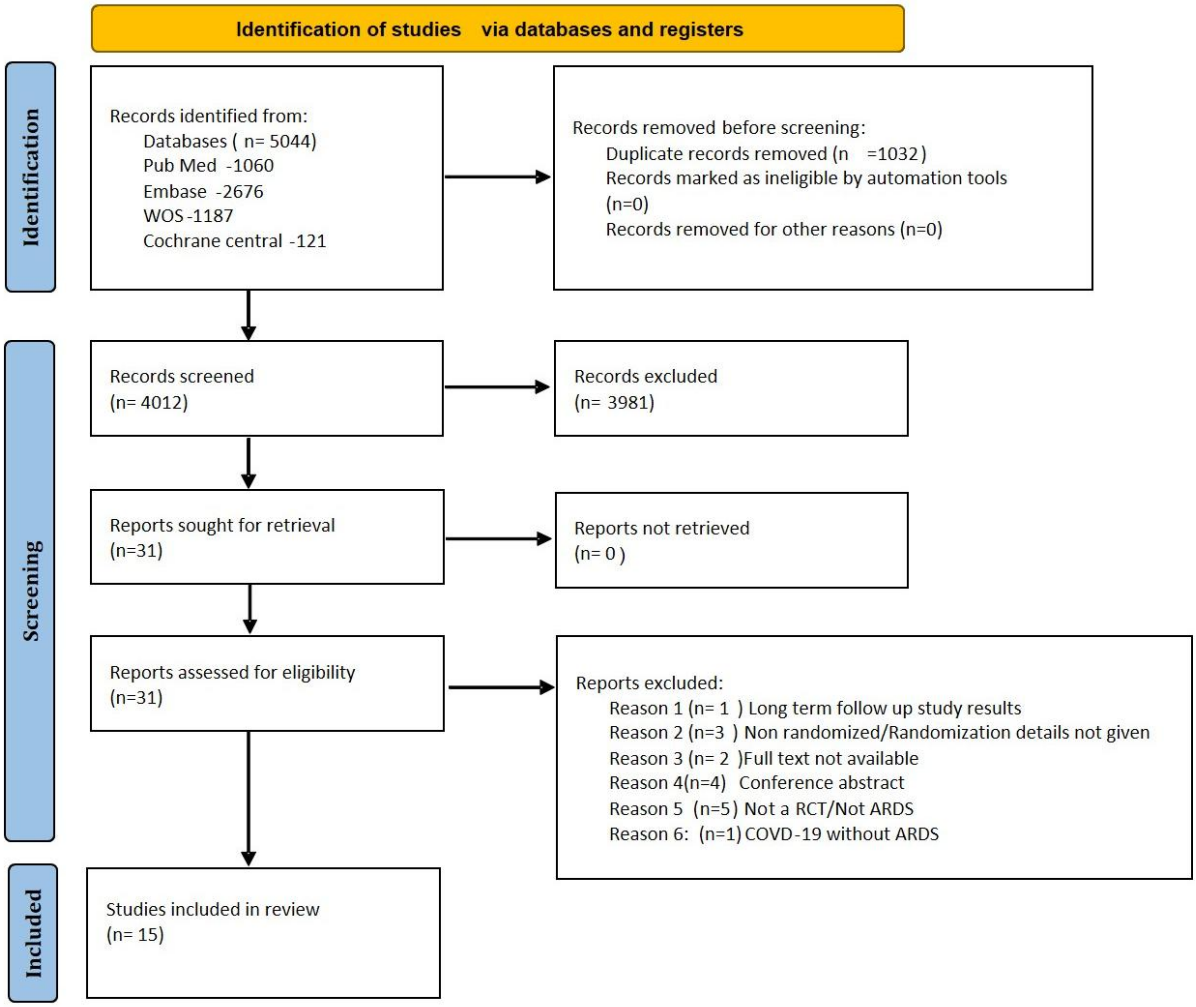
Domain	Embase	Searched on date 26-09-2023
P-ARDS	'adult respiratory distress syndrome'/exp OR 'ards' OR 'acute respiration distress syndrome' OR 'acute respiratory disease syndrome' OR 'acute respiratory distress syndrome' OR 'adult respiration distress' OR 'adult respiratory distress' OR 'adult respiratory distress syndrome' OR 'lung shock' OR 'posttraumatic lung failure' OR 'posttraumatic pulmonary insufficiency' OR 'respiratory distress syndrome, acute' OR 'respiratory distress syndrome, adult' OR 'respiratory distress, adult' OR 'shock lung' OR 'acute lung injury'/exp OR 'acute lung injury' OR `ali`	391,648
I- Stem-cells	'mesenchyme cell'/exp OR 'mesenchyma cell' OR 'mesenchymal cell' OR 'mesenchyme cell' OR 'mesenchymal stem cell'/exp OR 'mesenchymal progenitor cell' OR 'mesenchymal stem cell' OR 'mesenchymal stem cells' OR 'stem cell, mesenchymal' OR msc OR 'pluripotent stem cell'/exp OR 'pluripotent cell' OR 'pluripotent precursor cell' OR 'pluripotent progenitor cell' OR 'pluripotent stem cell' OR 'pluripotent stem cells' OR 'stem cell'/exp OR 'cell, stem' OR 'precursor cell' OR 'progenitor cell' OR 'stem cell' OR 'stem cells' OR 'induced pluripotent stem cell'/exp OR 'ips cell' OR 'induced pluripotent stem cell' OR 'induced pluripotent stem cells' OR 'mother cell'/exp OR 'colony forming cell'/exp OR 'cell, colony forming' OR 'colony forming cell' OR 'colony forming unit'/exp OR 'cfu' OR 'colony form unit' OR 'colony forming ability' OR 'colony forming capacity' OR 'colony forming unit' OR 'bone marrow stroma cell'/exp OR 'bone marrow stroma cell' OR 'bone marrow stromal cell' OR 'wharton jelly'/exp OR 'wharton jelly' OR 'mesenchymal stroma cell'/exp OR 'wharton jelly cell' OR 'mesenchymal stroma cell' OR 'mesenchymal stroma cells' OR 'mesenchymal stromal cell' OR 'mesenchymal stromal cells' OR 'teratocarcinoma cell line'/exp OR 'terato-carcinoma cell line' OR 'terato-carcinoma-derived cell line' OR 'teratocarcinoma cell line' OR 'teratocarcinoma-derived cell line' OR 'teratoid carcinoma cell line' OR 'teratomatous carcinoma cell line' OR 'embryonal carcinoma stem cell'/exp OR 'embryocarcinoma cell' OR 'embryocarcinoma cells' OR 'embryonal carcinoma cell' OR 'embryonal carcinoma cells' OR 'embryonal carcinoma stem cell' OR 'embryonal carcinoma stem cells' OR 'embryonic carcinoma cell' OR 'embryonic carcinoma cells' OR 'embryonic carcinoma stem cell' OR 'embryonic carcinoma stem cells' OR 'teratocarcinoma cell' OR 'teratocarcinoma cells' OR 'teratocarcinoma stem cell' OR 'teratocarcinoma stem cells' OR 'multipotent stem cell'/exp OR 'multipotent cell' OR 'multipotent precursor cell' OR 'multipotent progenitor cell' OR 'multipotent stem cell' OR 'multipotent stem cells' OR 'totipotent stem cell'/exp OR 'totipotent cell' OR 'totipotent precursor cell' OR 'totipotent progenitor cell' OR 'totipotent stem cell' OR 'totipotent stem cells' OR 'cancer stem cell'/exp OR 'cancer stem cell' OR 'cancer stem cells' OR 'neoplastic stem cell' OR 'neoplastic stem cells' OR 'stem cell, tumor' OR 'stem cell, tumour' OR 'tumor stem cell' OR 'tumor stem cells' OR 'tumor-initiating cell' OR 'tumor-initiating	955,365

	cells' OR 'tumour stem cell' OR 'tumour stem cells' OR 'hematopoietic stem cell'/exp OR 'bone marrow stem cell' OR 'haematopoietic precursor cell' OR 'haematopoietic progenitor cell' OR 'haematopoietic stem cell' OR 'haematopoietic stem cells' OR 'hematocytopoietic stem cell' OR 'hematopoietic precursor cell' OR 'hematopoietic progenitor cell' OR 'hematopoietic stem cell' OR 'hematopoietic stem cells' OR 'hemocytopoietic stem cell' OR 'hemopoietic stem cell' OR 'limbal stem cell transplantation'/exp OR 'limbal stem cell transplantation' OR 'limbal stem cell'/exp OR 'corneal epithelial stem cell' OR 'corneal limbal epithelial stem cell' OR 'limbal stem cell' OR 'limbal stem cells' OR mesc OR 'human embryonic stem cell'/exp OR 'cell, human embryonic stem' OR 'cells, human embryonic stem' OR 'hesc' OR 'hescs' OR 'human es cell' OR 'human es cells' OR 'human embryonic stem cell' OR 'human embryonic stem cells' OR 'stem cell, human embryonic' OR 'stem cells, human embryonic' OR 'colony forming unit e'/exp OR 'cfu e' OR 'colony forming unit e' OR 'erythroid precursor cell'/exp OR 'erythroid precursor' OR 'erythroid precursor cell' OR 'erythroid precursor cells' OR 'erythroid precursors' OR 'erythroid progenitor' OR 'erythroid progenitor cell' OR 'erythroid progenitor cells' OR 'erythroid progenitors' OR 'erythroid stem cell' OR 'erythroid stem cells' OR 'erythropoietic precursor' OR 'erythropoietic precursors' OR 'erythropoietic progenitor' OR 'erythropoietic progenitor cell' OR 'erythropoietic progenitors' OR 'erythropoietic stem cell' OR 'erythropoietic stem cells' OR 'precursor cell, erythroid' OR 'burst forming unit e'/exp OR 'bfu e' OR 'burst forming unit e' OR 'burst forming unit erythroid' OR 'burst-forming unit erythroid progenitor' OR 'erythroid burst forming unit'	
S-trials	'randomized controlled trial'/exp OR 'controlled trial, randomized' OR 'randomised controlled study' OR 'randomised controlled trial' OR 'randomized controlled study' OR 'randomized controlled trial' OR 'trial, randomized controlled' OR 'clinical trial'/exp OR 'clinical drug trial' OR 'clinical trial' OR 'major clinical trial' OR 'trial, clinical' OR feasibility OR 'safety'	3,943,463
	P&I&S	2,676
Domain	**Web of Science**	Searched on date 22-09-2023
P-ARDS	(((((((((TS=(acute respiratory distress syndrome)) OR TS=(acute respiration distress syndrome)) OR TS=(ARDS)) OR TS=(acute lung injury)) OR TS=(ALI)) OR TS=(adult respiration distress)) OR TS=(lung shock)) OR TS=(posttraumatic lung failure)) OR TS=(respiratory distress syndro*)) OR TS=(shock lung) and Preprint Citation Index (Exclude – Database)	1,46,717
I- Stem-cells	((((((((((((((((((((((((((((((((((((TS=(stem cell*)) OR TS=(Stem cell treatment)) OR TS=("Mesenchymal Stem Cells")) OR TS=("Mesenchymal Stromal Cells")) OR TS=(MSC)) OR TS=(MSCs)) OR TS=("Induced pluripotent stem cells")) OR TS=("iPSc")) OR TS=(progenitor cells)) OR TS=(mother cell*)) OR TS=(Colony-Forming Unit*)) OR TS=(mesenchymal)) OR TS=(Bone Marrow Stromal Cell*))	13,91,819

	OR TS=(Wharton Jelly Cell*)) OR TS=(Wharton's Jelly Cell*)) OR TS=(teratocarcinoma)) OR TS=(embryonal carcinoma Cell*)) OR TS=(pluripotent)) OR TS=(multipotent)) OR TS=(totipotent)) OR TS=(tumor initiating cell*)) OR TS=(Hematopoietic)) OR TS=(Limbal)) OR TS=("mESC")) OR TS=("mESCs")) OR TS=("hESCs")) OR TS=((Erythroid Precursor))) OR TS=(CFU-E)) OR TS=("CFU E")) OR TS=(CFU-Es)) OR TS=((Erythroid Progenitor Cell*))) OR TS=(Erythropoietic)) OR TS=((Burst-Forming Units))) OR TS=((Burst Forming Units))) OR TS=(BFU-E)) OR TS=((BFU E))) OR TS=(BFU-Es) and Preprint Citation Index (Exclude – Database)	
S-trials	((((((TS=(randomi*)) OR TS=(RCT)) OR TS=(non-randomi*)) OR TS=((non randomi*))) OR TS=(Placebo)) OR TS=(trial)) OR TS=((clinical trial)) and Preprint Citation Index (Exclude – Database)	25,76,714
	P&I&S	1,187

Cochrane Central Register of Controlled Trials (acute respiratory distress syndrome OR ARDS):ti,ab,kw AND (stem cell):ti,ab,kw" (Word variations have been searched)

iii. PRISMA Flow Diagram:



iv. Summary of included studies:

TRIAL-AUTHOR ET AL	STUDY POPULATION	INTERVENTION	COMPARATOR /CONTROL	OUTCOME ASSESSED
MSC-COVID – TRIAL-CÉCILE POCHON_2023[1]	Population: COVID-19 Moderate to Severe ARDS N (Int vs Com): 15:15 Age (years) Int Vs Comp: 61±12.59 vs 66 ±6,67 Male: female ratio Int Vs Comp: 13/2 vs 7/8	WJ-MSCs plus SOC Dose: 1×10^6 MSC/kg at day 0/1, 0.5×10^6 MSC/kg at day 3/4 and 5/6	Placebo plus SOC	Primary endpoint: Percentage of patients with a PaO2/FiO2>200mmHg at day 10 of treatment (WJ-MSC or placebo). Secondary endpoints: • PaO2/FiO2 evolution between the first day of infusion (day 0 or 1) and day 14 • Number of 28day ventilator free days • Vasopressor & extra-renal support free days, • Difference in SOFA score between day 14 and day 0, • 90 day all-cause mortality, • ICU length of stay, • Respiratory morbidity at day 90, • RT-PCR SARS-CoV-2 positivity at day 7, 14, and 21. Safety endpoints: • Infusion-related toxicity (hypersensitivity reaction within 6h of infusion), • D-dimers elevation at day 10, • Acquisition of anti-HLA antibodies at day 28 and day 90, • occurrence of thromboembolic events or infectious events within 90 days post-randomization
EXIT COVID-19 TRIAL-AMY L. LIGHTNER	Population: COVID-19-moderate to severe ARDS N (Int vs Com):	Exo Flo 15 ml and Exo Flo 10 ml (1.2 trillion BM-MSC derived extracellular	Placebo	Improvement in the mortality rate within 60 days Primary: Improvement in the mortality rate within 60 days from randomization. Secondary endpoints • Time to death, • Incidence of treatment-emergent serious adverse

_2023[2]	68:34 Age (years) Int Vs Comp: 59.4 vs58.5±11.76 Male: female ratio Int Vs Comp: 43/25 vs 24/10	vesicles per dose [2,000 extracellular vesicles secreted per cell; and 60-80 billion EV/mL]		events, • Proportion of discharged patients, • Time to hospital discharge at 7, 30, and 60 days from randomization, and • Ventilation free days. Exploratory outcome Measurements included viraemia, serum acute phase reactants, immune cell subset counts, SOFA scores, and Quality of Life (EQ-5D-5L) scores.
MUST-ARDS TRIAL-BELLINGAN G_2022[3]	Population: Moderate-to-Severe ARDS N (Int vs Com): 20:10 Age (years) Int Vs Comp: 51±14 vs 59±18 Male: female ratio Int Vs Comp: 13/7 vs 6/4	900 million cells diluted into 300 ml of Plasmalyte-A	Placebo-	Primary outcome • Safety and tolerability of multipotent adult progenitor cells Secondary safety outcomes • Assessment of vital signs and laboratory parameters through Day 28, and TEAEs through Day 365. Secondary efficacy outcomes • Ventilator-free days, • days free from intensive care unit (ICU), • Total length of hospital stay through Day 28 • Changes in PaO2/FiO2ratio and PEEP requirements from baseline through Days 1, 2, 3, 7 and 28; • Changes in respiratory physiologic measures (peak and plateau pressures) from baseline through the time the subject is extubated • All-cause mortality at Days 28, 90 and 365. Exploratory endpoints • Changes in circulating biomarkers of inflammation and lung injury between baseline and Days 1, 2, 3 and 7; • Health-related quality of life (EQ-5D-3L) at Days 28,

				90 and 365.
ONE-BRIDGE TRIAL-ICHIKADOK_2023[4]	Population: ARDS caused by COVID-19–induced pneumonia N (Int vs Com): 20:10 Age (years) Int Vs Comp: 69.2±13.2 vs 66.5±10.0 Male: female ratio Int Vs Comp: 16/4 vs10/0	9.0× 10^8 cells of BM derived multi-potent adult progenitor cells (invimestrocel) IV Infusion	Standard treatment	Primary endpoint • Number of days of survival free from mechanical ventilation (VFDs) during the first 28 days • VFDs Secondary efficacy endpoints • Ventilator weaning rate on day 28, re-intubation rate, mortality on days 28, 60, 90, and 180 after treatment administration, • Progression of chest imaging findings through day 90 Exploratory endpoints • Inflammation and lung injury –WBC, CRP, LDH, CXCL10. IL-1beta, IL-1R, IL-6, IL-8, IL-10 • EuroQol 5-Dimension 5-Level (EQ-5D-5L) QoL survey. Safety endpoints • AEs from informed consent to day 180 of follow-up or discontinuation.
ZARRABIM_2023[5]	Population: COVID-19 patients with ARDS N (Int vs Com): 19:24 Age (years) Int Vs Comp: 49.05 vs 49.4±11.7 Male: female ratio Int Vs Comp:	IV infusion of 100× 10^6 MSC cells **or** MSC as IV infusion and one dose of MSC-derived EVs 200× 10^6 through inhalation route	Placebo	Primary endpoint • Assessment of adverse events upto 28 days Secondary endpoints • Improving the clinical symptoms of the patients/complete blood count (CBC)/ arterial blood gas (ABG)/ biochemistry analysis/ inflammatory parameters Baseline, after first infusion, after second infusion, and 48 h after the second intervention.

	15/4 vs 16/6			
REBELATTO ET A_2022[6]	Population: COVID-19 with ARDS N (Int vs Com): 11:6 Age (years) Int Vs Comp: 53±15.3 vs 61.7±9.7 Male: female ratio Int Vs Comp: 8/3 vs 4/2	IV infusion of 5× 10^5 cells/kg UC-MSCs	Placebo	Primary outcome • Safety of allogenic UC-MSC infusion after the observation of infusional reactions and adverse events (AEs) Second outcome • Patient recovery - viral load, blood tests and plasma levels of infammatory cytokines, peripheral blood mononuclear cell (PBMC) assessment of T cell populations and PASC reduction evaluated by biochemical markers and CT scan
FATHI-KAZEROONI ET AL_2022[7]	Population: COVID-19 ARDS N (Int vs Com): 15:15 Age (years) Int Vs Comp: 46.43±11.91 vs 53.67±10.3 Male: female ratio Int Vs Comp: 9/6 vs 10/5	IV infusion of 5 mL of MenSCs-secretome derived from Menstrual blood derived MSC for 5 consecutive days for 60 min	Placebo	Primary endpoint: • Safety: adverse events within six hours; cardiac arrest or death within 24 h of every infusion. Secondary endpoints • Patient survival at 28 days after initial infusion and time to recovery
REALIST-COVID TRIAL)-GORMAN ELLEN A _2023[8]	Population: COVID-19–related moderate to severe ARDS N (Int vs Com): 30:29 Age (years)	ORBCEL-C (400 X10^6 CD362-enriched umbilical cord–derived MSCs in 200 ml Plasma-Lyte	Placebo	Primary efficacy outcome • Oxygenation index (OI) at Day 7 Secondary surrogate outcomes • Pulmonary and nonpulmonary organ dysfunction • OI at Days 4 and 14 • Respiratory compliance, driving pressure, PaO2:FIO2 (PF) ratio on Days 4, 7, and 14; SOFA

	Int Vs Comp: 58.4±9.2 vs 58.4±12.5 Male: female ratio Int Vs Comp: 24/6 vs 20/9			score on Days 4, 7, and 14. Clinical outcome • Extubation and reintubation, • ventilator-free days (VFDs) to Day 28, Duration of ventilation, • Lengths of ICU and hospital stays, • 28-and 90-day mortality. Long-term follow-up included • Diagnosis of interstitial lung disease at 1 year • Significant medical events and mortality at 2 years.
ZHENG G_2014[9]	Population: ARDS patients N (Int vs Com): 6:6 Age (years) Int Vs Comp: 66.7±20.4 vs 69.8±9.1 Male: female ratio Int Vs Comp: 6/0 vs 5/1	1 × 10^6 cells/kg single dose of allogeneic adipose-derived MSCs	Placebo	Primary endpoint • Occurrence of adverse events. Secondary efficacy endpoints • PaO2/FiO2 ratio, • Hospital indices (length of hospital stay, ventilator-free days and ICU-free days at day 28), • Serum biomarkers of ARDS including IL-6, IL-8 and SP-D.
AGHAYAN ET AL_2022[10]	Population: ARDS caused by COVID-19 N (Int vs Com): 10:10 Age (years) Int Vs Comp: 62.3 vs 58.4	single dose of 1× 10^6 cells/kg Allogeneic placenta-derived mesenchymal stem cells (PL-MSCs)	Standard treatment	Main outcome • Safety of intravenous PL-MSCs

	Male: female ratio Int Vs Comp: 6/4vs8/2			
DILOGO IH_2021[11]	Population: Critically ill COVID-19 ARDS N (Int vs Com): 20:20 Age (years) Int Vs Comp: - Male: female ratio Int Vs Comp: 15/5 vs 15/5	1 X 10^6 UC-MSCs /kg IV infusion+ SOC	Placebo+SOC	Primary outcome • Mortality rate • Length of ventilator usage Secondary outcomes • Length of stay in the ICU • Improvement in the routine laboratory value, including routine blood count, differential count, CRP, D-dimer, fibrinogen, and procalcitonin • Improvement in biomarker laboratory value of cytokines and lymphocyte subpopulation • AE or serious AE (SAE)
LANZONI G_2020[12]	Population: COVID-19 ARDS N (Int vs Com): 12:12 Age (years) Int Vs Comp: 58.58±15.93 vs 58.83±11.61 Male: female ratio Int Vs Comp: 5/7 vs 8/4	100 ± 20 × 10^6 UC-MSCs IV infusion at days 0 and 3.	Placebo	Primary endpoints • Safety, defined by the occurrence of prespecified infusion-associated adverse events (AEs) within 6 hours from each infusion; • Cardiac arrest or death within 24 hours postinfusion • Incidence of AEs. Secondary end points Clinical outcomes • survival at day 28 after treatment • time to recovery, defined as time to discharge or, if the subject was hospitalized, no longer requiring supplemental oxygen and no longer requiring COVID-19-related medical care • AEs, serious AEs (SAEs), Laboratory testing and mechanistic analyses • Viral load by SARS-CoV-2 RTPCR • Inflammatory cytokines, chemokines, and growth

				factors in peripheral blood plasma
START TRIAL MATTHAY ET AL_2019[13]	Population: Moderate to severe ARDS N (Int vs Com): 40:20 Age (years) Int Vs Comp: 55±17 vs 55±20 Male: female ratio Int Vs Comp: 23/17 vs 10/10	10×10^6 BM - MSC /kg IV infusion	Placebo	Primary outcome Safety of the MSC infusion, Secondary outcomes • All-cause mortality at day 28 and day 60, • number of ventilator-free days to day 28, • duration of ventilation in patients alive at day 28, • number of intensive-care-free days to day 28, • number of days free from organ failure to day 28 (• SOFA score • oxygenation index and lung injury score • Biological marker- IL-6. IL-8 and receptor for advanced glycation end products [RAGE]
MICHAEL E. BOWDISH_ 2023[14]	Population: COVID-19–Moderate to severe ARDS N (Int vs Com): 112:110 Age (years) Int Vs Comp: 61.8±13 vs 59.6±13.8 Male: female ratio Int Vs Comp: 79/33 vs75/35	2×10^6 MSC/kg IV infusion	Placebo	Primary endpoint • Reduction in all-cause mortality within 30 days. Secondary endpoint • Days alive off mechanical ventilation within 60 days • Mortality at 7, 14, 60, and 90 days and 12 months, • Resolution and/or improvement of ARDS, • Clinical improvement at Days 7, 14, 21, and 30
STROMA-COV-2 TRIAL - MONSEL A_2022[15]	Population: COVID-19 -mild-to-severe ARDS N (Int vs Com): 21:24	3×10^6 UC-MSCs/kg IV infusion	Placebo	Primary endpoint respiratory improvement assessed as PaO2/FiO2-ratio change between baseline (D0) and D7. Secondary and safety endpoints • All-cause mortality at D28 • Number of ventilator-free days to D28, • Duration of ventilation in patients alive on D28,

	Age (years) Int Vs Comp: 64±10.4 vs 63.2±11.4 Male: female ratio Int Vs Comp: 17/4 vs 20/4			• Number of intensive care-free days to D28, • Number of organ-failure–free days to D28, • SOFA score, lung injury score, driving pressure, and respiratory lung compliance. Safety endpoints were the number of Safety outcomes • Adverse events

v. Classification of studies on the basis of level of manipulation of the stem cell/ Stem cell derived product use *(interpreted by the Secretariat as defined by CDSCO* and the information provided in the trial itself):*

S. No.	Trial Details	Intervention	Level of manipulation	Information extracted from trial
1.	Cécile Pochon 2023	Wharton Jelly-derived Mesenchymal Stromal Cells (WJ-MSCs)	More	*"MSC were cultured until passage 2 and then frozen in a solution composed of 80% albumin and 10% Dimethyl sulfoxide (DMSO) at a minimum concentration of 1.106 MSC/ml."*
2.	Amy L. Lightner 2023	Bone marrow mesenchymal stem cell (BM-MSC)-derived extracellular vesicles (ExoFlo)	More	*"ExoFloTM 48 is an extracellular vesicle (EV) product manufactured per CGMP regulations from a single donor BM-MSC 49 culture that conveys the immunomodulatory and regenerative properties of BM-MSC without cellular therapy limitations."*
3.	Bellingan G 2022	Bone marrow-derived, allogeneic, multipotent adult progenitor cells	More	*"Cryogenically preserved multipotent adult progenitor cells suspended in PlasmaLyte-A containing DMSO and human serum albumin (HSA), were thawed, counted, assessed for viability during preparation of each clinical dose."*
4.	Ichikado K 2023	Invimestrocel	More	*"bone marrow–derived, allogeneic, multipotent adult progenitor cells"*
5.	Zarrabi M 2023	Allogenic mesenchymal stromal cells	More	*"We used good manufacturing practice (GMP)-certified MSCs for this study, which underwent a panel of quality control tests as part of their certificate of analysis."*
6.	Rebelatto 2022	Umbilical cord-Mesenchymal stromal cells (MSCs)	More	*"When the cell culture reached 70–80% confluence, cells were detached by treatment with 0.25% trypsin–EDTA and replated at a density of 8000 cells/cm² into 150 cm² culture flasks. At passage 3 (P3), cytogenetic analysis was performed. UC-MSCs were harvested*

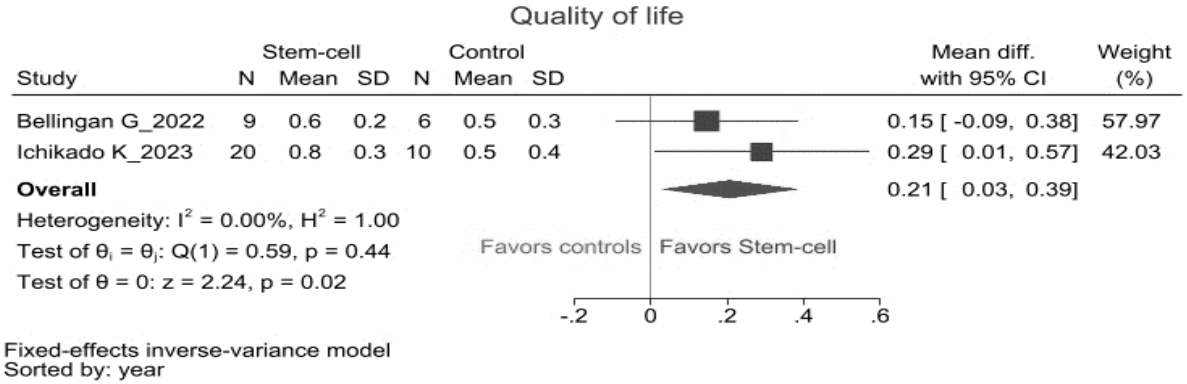
				and cryopreserved using a rate-controlled freezer at a final concentration of 10% dimethyl sulfoxide (Origen, Texas, USA) and 90% FBS."
7.	Fathi-Kazeroon i 2022	Cell-free Mesenchymal stromal cells (MSCs)	More	*"MenSCs were culture-expanded from a previously established and characterized master cell bank (MCB) derived from the menstrual blood collected from at least 5 healthy women."*
8.	Gorman Ellen A 2023	ORBCEL-C (CD362-enriched, umbilical cord–derived MSCs)	More	*"The ORBCEL-C cellular product consisted of allogeneic donor anti-CD362 antibody enriched human UC- derived mesenchymal stromal cells."*
9.	Zheng G 2014	allogeneic adipose-derived mesenchymal stem cells	More	*"MSCs were passaged up to a maximum of four times. After sufficient MSCs were expanded, cells were harvested and cryopreserved in 70% culture media, 20% fetal bovineserum and 10% DMSO."*
10.	Aghayan 2022	allogeneic placenta-derived mesenchymal stem cells (PL-MSCs)	More	*"At the fifth subculture, PL-MSCs were harvested at 90% confluency, centrifuged (200 g/5 min), resuspended in cryopreservation media (DMEM-LG+5% hPL+10% DMSO (CryoMACS DMSO, MiltenyiBiotec, Germany)), and aliquoted into 2 ml cryovials (Corning, USA). Mr. Frosty container (Nalgene, Thermo Fisher Scientific, USA) was applied for slow freezing of samples according to the manufacturer's instruction."*
11.	Lanzoni G 2020	umbilical cord mesenchymal stem cell (UC-MSC)	More	*"described.38 UC-MSCs were culture-expanded from a previously established and characterized master cell bank (MCB) derived from the subepithelial lining of a UC, collected from a healthy term delivery"*
12.	Matthay 2019	allogeneic mesenchymal stromal cells (MSCs)	More	*"At 70% confluence, MSCs were lifted and passaged at a low density (40–50 cells/cm^2) into 24 cell factories. At 70–80% confluence, the MSCs were harvested, washed, resuspended, and cryopreserved."*
13.	Michael E. Bowdish 2023	Allogeneic mesenchymal stromal cells	More	*"third-party, off-the-shelf suspension of ex-vivo cultured adult human mesenchymal stem cells intended for intravenous infusion."*
14.	Monsel A 2022	Umbilical cord-derived mesenchymal stromal cells (UC-MSCs)	More	*"the investigational advanced therapy medicinal product was a suspension of allogenic UC-MSCs, isolated from human UC Wharton's jelly by enzymatic digestion or the explant method, and amplified in vitro."*

* as defined by CDSCO in Annexure- I of the guideline document.

vi. Additional forest plots:

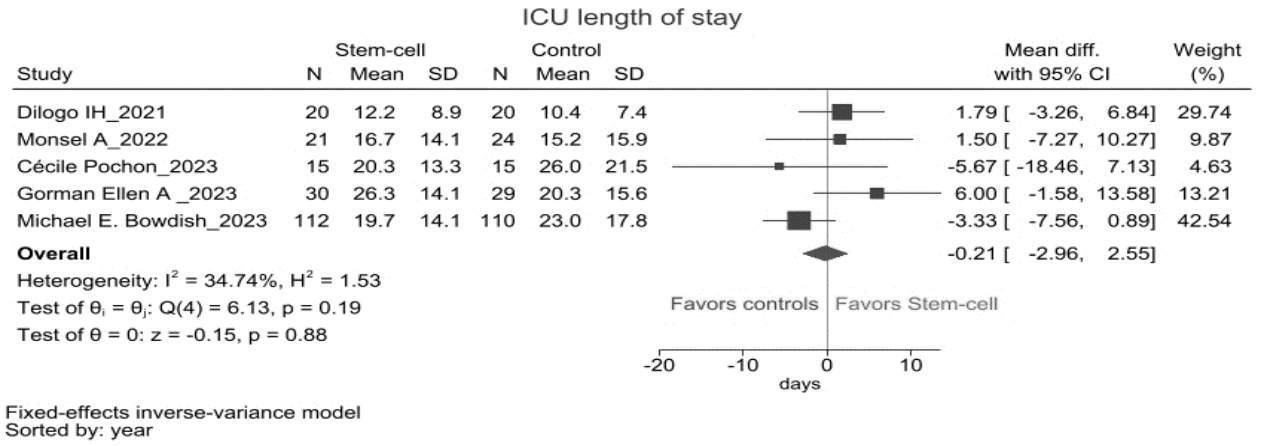
1. Quality of life: 2 trials, with a total of 45 participants, reported quality of life. The pooled analysis yielded a mean difference of 0.21 (95% CI: 0.03 to 0.39) between the stem cell group and usual care, which was statistically non-significant.

1.1. Effect of stem cell treatment on quality of life as compared to the SOC in patients with ARDS:



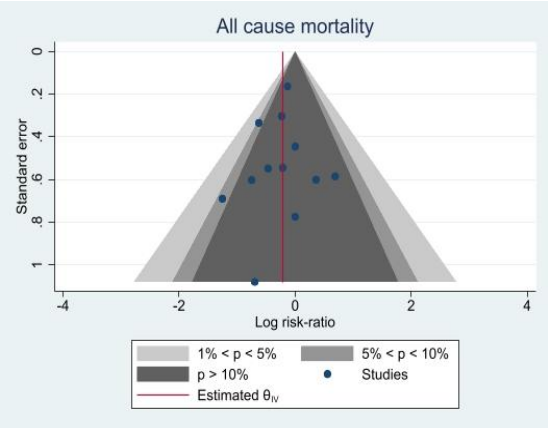
2. Length of ICU stay: 5 trials, with a total of 396 participants, reported length of ICU stay. The pooled analysis yielded a mean difference of -0.21 (95% CI: -2.96 to 2.55) between the stem cell group and usual care, which was statistically non-significant.

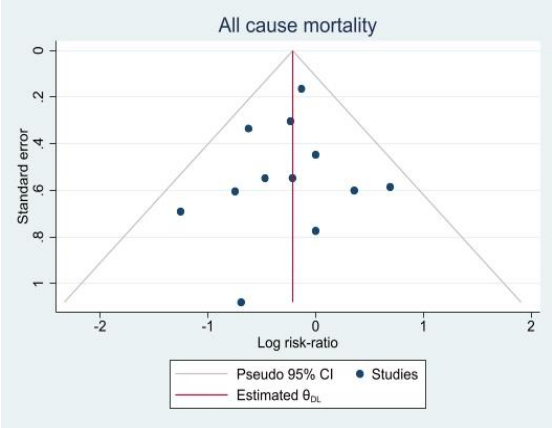
2.1. Effect of stem cell treatment on the length of ICU stay as compared to the SOC in patients with ARDS:

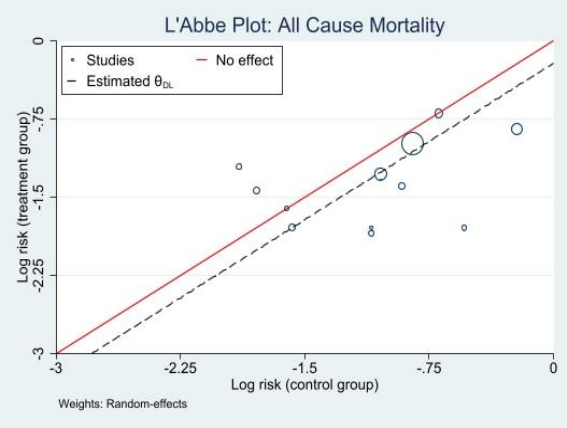


vii. Publication bias:

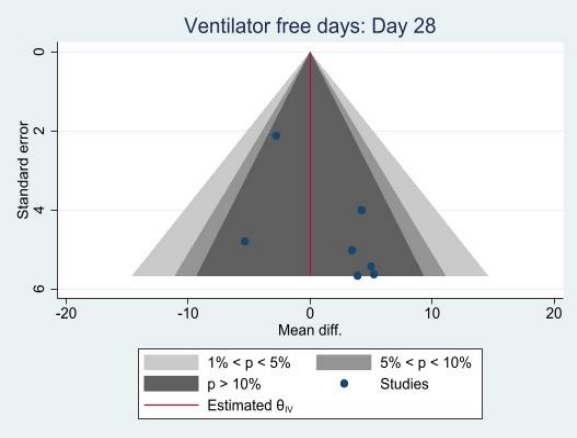
1. All cause mortality (Day 28):

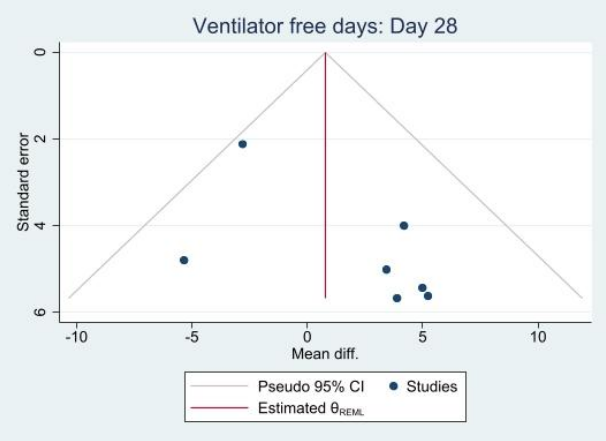




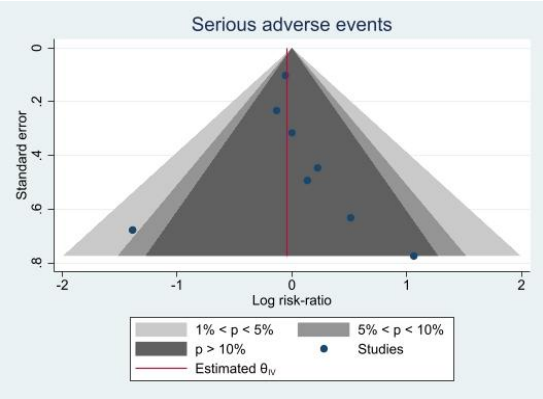


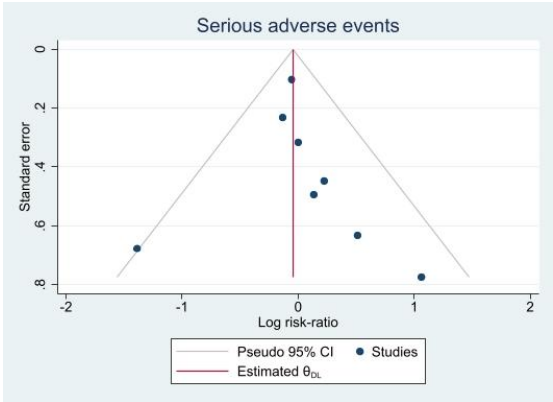
2. Ventilator free days:

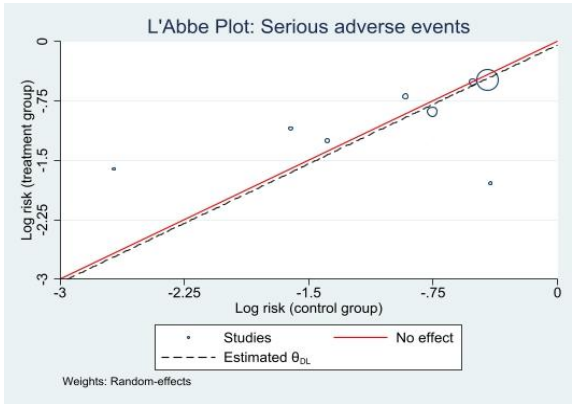




3. Serious adverse effects:







viii. Evidence to Decision Framework:

QUESTION

Efficacy and safety of stem cell therapy in acute respiratory distress syndrome?	
POPULATION:	Acute respiratory distress syndrome (ARDS)
INTERVENTION:	Stem cell therapy
COMPARISON:	Usual care
MAIN OUTCOMES:	All-cause mortality (D-28, D-60), ventilator free days (D-28), ICU free days (D-28), duration of hospital stay, serious adverse events
SETTING:	Tertiary care centers/ Hospitals
PERSPECTIVE:	Health System
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.[16] 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.
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	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.[17]	
Desirable Effects How substantial are the desirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
● Trivial ○ Small ○ Moderate ○ Large ○ Varies	**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. **All-cause mortality (60 days):** 4 trials, with a total of 209 participants,	

○ Don't know	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. **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. **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. **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.	
Undesirable Effects How substantial are the undesirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
● Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	**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.	
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 quality due to high risk of bias in the studies and inconsistency & imprecision in the reported 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	No direct research evidence was identified.	Main outcome is mortality which is likely to be valued by most patients.
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	It is less clear if benefits of stem cell intervention outweigh the harms, based on limited evidence.	

○ Favors the intervention ○ Varies ○ Don't know		
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 on the resources required for stem cell transplantation in patients with ARDS was identified.	However, there is indirect evidence in the form of Hematopoietic stem cell transplantation done for hematological conditions. The median cost of autologous transplant was USD, $ 12,500 (approx. Rs 10.5 lakhs) and the median cost of allogeneic transplant was $ 17,914 (approx. 15 lakhs) as reported by a private center in New Delhi, India.[18]
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 research evidence was identified.	The GDG was fairly confident that the certainty of evidence of resources required is moderate.

○ No included studies		
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	No research evidence was identified	As stem cell therapy is an expensive treatment offered only at tertiary centers, it is likely to reduce equity.

○ Don't know		
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.	Despite uncertainty regarding the risks and benefits associated with stem cell therapy, patients may still consider undergoing treatment.
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

	JUDGEMENT						
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 acute respiratory distress syndrome. It may be used only in the context of rigorously conducted randomized controlled trials.

Justification

Overall 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.

ix. Data Extraction:

Data Extraction Methods:

A comprehensive search of PubMed, Embase, Cochrane and Web of Science databases for randomized controlled trials was conducted from inception to September 2023. The screening process utilized Rayaan software. The critical outcomes were all-cause mortality, Ventilator free day, ICU free days and serious adverse events (SAEs)and these were compared between stem cell therapy and standard of care (SOC). Relative risks (RR) or mean differences and 95% confidence intervals were pooled using the random-effects model. Risk of bias was assessed using the ROB tool for the main outcomes. Publication bias was also evaluated. The quality of evidence was assessed using the GRADE tool.

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:

Study	**1**
Author Year (trial name if available)	Cécile Pochon_2023 MSC-COVID –Trial-
Study type:	Randomized, sham infusion-controlled, parallel-group, double-blind, superiority clinical trial, Phase 2a

Number of participants:	30
Countries, setting and Funding:	France, e ProgrammeHospitalier de Recherche Clinique supported by the French Ministry of Health.
Duration of study Follow up (post intervention):	28 days
Method of assessment of disease condition:	Berlin definition
Subgroup analysis within study	Nil
Inclusion criteria:	• Adults, had a positive RT-PCR for SARS-CoV-2 with moderate or severe ARDS according to the Berlin definition • Had been receiving invasive mechanical ventilation for less than 48 h.
Exclusion criteria:	• Invasive mechanical ventilation >48h, • Chronic respiratory disease under oxygen therapy, • History of functional class III or IV pulmonary hypertension (WHO classification), • Extracorporeal membrane oxygenation treatment, • *i*mmunosuppressive therapy, • Active solid tumor or in remission for less than 2years, malignant hematological disease, asplenia, hematopoietic stem cells or organ transplantation, • Expected death within 24h, • Positive blood pregnancy test at inclusion, • Participation in another interventional clinical trial
Recruitment/selection of patients:	Admitted patients in ICU
Intervention: Source and Type of stem cells	Umbilical cord Wharton Jelly Mesenchymal Stromal Cells in as solution of (albumin 4%, NaCl 0.9%, and ACD formula A, 75 to 100 mL
Intervention: Method of their characterization	MSCs were isolated from Wharton's jelly of umbilical cords, according to the explant method.
Intervention: Route of administration	IV infusion
Intervention: Dose	1×10^6 MSC/kg of body weight at day 1, 0.5×10^6 MSC/kg at day 4 and then, at day 6
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:	Primary endpoint: Percentage of patients with a PaO2/ FiO2>200mmHg at day 10

	of treatment (WJ-MSC or placebo). Secondary endpoints: • PaO2/FiO2 evolution between the first day of infusion (day 0 or 1) and day 14 • Number of 28day ventilator free days • Vasopressor & extra-renal support free days, • Difference in SOFA score between day 14 and day 0, • 90 day all-cause mortality, • ICU length of stay, • Respiratory morbidity at day 90, • RT-PCR SARS-CoV-2 positivity at day 7, 14, and 21.
Safety Outcomes reported with time points- Serious AE	• Infusion-related toxicity (hypersensitivity reaction within 6h of infusion), • D-dimers elevation at day 10, • Acquisition of anti-HLA antibodies at day 28 and day 90, • occurrence of thromboembolic events or infectious events within 90 days post-randomization
Safety Outcomes reported with time points- Other Adverse Events	-

Study	**2**
Author Year (trial name if available)	Amy L. Lightner, 2023, EXIT COVID-19 Trial-
Study type:	Multicenter, double-blind, randomized, placebo-controlled dosing trial – 3 arm, Phase 2
Number of participants:	34+34+34 =102
Countries, setting and Funding:	USA, Direct Biologics, LLC, USA
Duration of study Follow up (post intervention):	60 days
Method of assessment of disease condition:	SpO2 <94% on room air, partial pressure of arterial oxygen to fraction of inspired oxygen (PaO2/FiO2) <300 mm Hg and a respiratory rate >30 breaths/min, or lung infiltrates >50%
Subgroup analysis within study	Yes
Inclusion criteria:	• Male or female aged 18-85. • COVID-19 positive as defined by positive RT-PCR SARS-CoV-2. • Moderate to severe ARDS as defined by modified Berlin definition,

	• Hypoxia requiring non-invasive oxygen support such as Nasal Cannula (NC), Non rebreather (NRB), Bilevel Positive Airway Pressure (BIPAP), Continuous Positive Airway Pressure (CPAP), high flow nasal cannula oxygen (HFNC O2) or mechanical ventilation (MV) despite initiating SOC • Male or female of reproductive potential must agree to use of double barrier method of highly effective birth control contraception
Exclusion criteria:	• Vulnerable populations • Active malignancy requiring treatment within the last five years. • Major physical trauma in the last 5 days, • Active tuberculosis or cystic fibrosis. • Severe chronic respiratory disease including COPD or pulmonary fibrosis requiring home oxygen > 5L/min. • Use of ECMO during the current hospitalization. • Pre-existing pulmonary hypertension. • Severe pre-existing hepatic impairment • Pre-existing Chronic Kidney Disease (CKD) stage IIIb or End Stage Renal Disease (ESRD) prior to onset of COVID-19 (stage I, II, and IIIa are acceptable) • Irreversible coagulopathy • Non-COVID-19 Pneumonia • Endotracheal intubation duration ≤ 24 hours. • Moribund—expected survival < 24 hours. • Severe metabolic disturbances on presentation (e.g., ketoacidosis, pH < 7.3)
Recruitment/selection of patients:	Inpatient hospital settings
Intervention: Source and Type of stem cells	Bone marrow mesenchymal stem cell (BM-MSC)-derived extracellular vesicles (ExoFlo)
Intervention: Method of their characterization	ISCT definition.
Intervention: Route of administration	Intravenous infusion
Intervention: Dose	ExoFlo 15 ml – 60-80 billion EV/mL ExoFlo 10 ml- 60-80 billion EV/mL A repeat of the same study treatment given on Day 4 if the patient had not recovered
Intervention: Dose - If the trial has taken multiple doses, then which dose values has been used for MA	

Efficacy Outcomes reported with time points:	Primary: Improvement in the mortality rate within 60 days from randomization. Secondary endpoints • Time to death, • Proportion of discharged patients, • Time to hospital discharge at 7, 30, and 60 days from randomization, and • Ventilation free days. Exploratory outcome Measurements included viraemia, serum acute phase reactants, immune cell subset counts, SOFA scores, and Quality of Life (EQ-5D-5L) scores
Safety Outcomes reported with time points- Serious AE	Incidence of treatment-emergent serious adverse events – tll day 60
Safety Outcomes reported with time points- Other Adverse Events	

Study	**3**
Author Year	Bellingan G_2022, MUST-ARDS Trial-
Study type:	Multicentre, randomised, double-blind, placebo-controlled phase 1/2 trial
Number of participants:	30 (20+10 control)
Countries, setting and Funding:	USA & UK, National Institutes of Health, Innovate UK, and Athersys, Inc
Duration of study Follow up (post intervention):	28 days
Method of assessment of disease condition:	Berlin definition
Subgroup analysis within study	-
Inclusion criteria:	• Male or female, age 18-90 years • Diagnosis of a new acute onset of moderate to severe ARDS, as defined by the Berlin definition • Able to receive investigational medicinal product within 96 hours of meeting the last of the ARDS diagnosis
Exclusion criteria:	• Moribund subject not expected to survive up to 48 hours; • Concurrent illness that shortens life expectancy to less than 6 months; • Home mechanical ventilation for chronic respiratory failure • Diffuse alveolar hemorrhage with or without vasculitis • Severe ILD needing supplemental oxygen; • Severe COPD with recent FEV1/FVC ratio <0.3 (if available) or the use of home

	oxygen; • History of chronic pulmonary hypertension (WHO Class III or IV); • History of lung transplantation; • ST-segment elevation myocardial infarction (STEMI) within the last 6 months; • Mean arterial pressure (MAP) <60 mmHg while on 2 or more vasopressors with or without inotropic support; • Severe chronic liver disease (Childs-Pugh Score >10); • Known anaphylaxis or religious objection to bovine or porcine products; • Previous autologous, allogeneic bone marrow or peripheral stem cell transplant to treat conditions other than hematologic malignancies; • Any history of malignancy within the last 2 years, with the exception of adequately treated basal or squamous cell carcinoma of the skin or hematologic malignancy treated with bone marrow or peripheral stem cell transplantation; • History of human immunodeficiency virus (HIV) infection • Clinical findings that, in the opinion of the Investigator, raise significant doubt that ARDS is the primary etiology of the subject's hypoxemia and chest radiography criteria; • Other serious medical or psychiatric illness • Prior participation in any other clinical trial • Significant sustained improvement in oxygenationfollowing initial diagnosis of ARDS suggesting resolving ARDS (P/F ratio > 300 mmHg (40 kPa)).
Recruitment/selection of patients:	
Intervention: Source and Type of stem cells	Bone marrow derived multipotent adult progenitor cells
Intervention: Method of their characterization	Cryogenically preserved multipotent adult progenitor cells suspended in PlasmaLyte-A
Intervention: Route of administration	IV infusion
Intervention: Dose	900 million cells diluted into 300 ml of PlasmaLyte-A (one dose)
Intervention: Dose - If the trial has taken multiple doses, then which dose values has been used for MA	Yes, 900 million cells diluted into 300 ml of PlasmaLyte-A- cohort 3
Efficacy Outcomes reported with time points:	• Ventilator-free days, • Days free from intensive care unit (ICU), • Total length of hospital stay through Day 28

	• Changes in PaO2/FiO2ratio and PEEP requirements from baseline through Days 1, 2, 3, 7 and 28; • Changes in respiratory physiologic measures (peak and plateau pressures) from baseline through the time the subject is extubated • All-cause mortality at Days 28, 90 and 365. Exploratory endpoints • Changes in circulating biomarkers of inflammation and lung injury between baseline and Days 1, 2, 3 and 7; • Health-related quality of life (EQ-5D-3L) at Days 28, 90 and 365
Safety Outcomes reported with time points- Serious AE	• Safety and tolerability of multipotent adult progenitor cells • Assessment of vital signs and laboratory parameters through Day 28, and TEAEs through Day 365.
Safety Outcomes reported with time points- Other Adverse Events	

Study	**4**
Author Year	IchikadoK_2023, ONE-BRIDGE Trial
Study type:	Randomized, open-label, standard therapy–controlled, phase 2 multicenter study
Number of participants:	30
Countries, setting and Funding:	Japan, Healios K.K., licensee (in Japan) of invimestrocel
Duration of study Follow up (post intervention):	180 days
Method of assessment of disease condition:	Berlin definition
Subgroup analysis within study	-
Inclusion criteria:	• Aged 20–90 years, diagnosed with ARDS (according to the Berlin Defnition caused by pneumonia, • Receiving mechanical ventilation, • Could receive the investigational product within 72 h after ARDS diagnosis. • Patients who were at a high risk of progressive pulmonary fibroproliferation associated with secondary septic syndrome and could not be rescued by conventional treatments were included based on an estimated HRCT score≥211

Exclusion criteria:	• Patients who were likely to die of severe systemic organ failure in a few days without confirming the effect of invimestrocel based on an APACHE II score≥27 • Life expectancy of expectancy of<6 months, • On mechanical ventilation for≥1 week, • Had suspected acute exacerbation of chronic pulmonary fibrosis, diffuse alveolar hemorrhage, chronic respiratory disease requiring continuoushome oxygen therapy, severe COPD (GOLD stage III or higher • Chronic pulmonary hypertension, • History of lobectomy/ single lung pneumonectomy, or lung transplantation, or severe chronic liver disease. • Patients with ARDS due to trauma or other non-infectious factors such as pancreatitis
Recruitment/selection of patients:	medical centers in Japan
Intervention: Source and Type of stem cells	BM derived multi-potent adult progenitor cells (invimestrocel)
Intervention: Method of their characterization	ex vivo culture
Intervention: Route of administration	IV Infusion
Intervention: Dose	9.0×10^{8} cells- one dose
Intervention: Dose - If the trial has taken multiple doses, then which dose values has been used for MA	
Efficacy Outcomes reported with time points:	• Number of days of survival free from mechanical ventilation (VFDs) during the first 28 days • Ventilator Free Days • Ventilator weaning rate on day 28, re-intubation rate, mortality on days 28, 60, 90, and 180 after treatment administration, • Progression of chest imaging findings through day 90 • Inflammation and lung injury –WBC, CRP, LDH, CXCL10. IL-1beta, IL-1R, IL-6, IL-8, IL-10 • EuroQol 5-Dimension 5-Level (EQ-5D-5L) QoL survey.
Safety Outcomes reported with time points- Serious AE	AEs from informed consent to day 180 of follow-up or discontinuation
Safety Outcomes reported with time points- Other Adverse Events	

Study	**5**
Author Year	Zarrabi M_2023
Study type:	Phase II randomized, multicentric clinical trial
Number of participants:	MSC group (n=11) MSC+EV group (n=8) Control group (n=24)
Countries, setting and Funding:	Iran, Royesh Venture Capital Fund and CellTech Pharmed
Duration of study Follow up (post intervention):	28 days
Method of assessment of disease condition:	Berlin criteria
Subgroup analysis within study	-
Inclusion criteria:	• Age between 18 and 65, • Confirmation of SARS-CoV-2 infection by qRT-PCR, Diagnosis of ARDS according to the Berlin criteria [• Requiring supplemental oxygen therapy, • Pneumonia and progressive status (>50% in 24–48 h), SPO2/FiO2≤300 mmHg, ICU admission<48 h, and a SOFA score between 2 and 3
Exclusion criteria:	• Allergies or sensitivity to cell-based products • History for malignancies • other viral respiratory co-infections, • severe renal or liver failure • Interstitial lung disease, • Underlying immunocompromised disease, • Those on extracorporeal life support
Recruitment/selection of patients:	Masih Daneshvari and Shariati hospitalsin Tehran, Iran
Intervention: Source and Type of stem cells	Mesenchymal stromal cells derived from Perinatal tissue
Intervention: Method of their characterization	characterization of EVs according to the MISEV2018 guideline
Intervention: Route of administration	MSC cells intravenously Extravesicles by inhalation
Intervention: Dose	100× 10^6cells (2 IV infusions) IV infusion of 100× 10^6 MSC cells derived from perinatal tissue- one dose of 100× 10^6 Perinatal tissue derived MSC as IV infusion and one dose of

	MSC-derived EVs 200× 10^6 through inhalation route
Intervention: Dose - If the trial has taken multiple doses, then which dose values has been used for MA	Both were combined and taken for analysis
Efficacy Outcomes reported with time points:	• Improving the clinical symptoms of the patients/complete blood count (CBC)/ arterial blood gas (ABG)/ biochemistry analysis/ inflammatory parameters Baseline, after first infusion, after second infusion, and 48 h after the second intervention.
Safety Outcomes reported with time points- Serious AE	
Safety Outcomes reported with time points- Other Adverse Events	Assessment of adverse eventsupto 28 days

Study	**6**
Author Year	Rebelatto et a_2022
Study type:	Phase I/II, prospective, single-center, randomized, double-blind, placebo-controlled clinical trial
Number of participants:	17 (11 intervention+6)
Countries, setting and Funding:	Brazil, Grants from the ProjetosIndividuais no Combate à Covid-19—Universidade Federal do Paraná (N° 3748), PontifíciaUniversidade Católica do Paraná with resources from Banco Regional de Desenvolvimento do Extremo Sul (BRDE) (N° 01/2020, 03/2020) and Brazilian Ministry of Health—Brazilian National Program of Genomic and Precision Health/CNPq (N° 403624/2020-7)
Duration of study Follow up (post intervention):	120 days
Method of assessment of disease condition:	critically ill patients (WHO ordinal scale score 6 and 7), arterial oxygen partial pressure (PaO2)/oxygen absorption concentration (FiO2) ≤300 mmHg
Subgroup analysis within study	-
Inclusion criteria:	• Patients over 18 years old • Diagnosed with COVID-by RT-PCR • Require intensive care surveillance and IMV—critically ill patients (WHO ordinal scale score 6 and 7), arterial oxygen partial pressure (PaO2)/oxygen absorption concentration (FiO2) ≤300 mmHg
Exclusion criteria:	• Use of any investigational products,

	• Previous or current history of malignancy under treatment; preexistingthromboembolic disease; • concomitant infection of HIV/or tuberculosis • Pregnancy • Pre-existing transplant • Use of immunosuppressive therapy • Greater than 72 h of ICU admission.
Recruitment/selection of patients:	recruited from the Complexo Hospital de Clínicas, Universidade Federal do Paraná, a referral public hospital
Intervention: Source and Type of stem cells	Allogenic Umbilical Cord-Mesenchymal stem cellStem Cells
Intervention: Method of their characterization	Method name not mentioned
Intervention: Route of administration	IV infusion
Intervention: Dose	5×10^5 cells/kg UC-MSCs – 3 doses
Intervention: Dose - If the trial has taken multiple doses, then which dose values has been used for MA	
Efficacy Outcomes reported with time points:	Patient recovery - viral load, blood tests and plasma levels of infammatory cytokines, peripheral blood mononuclear cell (PBMC) assessment of T cell populations and PASC reduction evaluated by biochemical markers and CT scan Viral load was performed at baseline and after cell therapy on days 2, 4, 6 and 14, Blood count, serologic tests, biochemistry, cell subpopulation analysis and inflammatory cytokines baseline, on days 2, 4, 6 and 14 ,2months and 4 months
Safety Outcomes reported with time points- Serious AE	Safety of allogenic UC-MSC infusion after the observation of infusional reactions and adverse events (AEs)within 24 h after each infusion
Safety Outcomes reported with time points- Other Adverse Events	

Study	**7**
Author Year	Fathi-Kazerooni et al_2022
Study type:	Phase I and II randomized controlled clinical trial
Number of participants:	30 (15+15)
Countries, setting and Funding:	Iran, Avicenna Research Institute (99/3436) and Zayabiotech Company supported this work

Duration of study Follow up (post intervention):	28 days
Method of assessment of disease condition:	RR>30 times/min, resting oxygen saturation of 90% or less, arterial partial pressure of oxygen/oxygen concentration ≤300 mmHg, and pulmonary infiltration greater than 50% in 24–48 hrs
Subgroup analysis within study	-
Inclusion criteria:	• Age 25–75 years, • Positive PCR result on SARS-CoV-2 • RR>30 times/min, • Resting oxygen saturation of 90% or less, • Arterial partial pressure of oxygen/oxygen concentration ≤300 mmHg, • Pulmonary infiltration greater than 50% in 24–48 h
Exclusion criteria:	• Pregnancy or breastfeeding, • History of drug reactions, • Pneumonia caused by bacteria, Mycoplasma, Chlamydia, Legionella, fungi or other viruses, • Airway obstruction due to lung cancer or unknown factors, • Carcinoid syndrome, • Longterm use of immunosuppressive drugs, • Hemodialysis or peritoneal dialysis, • Creatinine clearance <15 mL/min, • Moderate to severe liver disease (Child–Pugh score>12), • Deep vein thrombosis (DVT) or pulmonary embolism • Under ECMO • HIV, hepatitis B virus, or hepatitis C virus infections
Recruitment/selection of patients:	Intensive care unit at the Imam Khomeini Hospital Complex
Intervention: Source and Type of stem cells	MenSCs- secretome derived from allogenic Menstrual blood
Intervention: Method of their characterization	MenSCs were culture-expanded from a previously established and characterized master cell bank (MCB) derived from the menstrual blood collected from at least 5 healthy women
Intervention: Route of administration	IV infusions
Intervention: Dose	5 mL of MenSCs-derived secretome diluted in 100 mL of normal saline for 5 consecutive days for 60 min

Intervention: Dose - If the trial has taken multiple doses, then which dose values has been used for MA	
Efficacy Outcomes reported with time points:	Patient survival at 28 days after initial infusion and time to recovery
Safety Outcomes reported with time points- Serious AE	Safety: adverse events within six hours; cardiac arrest or death within 24 h of every infusion.
Safety Outcomes reported with time points- Other Adverse Events	AE with in 28 days follow up

Study	**8**
Author Year	REALIST-COVID Trial)-Gorman Ellen A _2023
Study type:	Multicenter, randomized, double-blind, allocation-concealed, placebo-controlled trial
Number of participants:	59 (30+29)
Countries, setting and Funding:	UK, Wellcome Trust Health Innovation Challenge Fund (reference 106939/Z/15/Z) and the Northern Ireland Health and Social Care Research and Development Fund for needs-led research
Duration of study Follow up (post intervention):	2 years but for analysis 90 days -time point taken
Method of assessment of disease condition:	Berlin definition
Subgroup analysis within study	
Inclusion criteria:	• Moderate to severe ARDS as defined by the Berlin definition • Patient is receiving invasive mechanical ventilation. • COVID-19 based on clinical diagnosis or PCR test.
Exclusion criteria:	• More than 72 h from the onset of ARDS* • Age < 16 years • Patient is known to be pregnant • Major trauma in prior 5 days • Presence of any active malignancy (other than non-melanoma skin cancer) that required treatment within the last year. • WHO Class III or IV pulmonary hypertension • Venous thromboembolism currently receiving anti-coagulation or within the past 3 months • Currently receiving extracorporeal life support (ECLS)

	• Severe chronic liver disease with Child-Pugh score > 12 • DNAR (Do Not Attempt Resuscitation) order in place • Treatment withdrawal imminent within 24 h • Prisoners • Previously enrolled in the REALIST trial
Recruitment/selection of patients:	12 ICUs across the United Kingdom
Intervention: Source and Type of stem cells	umbilical cord–derived MSCs (ORBCEL-C)
Intervention: Method of their characterization	
Intervention: Route of administration	IV infusion
Intervention: Dose	$400X10^6$ cells CD362-enriched umbilical cord–derived MSCs in 200 ml Plasma-Lyte 148 (single dose)
Intervention: Dose - If the trial has taken multiple doses, then which dose values has been used for MA	
Efficacy Outcomes reported with time points:	• Oxygenation index (OI) at Day 7 • Pulmonary and nonpulmonary organ dysfunction • OI at Days 4 and 14 • Respiratory compliance, driving pressure, PaO2:FIO2 (PF) ratio on Days 4, 7, and 14; SOFA score on Days 4, 7, and 14. • Extubation and reintubation, • ventilator-free days (VFDs) to Day 28, • Duration of ventilation, • Lengths of ICU and hospital stays, • 28-and 90-day mortality.
Safety Outcomes reported with time points- Serious AE	SAEs within 90 days
Safety Outcomes reported with time points- Other Adverse Events	AEs within 90 days

Study	**9**
Author Year	Zheng G_2014
Study type:	Single-center, randomized, double-blind, and placebo-controlled study

Number of participants:	12 (6:6)
Countries, setting and Funding:	China, Nonfunded
Duration of study Follow up (post intervention):	28 days
Method of assessment of disease condition:	Berlin definition
Subgroup analysis within study	-
Inclusion criteria:	• 18 years of age • Diagnosed within 48 hours with a PaO2/FiO2 ratio of < 200
Exclusion criteria:	Pre-existing severedisease of any major organs, pregnancy, pulmonary hypertension, malignant disease, HIV infection or if informed consent could not be obtained
Recruitment/selection of patients:	Shaoxing Second Hospital
Intervention: Source and Type of stem cells	Allogeneic adipose-derived Mesenchymal Stem cells
Intervention: Method of their characterization	cultured MSCs
Intervention: Route of administration	IV infusion
Intervention: Dose	1 × 106 cells/kg of body weight single dose
Intervention: Dose - If the trial has taken multiple doses, then which dose values has been used for MA	-
Efficacy Outcomes reported with time points:	• PaO2/FiO2 ratio, • Hospital indices (length of hospital stay, ventilator-free days and ICU-free days at day 28), • Serum biomarkers of ARDS including IL-6, IL-8 and SP-D
Safety Outcomes reported with time points- Serious AE	Occurrence of adverse events – 28 days
Safety Outcomes reported with time points- Other Adverse Events	

Study	**10**
Author Year	Aghayan et al_2022
Study type:	Non-blinded Phase I randomized trial
Number of participants:	20 (10:10)
Countries, setting and Funding:	Iran, e Motamed Cancer Institute, Tehran, Iran
Duration of study Follow up (post intervention):	28 days

Method of assessment of disease condition:	ARDS induced by COVID-19
Subgroup analysis within study	-
Inclusion criteria:	• ≥18 years of age, • Evidence of pneumonia by chest CT-scans and/or confrmation of SARSCoV-2 by qRT-PCR Pregnancy or breastfeeding Bilateral opacity of the lungs on CT scan, • Requires mechanical ventilation to increase oxygen saturation • PaO2/FiO2 ratio≤200
Exclusion criteria:	• H/o of chronic pulmonary disease with PaCO2>50 mmHg • History of using oxygen at home • Pregnancy or breastfeeding • H/o pulmonary embolism or DVT in the past 3 months • H/Oof lung transplantation • Active malignancy that has been treated for the past two years • More than 96 h have passed since the diagnosis of ARDS • Moderate to severe liver failure (Childs-Pugh Score>12) • Extensive trauma in the last 5 days Existence of severe and irreversible disease with a probability of life expectancy of fewer than 6 months
Recruitment/selection of patients:	ICU
Intervention: Source and Type of stem cells	Allogeneic placenta-derived mesenchymal stem cells (PL-MSCs)
Intervention: Method of their characterization	-
Intervention: Route of administration	IV infusion
Intervention: Dose	single dose of 1×10^6 cells/kg
Intervention: Dose - If the trial has taken multiple doses, then which dose values has been used for MA	-
Efficacy Outcomes reported with time points:	Mortality
Safety Outcomes reported with time points- Serious AE	Safety of intravenous PL-MSCs for 24 h after the transplantation
Safety Outcomes reported with time points- Other	

Adverse Events	

Study	**11**
Author Year	DILOGO IH_2021
Study type:	multicentered, double-blind, randomized clinical trial
Number of participants:	40(20:20)
Countries, setting and Funding:	Indonesia, Institutional funding from Ministry of Research, Technology and Higher Education, Indonesia
Duration of study Follow up (post intervention):	15 days
Method of assessment of disease condition	Partial pressure of oxygen in arterial blood (PaO2)/the fraction of inspired oxygen (FiO2) lower than 300 mmHg and supported by mechanical ventilation
Subgroup analysis within study	
Inclusion criteria:	• Age 18-95 years • Critically ill patients with RT-PCR-confirmed COVID-19 • Leukopenia and lymphopenia in peripheral blood and differential count, • Presenting with pneumonia on chest x-ray and/or ground-glass opacity on thorax computed tomography (CT) scan
Exclusion criteria:	• Any history of malignancy, • Pregnant or showed a positive pregnancy test, any history of or currently taking part in another clinical trial in the last3 months
Recruitment/selection of patients:	COVID-19 referral hospitals in Jakarta (Sulianti Saroso Infection Disease Hospital, Persahabatan Central General Hospital, Cipto Mangunkusumo National Central General Hospital, and Universitas Indonesia Hospital)
Intervention: Source and Type of stem cells	Umbilical cord derived mesenchymal stem cell
Intervention: Method of their characterization	-
Intervention: Route of administration	IV infusion+ SOC
Intervention: Dose	1 X 10^6 UC-MSCs /kg single dose
Intervention: Dose - If the trial has taken multiple doses, then which dose values has been used for MA	-
Efficacy Outcomes reported with time points:	• Mortality rate

	• Length of stay in the ICU • Improvement in the routine laboratory value, including routine blood count, differential count, CRP, D-dimer, fibrinogen, and procalcitonin • Improvement in biomarker laboratory value of cytokines and lymphocyte subpopulation
Safety Outcomes reported with time points- Serious AE	AE or serious AE (SAE)
Safety Outcomes reported with time points- Other Adverse Events	

Study	**12**
Author Year	Lanzoni G_2020
Study type :	Double-blind, phase 1/2a randomized controlled trial
Number of participants:	24 (12:12)
Countries, setting and Funding:	USA, National Center for Advancing Translational Sciences, Grant/Award Numbers: UL1TR002736, UL1TR000460
Duration of study Follow up (post intervention):	28 days
Method of assessment of disease condition:	COVID-19 ARDS
Subgroup analysis within study	-
Inclusion criteria:	• Patient currently hospitalized • Aged ≥ 18 years, • Peripheral capillary oxygen saturation (SpO2) ≤ 94% at room air, or requiring supplemental oxygen at screening, • PaO2/FiO2 ratio < 300 mmHg, • Bilateral infiltrates on frontal chest radiograph or bilateral ground glass opacities on a chest CT scan
Exclusion criteria:	• PaO2/FiO2 ≥ 300 at the time of enrollment • A previous MSC infusion not related to this trial • History of Pulmonary Hypertension (WHO Class III/IV) • H/o of left atrial hypertension or decompensated Left HF • Pregnant or lactating patient

	• Unstable arrhythmia • Patients with previous lung transplant • Patients currently receiving chronic dialysis • Patients currently receiving ECMO • Presence of any active malignancy • Any other irreversible disease or condition for which 6-month mortality is estimated to be greater than 50% • Moderate to severe liver disease (AST and ALT >5 X ULN) • Severe chronic respiratory disease with a PaCO2> 50 mm Hg or the use of home oxygen • Baseline QT prolongation Moribund patient not expected to survive > 24 hours
Recruitment/selection of patients:	UHealth System/Jackson Health System (UHS/JHS), in Miami, Florida
Intervention: Source and Type of stem cells	Umbilical cord derived mesenchymal stem cell
Intervention: Method of their characterization	-
Intervention: Route of administration	IV infusion
Intervention: Dose	$100 \pm 20 \times 10^6$ UC-MSCs each, in 50 mL vehicle solution at days 0 and 3.
Intervention: Dose - If the trial has taken multiple doses, then which dose values has been used for MA	-
Efficacy Outcomes reported with time points:	• Survival at day 28 after treatment
Safety Outcomes reported with time points- Serious AE	• SAEs
Safety Outcomes reported with time points- Other Adverse Events	• Cardiac arrest or death within 24 hours post infusion

Study	**13**
Author Year	START trial Matthay et al_2019
Study type:	Prospective, double-blind, multicentre, phase 2a randomised trial
Number of participants:	60 (40 intervention: 20)
Countries, setting and Funding:	USA, National Heart, Lung, and Blood Institute Production Assistance for Cellular Therapies Program (U01 HL108713 and HHSN26820100008C)

Duration of study Follow up (post intervention):	60 days
Method of assessment of disease condition:	Ratio of partial pressure of oxygen to fractional inspired oxygen
Subgroup analysis within study	
Inclusion criteria:	• Endotracheally intubated, • Had a PaO2:FiO2 less than 27 kPa, • mechanically ventilated with at least 8 cm H2O positive end expiratory pressure (PEEP), • Had bilateral pulmonary infiltrates consistent with pulmonary oedema on chest radiographs, Had no clinical evidence of left-heart failure or volume overload as the primary cause of the pulmonary oedema
Exclusion criteria:	• Age younger than 18 years, • ARDS present for more than 96 h, • pregnancy or breastfeeding, • Having received treatment for cancer in the past 2 years • Underlying medical status with life expectancy less than 6 months, • Moderate to severe liver disease (Child-Pugh score >12), Severe chronic lung disease with the use of home oxygen, or partial arterial pressure of carbon dioxide greater than 7 kPa, and not being committed to fullsupport
Recruitment/selection of patients:	Five university medical centres in the USA (University of California San Francisco, Stanford University, University of Pittsburgh Medical Center, Ohio State University, and Massachusetts General Hospital).
Intervention: Source and Type of stem cells	
Intervention: Method of their characterization	
Intervention: Route of administration	IV infusion
Intervention: Dose	10×10^6 BM-MSC /kg single dose
Intervention: Dose - If the trial has taken multiple doses, then which dose values has been used for MA	
Efficacy Outcomes reported with time points:	Safety of the MSC infusion
Safety Outcomes reported with time points- Serious	• All-cause mortality at day 28 and day 60,

AE	• Number of ventilator-free days to day 28, • Duration of ventilation in patients alive at day 28, • Number of intensive-care-free days to day 28,
Safety Outcomes reported with time points- Other Adverse Events	

Study	**14**
Author Year	Michael E. Bowdish_2023
Study type:	Randomized, parallel, sham infusion-controlled phase 3 trial
Number of participants:	112 -intervention and 110 control. Total -222
Countries, setting and Funding:	USA
Duration of study Follow up (post intervention):	12 months
Method of assessment of disease condition:	modified Berlin criteria
Subgroup analysis within study	
Inclusion criteria:	• Adults with SARS-CoV-2, confirmed by RT PCR, • Mechanical ventilation for moderate or severe ARDS.
Exclusion criteria:	• Receiving ECMO, • Evidence of bacterial pneumonia, • Massively obese • Untreated HIV, • Malignancy within 12 months of active treatment, • Elevated liver function tests (LFTs) (• Intubated for more than 72 hours at the time of randomization Prior history of respiratory disease requiring supplemental oxygen
Recruitment/selection of patients:	Not given
Intervention: Source and Type of stem cells	Bone marrow derived MSCs (remestemcel-L)
Intervention: Method of their characterization	-
Intervention: Route of administration	IV infusion
Intervention: Dose	2×10^6 MSC/kg 3 infusions
Intervention: Dose - If the trial has taken multiple	-

doses, then which dose values has been used for MA	
Efficacy Outcomes reported with time points:	• All-cause mortality at day 14 and day 30 • Duration of hospitalization • ICU length of stay
Safety Outcomes reported with time points- Serious AE	• SAES
Safety Outcomes reported with time points- Other Adverse Events	

Study	**15**
Author Year	STROMA-CoV-2Trial -Monsel A_2022
Study type:	Multicentre, double-blind, randomized, placebo-controlled phase 2b trial
Number of participants:	21-intervention and 24 placebo. Total-45
Countries, setting and Funding:	France, French Ministry of Health (Programme Hos- pitalier de Recherche Clinique National COVID-19 2020) and by the French National Research Agency (ANR Flash COVID-19)
Duration of study Follow up (post intervention):	28 days
Method of assessment of disease condition:	Berlin criteria
Subgroup analysis within study	-
Inclusion criteria:	• Age > 18 years, • Berlin criteria-defined ARDS (mild-to-severe) for < 96 h, • RT-PCR-confirmed SARS–CoV-2 infection, and were receiving respiratory support
Exclusion criteria:	• Acute respiratory distress syndrome present for>96 h • Pulmonary fibrosis • Pulmonary hypertension (WHO class III /IV) • Pulmonary embolism within the previous 3 months • Extracorporeal membrane oxygenation or life support • Immunocompromised status • Pregnancy or breastfeeding • Treatment for cancer in the past 2 years

	• Underlying medical condition with life expectancy<6 months • Moderate-to-severe liver disease (Child–Pugh score>12) • Severe chronic lung disease with the use of home oxygen and/or partial arterial pressure of carbon dioxide>50 mm Hg • Patients not committed to full support • Participation in another trial of COVID-19 therapeutics
Recruitment/selection of patients:	ICUs in eight French university hospitals.
Intervention: Source and Type of stem cells	Umbilical cord derived Mesenchymal Stromal Cells
Intervention: Method of their characterization	
Intervention: Route of administration	IV infusion
Intervention: Dose	3×10^6 UC-MSCs/kg single dose
Intervention: Dose - If the trial has taken multiple doses, then which dose values has been used for MA	
Efficacy Outcomes reported with time points:	• All-cause mortality at D28 • PaO2/FiO2-ratio change between baseline (D0) and D7 • Number of ventilator-free days to D28, • Number of intensive care-length • SOFA Score
Safety Outcomes reported with time points- Serious AE	SAEs
Safety Outcomes reported with time points- Other Adverse Events	

x. List of excluded studies:

S. No.	Study	Exclusion Reason
1.	Li, Tian-Tian et al. Human mesenchymal stem cell therapy in severe COVID-19 patients: 2-year follow-up results of a randomized, double-blind, placebo-controlled trial. EBIOMEDICINE - Volume 92, Issue 0, pp. - published 2023-06-01	Not RCT study. Long term follow-up study results
2.	Shaz BH et al. Feasibility Study of Cord Tissue Derived Mesenchymal Stromal Cells in COVID-19-Related Acute Respiratory Distress Syndrome Stem cells translational medicine - Volume 12, Issue 4, pp. 185-193 - published 2023-04-17	Non- randomized study- feasibility study
3.	Yip et al. Human Umbilical Cord-Derived Mesenchymal Stem Cells for Acute Respiratory Distress Syndrome. CRITICAL CARE MEDICINE - Volume 48, Issue 5, pp. E391-E399 - published 2020-05-01	Non- randomized study- feasibility study
4.	NajmehKaffashFarkha et al. Mesenchymal stromal cell therapy for COVID-19-induced ARDS patients: a successful phase 1, control-placebo group, clinical trial. STEM CELL RESEARCH & THERAPY - Volume 13, Issue 1, pp. - published 2022-06-28	Non- randomized study
5.	Kaffash et al. Specific Clinical and Immunological Changes Following Mesenchymal Stem Cell Transplantation in COVID-19-induced Acute Respiratory Distress Syndrome Patients: A Phase-I Clinical Trial. IRANIAN JOURNAL OF ALLERGY ASTHMA AND IMMUNOLOGY - Volume 21, Issue 6, pp. 687-703 - published 2022-12-01	Non- randomized study
6.	Stewart, D.J et all. Mesenchymal Stem/Stromal Cells: PRELIMINARY RESULTS FOR THE CELLULAR IMMUNO-THERAPY FOR COVID-19-RELATED ARDS MULTICENTRE CANADIAN RANDOMIZED CLINICAL TRIAL: CIRCA-19 PHASE 2 RCT. Cytotherapy - Volume 25, Issue 6, pp. S30 - published 2023-01-01	Conference proceedings /abstract
7.	Gardiner, H.J et al REPAIR OF ACUTE RESPIRATORY DISTRESS SYNDROME IN COVID-19 BY STROMAL CELLS (REALIST-COVID TRIAL): 1 YEAR FOLLOW UP FOR SAFETY AND PULMONARY DYSFUNCTION. Thorax - Volume 77, Issue 0, pp. A30 - published 2022-01-01	Conference proceedings /abstract
8.	Gorman, E. Repair of Acute Respiratory Distress Syndrome in COVID-19 by Stromal Cell Administration (REALIST-COVID) Phase 2 Randomised Controlled Trial. Am. J. Respir. Crit. Care Med. - Volume 205, Issue 1, pp. - published 2022-01-01	Conference proceedings /abstract
9.	Wick, K.D et al. Mesenchymal stromal cells reduce airspace biomarkers of lung injury in patients with ARDS. Am. J. Respir. Crit. Care Med. - Volume 203, Issue 9, pp. - published 2021-01-01	Conference proceedings /abstract
10.	Gregoire Celine et al Bone Marrow-Derived Mesenchymal Stromal Cell Therapy in Severe COVID-19: Preliminary Results of a Phase I/II Clinical Trial. FRONTIERS IN IMMUNOLOGY - Volume 13, Issue 0, pp. - published 2022-07-04	Not an RCT. Retrospectively compared the outcomes of these MSC-treated patients with those of 24 matched control

11.	Mesenchymal stromal cells reduce evidence of lung injury in patients with ARDS. JCI INSIGHT - Volume 6, Issue 12, pp. - published 2021-06-22	cohort study nested within the START trial. Air space and plasma biomarkers compared with outcomes.
12.	Ventura-Carmenate et al. Safety and efficacy of autologous non-hematopoietic enriched stem cell nebulization in COVID-19 patients: a randomized clinical trial, Abu Dhabi 2020. Transl. Med. Commun. - Volume 6, Issue 1, pp. - published 2021-01-01	COVD-19 without ARDS
13.	Gorman E et al. Repair of acute respiratory distress syndrome by stromal cell administration (REALIST) trial: A phase 1 trial. EClinicalMedicine - Volume 41, Issue 0, pp. 101167 - published 2021-11-01	Non-randomized phase I study. Only in 9 patients
14.	Wilson, J. G et al. Mesenchymal Stem (stromal) Cells for Treatment of Ards: A Phase 1 Clinical Trial. AMERICAN JOURNAL OF RESPIRATORY AND CRITICAL CARE MEDICINE - Volume 191, Issue 0, pp. - published 2015-01-01	Non-randomized Phase I study. Included only 9 patients
15.	Perlee, Desiree et al. Intravenous Infusion of Human Adipose Mesenchymal Stem Cells Modifies the Host Response to Lipopolysaccharide in Humans: A Randomized, Single-Blind, Parallel Group, Placebo Controlled Trial. STEM CELLS - Volume 36, Issue 11, pp. 1778-1788 - published 2018-11-01	Outcomes are not of our interest.
16.	Karyana, Muhammad; Safety of DW-MSC infusion in patients with low clinical risk COVID-19 infection: a randomized, double-blind, placebo-controlled trial. STEM CELL RESEARCH & THERAPY - Volume 13, Issue 1, pp. - published 2022-04-01	COVID-19 without ARDS

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