Evidence-based Guidelines for the use of Stem Cell Therapy

Endocrinological Conditions

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DISCLAIMER

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

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MESSAGE

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

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

Dr. Rajiv Bahl
Secretary DHR & DG, ICMR

Dr. Sunita Sharma
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

CI	:	Confidence Interval
DoI	:	Declaration of Interest
DM	:	Diabetes Mellitus
EtD	:	Evidence to Decision
GBD	:	Global Burden of Disease
GDG	:	Guideline Development Group
GDT	:	Guideline Development Tool
GRADE	:	Grading of Recommendations Assessment, Development and Evaluation
HbA1C	:	Glycated Hemoglobin
MCID	:	Minimal Clinical Important Difference
MD	:	Mean Difference
NICE	:	National Institute for Health and Care Excellence
PICO	:	Patient/Population, Intervention, Comparator/Control, and Outcome(s)
QoL	:	Quality of Life
RCTs	:	Randomized Controlled Trials
RoB 2	:	Risk of Bias 2
RR	:	Relative Risk
SAEs	:	Severe Adverse Events
SMD	:	Standardized Mean Difference
SR/MA	:	Systematic Review/Meta-Analysis
T1DM	:	Type 1 Diabetes Mellitus
T2DM	:	Type 2 Diabetes Mellitus
UI	:	Uncertainty Interval
WHO	:	World Health Organization

EXECUTIVE SUMMARY

1. Background & Rationale:

Diabetes is a serious, chronic disease characterized by elevated blood glucose concentrations caused by either insulin deficiency or insulin resistance. Type 1 Diabetes Mellitus (T1DM) is a chronic autoimmune disease characterized by destruction of insulin-producing beta cells in the pancreas leading to insulin deficiency while Type 2 Diabetes Mellitus is a chronic metabolic disorder characterized by insulin resistance. As per the GBD estimates in 2021, there were 529 million (95% uncertainty interval [UI] 500–564) people living with diabetes worldwide, and the global age-standardized total diabetes prevalence was 6.1% (5.8–6.5).[1] Management of Type 1 diabetes mellitus involves an integrated approach consisting of insulin replacement therapy along with lifestyle modifications and nutritional support to prevent complications and maintain quality of life. Management of type 2 diabetes mellitus involves a combination of lifestyle changes and pharmacotherapy. Lately, stem cell therapy is being investigated as a therapeutic option in diabetes It is quintessential to take an evidence-based approach during the development of such regenerative therapies, with the best quality evidence being sought to determine the true effectiveness and efficacy of such approaches. The overall goal of these guidelines is to provide evidence-based recommendations for the use of stem cell therapy in Diabetes Mellitus.

2. Target audience:

The recommendations in this guideline are intended to inform the policy makers, patients and health care professionals especially endocrinologists practicing in secondary and tertiary care centers as well as researchers and scientists working in the field of regenerative medicine regarding the efficacy and safety of stem cell therapy in Diabetes Mellitus (Type 1 and Type 2).

3. Guideline Development Methods:

The guideline was developed using standard methodology as described by international agencies like the World Health Organization (WHO) and National Institute for Health and Care Excellence (NICE).[2,3] 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 commissioning systematic review & meta-analysis, (iii) Review of evidence profiles and grading the certainty of evidence (iv) Formulation of recommendations using the Evidence to Decision (EtD) framework (v) Drafting the guideline (vi) External review and (vii) Dissemination of guidelines. The GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach 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 Guideline Development Tool (GDT) software. This included assessment of the effects (balance between the 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 via

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 Diabetes Mellitus, 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 Diabetes Mellitus (both type 1 and type 2). 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 glucose control and quality of life in patients with diabetes mellitus. In patients with Type 1 Diabetes Mellitus, there was trivial improvement in insulin independence and quality of life. In patients with Type 2 Diabetes Mellitus, there was a small reduction in the insulin requirement in the stem cell group as compared to usual care. However, the reduction in HbA1C was statistically non-significant between the two groups. Hence, the committee decided to make the overall judgement of desirable effects as trivial. In both the groups, there is a small increase in undesirable effects with the use of stem cell therapy.

[#] 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).

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I. GUIDELINE DEVELOPMENT PROCESS

1. Introduction:

A new process has been established in the MoHFW where in 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 among stakeholders i.e. patients, clinicians, and the society in general. The generation of such evidence included collation of evidence from systematic review (SR) and meta-analysis (MA) of existing literature on well-defined review questions. Finally, the evidence obtained from SR & MA is graded for its certainty using the GRADE approach. This grading is done to assess the certainty of evidence and formulate recommendations using the EtD framework. Such rigorously developed evidence-based guidelines have the potential to address the research to policy gap by translating the best available evidence of any healthcare intervention into practice (Figure 1).

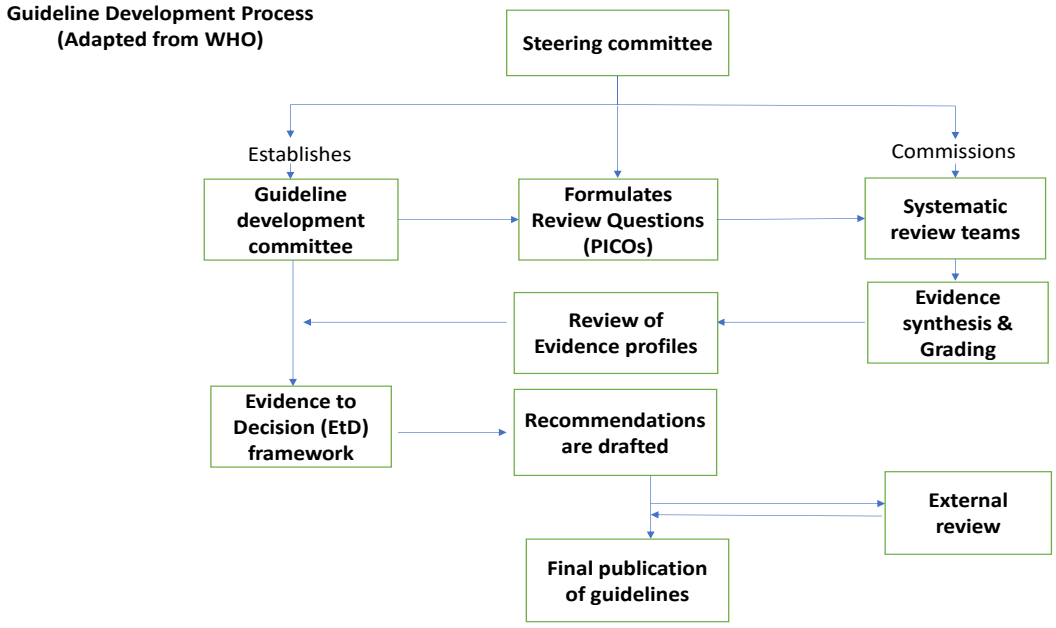

Figure 1: Guideline Development Process –adapted from WHO[1]

2. Rationale/Scope:

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

The disease condition included for review in the present guidelines is Type 1 & Type 2 diabetes mellitus. This was selected based on the directives from the MoHFW and a review of literature on the therapeutic use of stem cell therapy in endocrinological 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 endocrinologists practicing in secondary and tertiary care centers as well as researchers and scientists working in the field of regenerative medicine regarding the safety and efficacy of stem cell therapy in Diabetes Mellitus.

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 and was involved 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 for the guidelines for conducting systematic reviews for addressing the question, to decide on the critical outcomes and formulate the 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 the requisite technical skills and diverse perspectives needed for the formulation of the guidelines. These members were free from any conflict of interest in order to formulate unbiased recommendations. The subject experts, stem cell experts and methodologists provided critical inputs on the formulation of review questions in the PICO format. After completion of the systematic reviews, the evidence profiles were reviewed by the DHR secretariat and guideline methodologists with the help of subject experts. Finally, the GDG examined and interpreted the whole body of evidence and made judgments in the meetings using the EtD framework in the GRADEpro GDT tool.

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

All the potential GDG members had submitted the duly filled Declaration of Interests (DoIs) form that was adapted from the WHO.[1] 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 with a total of 28 conditions. In endocrinological disease condition, Type 1 diabetes mellitus & Type 2 diabetes mellitus were included for review.

Thereafter, the GDG held a meeting to decide on the key review questions for Diabetes Mellitus 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 the relevant prespecified 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 the experts in the respective fields 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 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 SR teams were instructed to design the literature searches on the following databases: PubMed, Embase, Web of Science, and Cochrane CENTRAL. **Only randomized controlled trials were included in the systematic review.** No grey literature was included. However, hand-searching of references of relevant review articles was 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 that include well characterized stem cells or stem cell-derived products were included.

In addition, few conditions precluded the trial from being included in the final body of evidence in the EtD framework.

- No evidence of randomization
- More than 30% of enrolled 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 avoided. All the 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) has to be minimized, as it

is easier to interpret the mean difference (MD) regarding 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 was 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):

It 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 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 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. The 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 the agreement by 75% or more of the GDG members. Consensus was reached for the recommendation in this guideline and there were no strong disagreements. The GDG also identified caveats in the existing evidence and highlighted prioritized the 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 outweigh 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, accuracy and completeness of the evidence (randomized controlled trials only), validity of the justification provided for each recommendation. 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 rectify any factual errors and the document was finalized, thereafter.

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II. RECOMMENDATIONS

1. DIABETES MELLITUS:

A. BACKGROUND:

Diabetes is a serious, chronic disease characterized by elevated blood glucose levels caused by either insulin deficiency or insulin resistance. Type 1 Diabetes Mellitus (T1DM) is a chronic autoimmune disease characterized by destruction of insulin-producing beta cells in the pancreas leading to insulin deficiency while Type 2 Diabetes Mellitus is a chronic metabolic disorder characterized by insulin resistance. The chronic hyperglycemic state due to diabetes leads to complications such as retinopathy, neuropathy and nephropathy, if adequate glycemic control is not maintained. As per the GBD estimates in 2021, there were 529 million (95% uncertainty interval [UI] 500–564) people living with diabetes worldwide, and the global age-standardized total diabetes prevalence was 6.1% (5.8–6.5)[1]. The standard of care for T1DM is frequent glucose monitoring and insulin replacement therapy through various insulin preparations. T2DM is predominantly treated with oral hypoglycemic drugs and may require insulin in later stages of the disease for optimum control. Diabetes management requires significant physical, mental and psychological effort from the patients and their families. Since diabetes is a chronic disease, there is an unmet need to search for curative therapeutic options to preserve or regenerate beta cells and maintain glucose homeostasis.

B. RECOMMENDATIONS:

Stem cell therapy is **not recommended** in routine clinical practice for the treatment of Diabetes Mellitus (type 1 and type 2).

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 glucose control and quality of life in patients with diabetes mellitus. In patients with Type 1

Diabetes Mellitus, there was trivial improvement in insulin independence and quality of life. In patients with Type 2 Diabetes Mellitus, there was a small reduction in the insulin requirement in the stem cell group as compared to usual care. However, the reduction in HbA1C was statistically non-significant between the two groups. Hence, the committee decided to make the overall judgement of desirable effects as trivial.
In both the groups, there is a small increase in undesirable effects with the use of stem cell therapy.
Results should be interpreted with caution, in view of various study limitations like high risk of bias, small number of participants and/or events in the included studies and different sources of stem cell use. In addition, the follow up period was too small to comment on the side effect profile and long-term safety.

C. SUMMARY OF EVIDENCE:

Key Question: In patients with Diabetes Mellitus (both type 1 and type 2), what is the efficacy and safety of stem cell therapy as compared to usual care?

Included Studies: Literature search was done using PubMed, Embase, Web of science and Cochrane database for peer-reviewed articles and there were no restrictions on the publication date. The electronic search of included databases yielded a total of 11,026 potential research articles, of which 1,778 duplicates were removed. After title and abstract screening, 135 articles were included for full text screening. Out of these, 20 RCTs were eligible for inclusion in the current review. [2-21]
The studies were published from 2005 to 2023 and were conducted in Argentina, Australia, China, Ireland, Italy, United Kingdom, Sweden, India, Iran, and the United States with sample sizes ranging from 15 to 91 patients. The studies included patients with T1DM (9 studies), T2DM (11 studies), one study included both type of diabetes and one study did not mention the type of diabetes. These patients had an average diabetes history ranging from recent onset to 19.6 years. The follow-up period ranged from 3 to 96 months. As per the design of these studies were considered, six were open label randomized controlled trials, six studies were single blinded, seven studies were double blinded and one study was triple blinded randomized controlled trial. Intervention reported in studies is as follows: 9 studies used mesenchymal stem cells, 5 studies used bone marrow mononuclear cells, 2 studies reported combination of mesenchymal stem cells and bone marrow mononuclear cells, 1 reported umbilical cord blood, 2 studies with each using hematopoietic stem cells and mesenchymal precursor cells, respectively. Eleven studies used saline as placebo in the control arm while other studies used usual diabetic care (4 studies), human serum albumin and DMSO (1 study), Cryostar CS10 fluid (1 study), prostaglandin E1 (1 study) and unspecified placebo/control in two studies.

Critical outcomes reviewed and their MCID:

S. No.	Outcome reviewed- Type 1 DM	What does it measure?	MCID decided by the GDG
1.	Insulin independence	Independence from external insulin administration	-

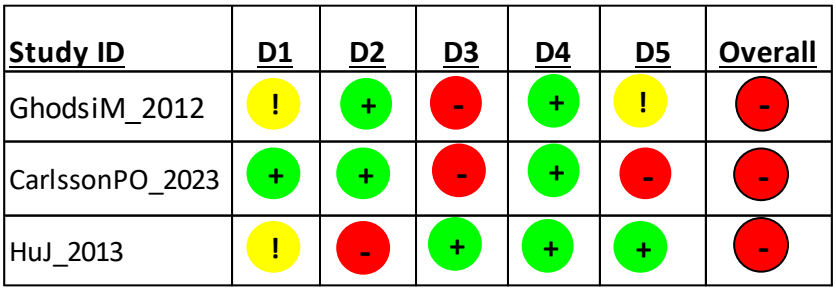
2.	Hypoglycemic episodes	Hypoglycemia was defined as each blood glucose recording below 70 mg/dl	-
3.	Quality of Life: SF-36 Range:0-100 Higher is better	Patient-reported questionnaire that measures health-related quality of life	An absolute change of 20 points
4.	SAEs	Serious Adverse Events	-

S. No.	**Outcome reviewed- Type 2 DM**	**What does it measure?**	**MCID decided by the GDG**
1.	HbA1C	Average blood glucose levels over 2-3 months with higher levels indicating poor glycemic control	An absolute change of 0.5%
2.	Insulin requirement	Dose of insulin required per day	A change of 8 IU/day (20% of control arm)
3.	SAEs	Serious Adverse Events	-

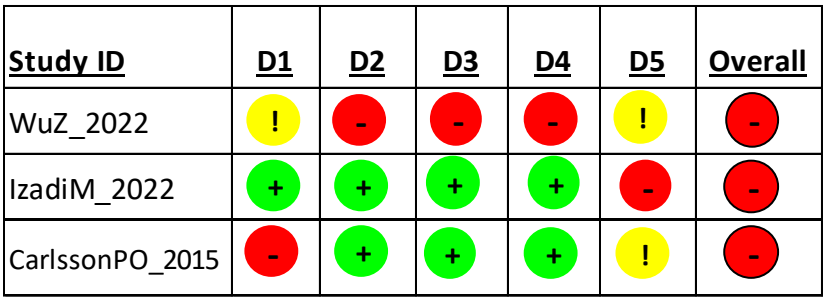
Risk of bias Assessment:

Type 1 Diabetes Mellitus:

1. Insulin independence:



2. Hypoglycemic episodes:



3. Serious adverse events:

Study ID	D1	D2	D3	D4	D5	Overall
CaiJ_2016	!	!	+	+	+	!
HallerMJ_2013	!	!	+	+	+	!
CarlssonPO_2023	+	+	-	+	+	-
HuJ_2013	!	-	+	+	+	-
CarlssonPO_2015	-	+	+	+	!	-
HuangP_2005	-	+	+	+	!	-
EsfahaniN_2015	!	+	-	-	!	-

Type 2 Diabetes Mellitus:

1. HbA1c (6 months):

Study ID	D1	D2	D3	D4	D5	Overall
GhodsiM_2012	!	+	-	+	!	-
EstradaEJ_2019	-	-	+	-	-	-
SoodV_2017	!	-	-	!	-	-
PericoN_2023	+	-	+	+	+	-
BhansaliS_2016	!	-	+	!	!	-
BhansaliA_2014	!	+	-	+	!	-
HuJ_2016	!	+	+	+	!	!
ZangL_2022	!	+	-	+	!	-

2. HbA1c (12 months):

Study ID	D1	D2	D3	D4	D5	Overall
GhodsiM_2012	!	+	-	+	!	-
ZangL_2022	!	+	-	+	!	-
EstradaEJ_2019	-	-	+	-	-	-
HuJ_2016	!	+	+	+	!	!
PericoN_2023	+	-	+	+	+	-
BhansaliS_2016	!	-	+	!	!	-
BhansaliA_2014	!	+	-	+	!	-

3. Insulin requirement (6 months):

Study ID	D1	D2	D3	D4	D5	Overall
EstradaEJ_2019	-	-	+	-	-	-
SoodV_2017	!	-	-	!	-	-
BhansaliA_2014	!	+	-	+	!	-
HuJ_2016	!	+	+	+	!	!
ZangL_2022	!	+	-	+	!	-
BhansaliS_2016	!	-	+	!	!	-

4. Insulin requirement (12 months):

Study ID	D1	D2	D3	D4	D5	Overall
EstradaEJ_2019	-	-	+	-	-	-
BhansaliS_2016	!	-	+	!	!	-
BhansaliA_2014	!	+	-	+	!	-
HuJ_2016	!	+	+	+	!	!
ZangL_2022	!	+	-	+	!	-

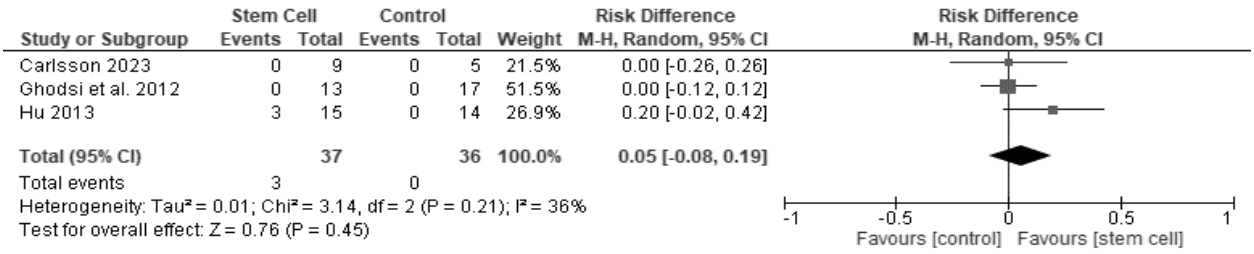
4. Serious adverse events:

Study ID	D1	D2	D3	D4	D5	Overall
PericoN_2023	+	-	+	+	+	-
HuangP_2005	-	+	+	+	!	-
BhansaliS_2016	!	-	+	!	!	-
SkylerJS_2015	+	!	+	+	!	!
PackhamDK_2016	!	+	+	+	+	!
EsfahaniN_2015	!	+	-	-	!	-

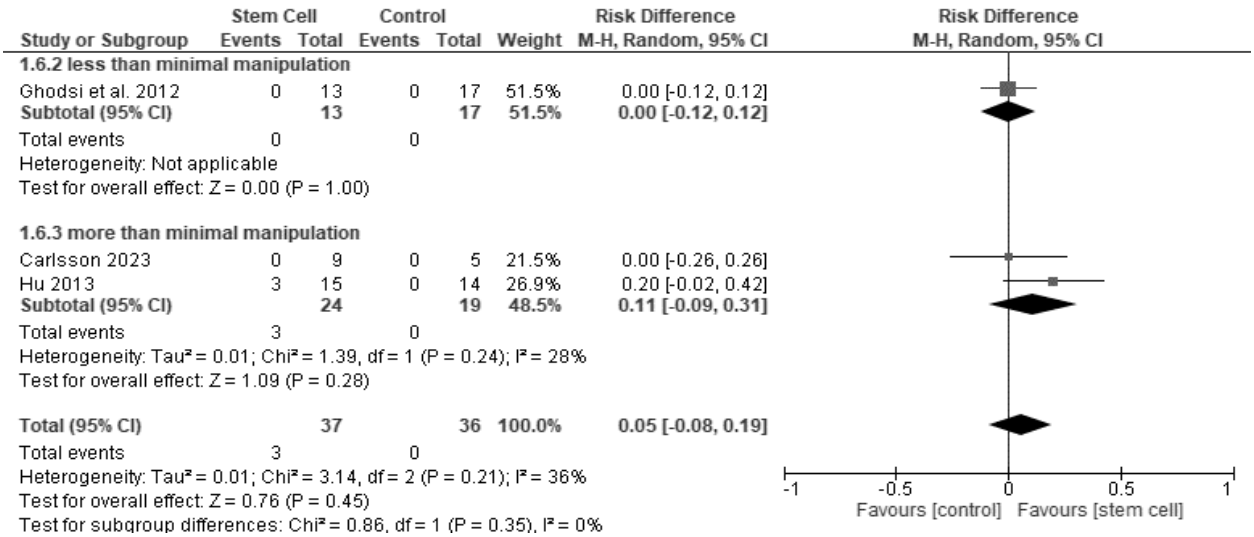
Type 1 DIABETES MELLITUS

Desirable Effects:

1. Insulin independence: Three trials with 73 participants reported insulin independence at the end of one year post transplantation. The evidence showed a 5% absolute increase [RD: 0.05 (-0.08 to 0.19)] in insulin independence. However, the risk difference was statistically non-significant.



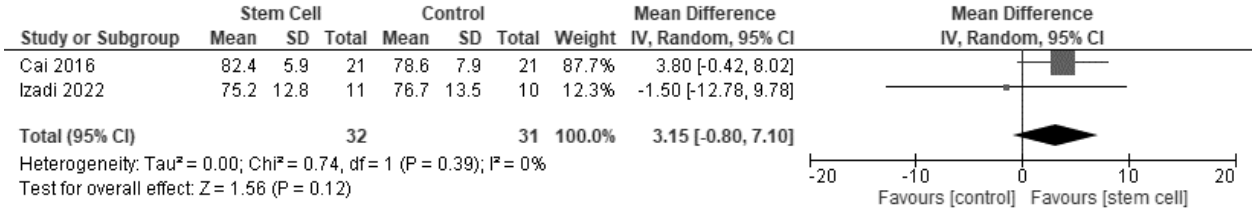
1.1 Insulin independence, **based on level of stem cell manipulation**:



2. Hypoglycemic episodes: Three studies with a total of 68 participants reported hypoglycemic episodes among type 1 Diabetes Mellitus patients. Out of these, data from two studies could be pooled for meta-analysis. The evidence suggested a 3% absolute increase [RD: 0.03, 95% CI (-0.14, 0.20)] in incidence of hypoglycemic episodes in stem cell arm as compared to usual care. However, the difference was statistically non-significant. Both the studies reporting hypoglycemic index used stem cells with more than minimal manipulation.

Izaddi et al. 2022[4] reported hypoglycemic rates as events per patient-year. There were 24 events per patient-year in stem cell arm as compared to 34 events per patient-year in usual care arm at the end of one year.

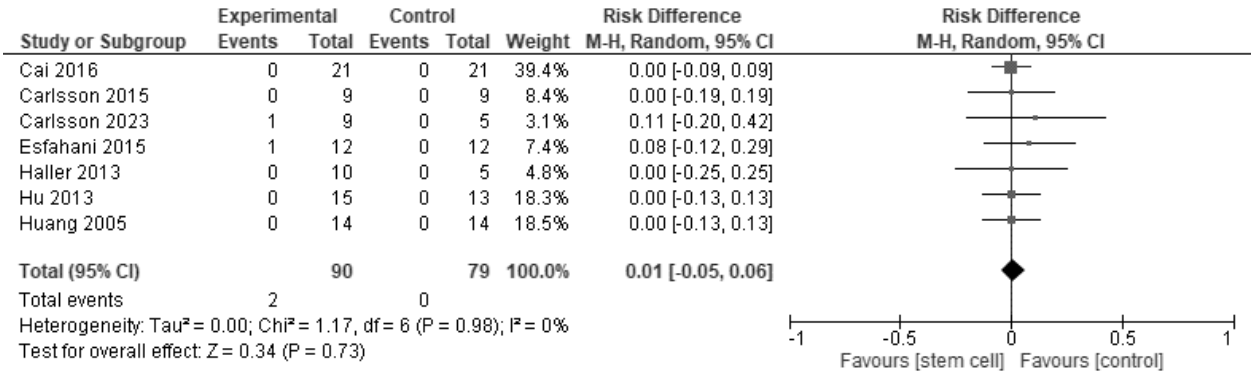
3. Quality of life: Evidence from 2 trials with a total of 63 participants reporting Quality of Life (QoL) at 12 months yielded a mean difference of 3.15 (95% CI: -0.80 to 7.10) between the stem cell arm and the usual care arm. The difference was statistically non-significant. Both the studies reporting quality of life used stem cells with more than minimal manipulation.



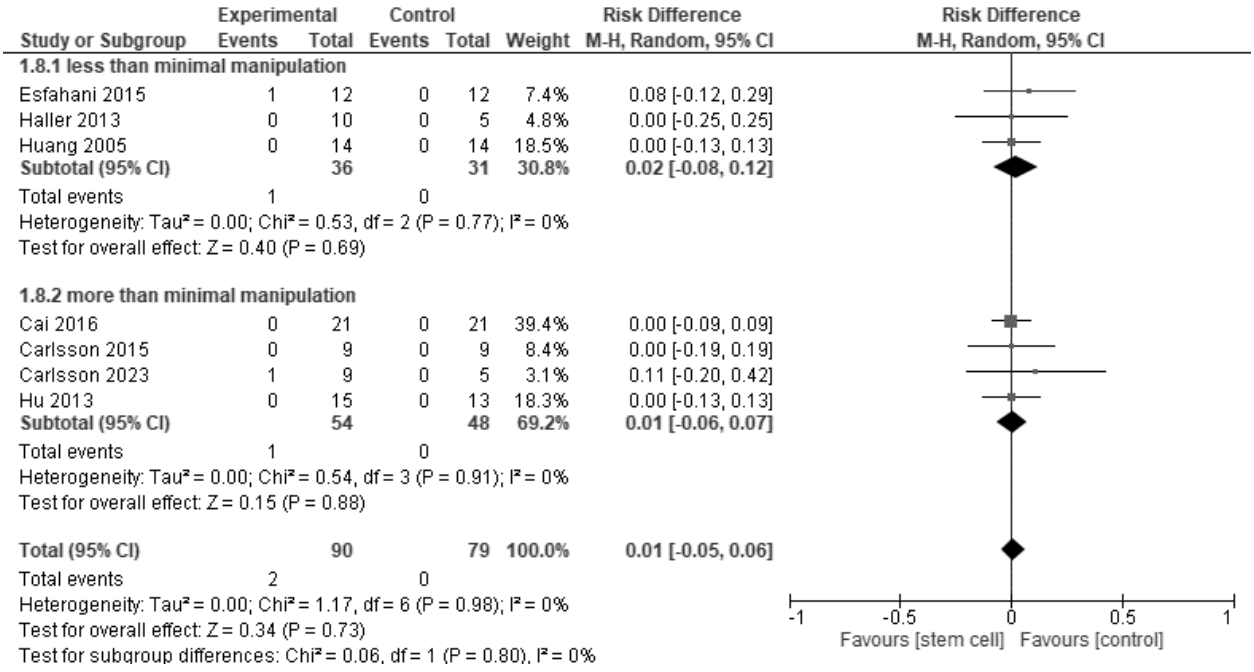
Undesirable effects:

4. Serious Adverse Events (SAEs): Seven studies with a total of 169 participants reported serious adverse events in a follow-up ranging between 3-36 months. The evidence suggested a 1% absolute increase in the incidence of SAEs [RD: 0.01, 95% CI (-0.05, to 0.06)] in the stem cell arm as compared to usual care. There is no statistically significant difference in SAE between the two groups.

The SAE reported by Carlsson et al. 2023[3] was unrelated to investigational product as participant became pregnant and was terminated from the trial. Nasli-Esfahani et al. 2015[14] reported a case of transitional meningioma causally related to stem cell transplantation.



4.1. Serious adverse events**, based on level of stem cell manipulation:**



Summary of findings:

Stem cell therapy compared to usual care for type 1 diabetes mellitus

Patient or population: Type 1 diabetes mellitus
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**				
Insulin independence	-	RD 0.05 higher (0.08 lower to 0.19 higher)	-	73 (3 RCTs)	⊕◯◯◯ Very low[a,b]	
Hypoglycemic episodes	-	RD 0.03 higher (0.14 lower to 0.20 higher)	-	47 (2 RCTs)	⊕◯◯◯ Very low[a,b]	
Quality of life (QoL) assessed w h: SF-36	The mean QoL in the usual care arm was 77.65 (range: 76.7 to 78.6)	MD 3.15 higher (0.8 lower to 7.1 higher)	-	63 (2 RCTs)	⊕◯◯◯ Very low[a,b]	
Serious Adverse Events	-	RD 0.01 higher (0.05 lower to 0.06 higher)	-	169 (7 RCTs)	⊕◯◯◯ Very low[a,b]	

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

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

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

Explanations
a. Downgraded two levels for risk of bias as more than 2/3 rd of studies (by wt.) were at high risk of bias.
b. Downgraded by one level for imprecision as CI crosses line of null effect.

Evidence profile:
Stem cell therapy compared to usual care for type 1 diabetes mellitus

Certainty assessment							Summary of findings				
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With [usual care]	With [Stem cell therapy]		Risk with [usual care]	Risk difference with [Stem cell therapy]
Insulin independence											
73 (3 RCTs)	Very serious[a]	Not Serious	Not serious	Serious[b]	None	⊕◯◯◯ Very low[a,b]	0/19	3/24	-	-	RD 0.05 higher (0.08 lower to 0.19 higher)
Hypoglycemic episodes											
47 (2 RCTs)	Very serious[a]	Not serious	Not serious	Serious[b]	None	⊕◯◯◯ Very low[a,b]	3/22	4/25	-	-	RD 0.03 higher (0.14 lower to 0.20 higher)
Quality of life (assessed with: SF-36)											
63 (2 RCTs)	Very serious[a]	Not Serious	Not serious	Serious[b]	None	⊕◯◯◯ Very low[a,b]	-	-	-	The mean QoL in the usual care arm was 77.65 (range: 76.7 to 78.6)	MD 3.15 higher (0.8 lower to 7.1 higher)
Serious Adverse Events											
169 (7 RCTs)	Very serious[a]	Not Serious	Not serious	Serious[b]	None	⊕◯◯◯ Very low[a,b]	0/79	2/90	-	-	RD 0.01 higher (0.05 lower to 0.06 higher)

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

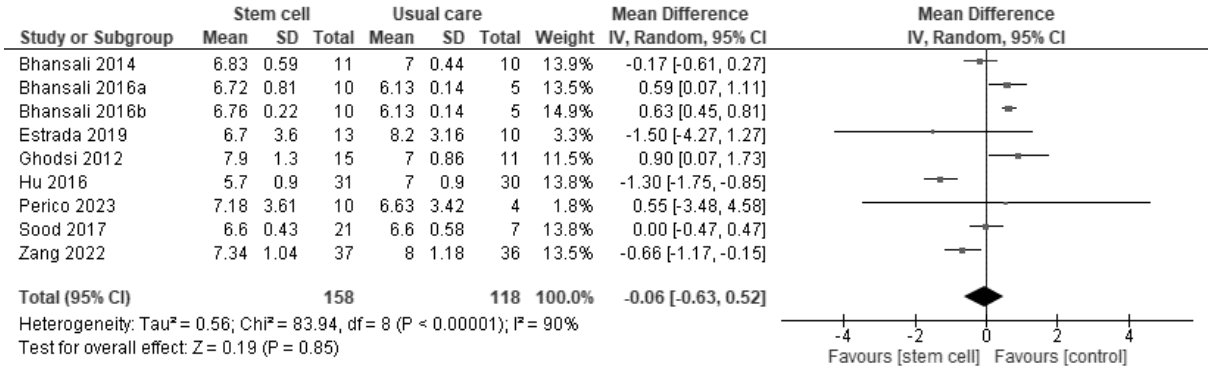
Explanations
a. Downgraded two levels for risk of bias as more than 2/3 rd of studies (by wt.) were at high risk of bias.
b. Downgraded by one level for imprecision as CI crosses line of null effect.

Type 2 DIABETES MELLITUS

Desirable Effects:

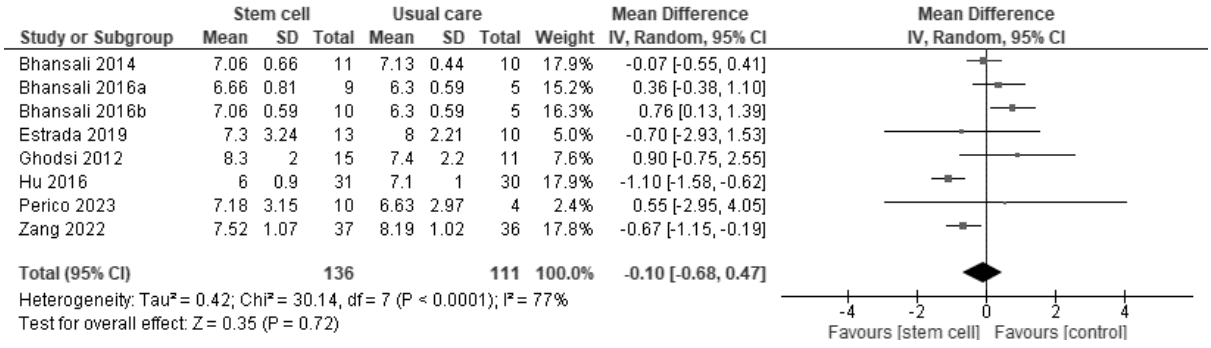
1. HbA1C: Evidence from 8 trials with a total of 276 participants reporting HbA1c percentage at 6 months yielded a mean difference of -0.06 (95% CI: -0.63 to 0.52) between the stem cell arm and the usual care arm. Seven trials with 247 participants showed a mean difference of -0.10 (95% CI: -0.68 to 0.47) at the end of 12 months. The differences at both the time points were statistically non-significant.

1.1 Forest plot of HbA1C percentage among type 2 DM at 6 months:



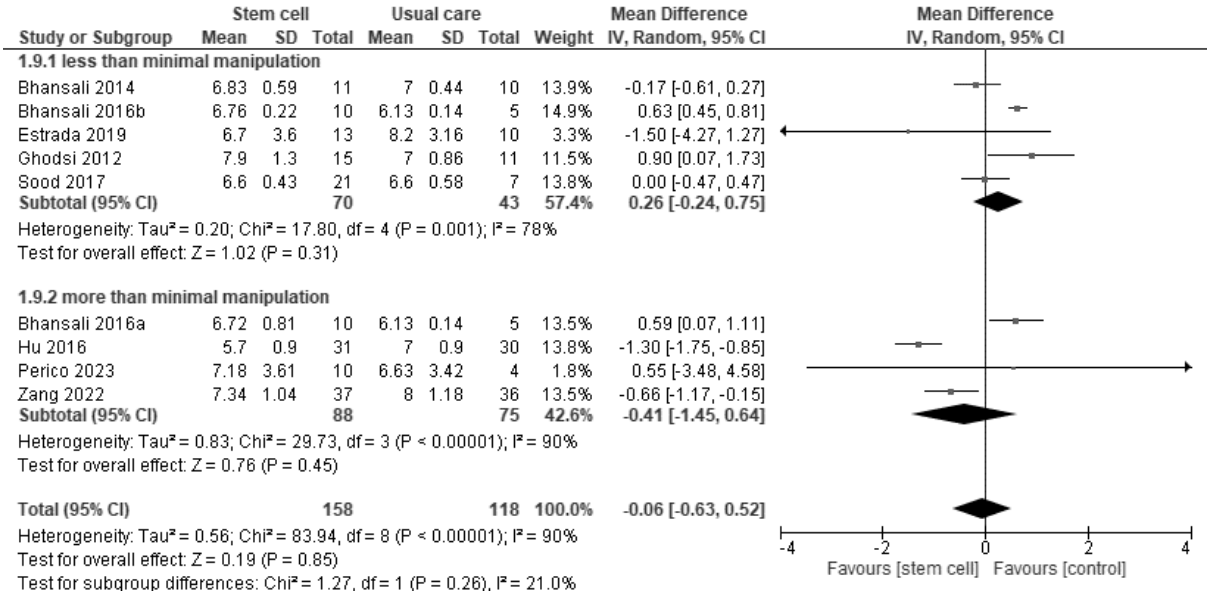
* BhansaliS_2016a – represents mesenchymal cells as intervention
BhansaliS_2016b – represents mononuclear cells as intervention

1.2. Forest plot of HbA1C percentage among type 2 DM at 12 months:

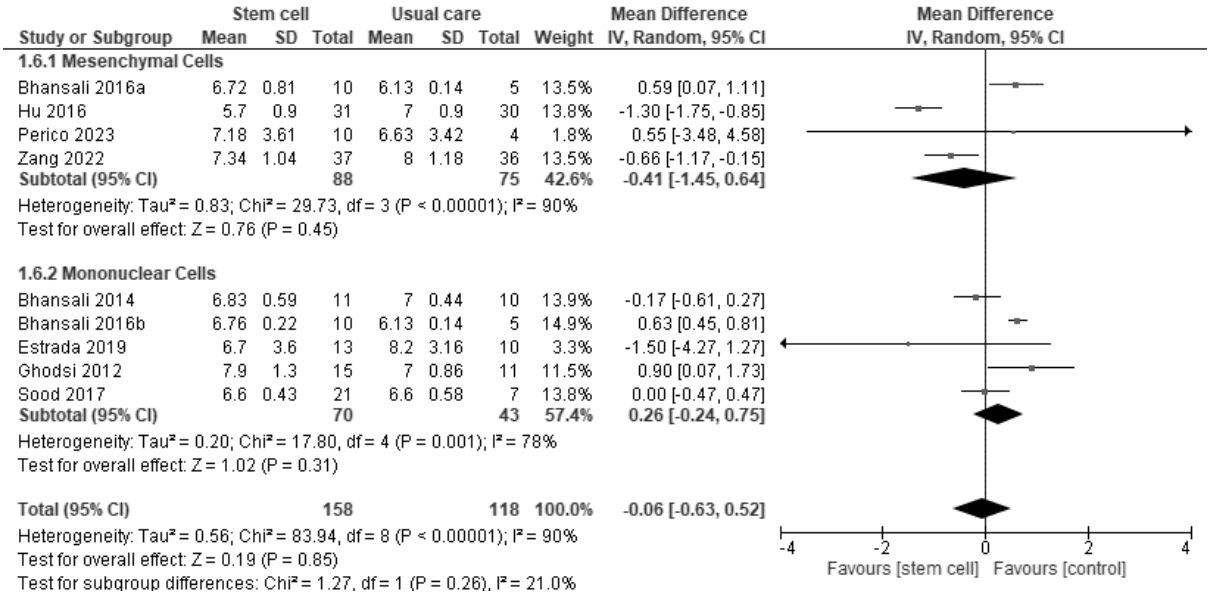


Subgroup analysis:

1.3. Forest plot of HbA1C percentage among type 2 DM at 6 months**, based on level of stem cell manipulation**:

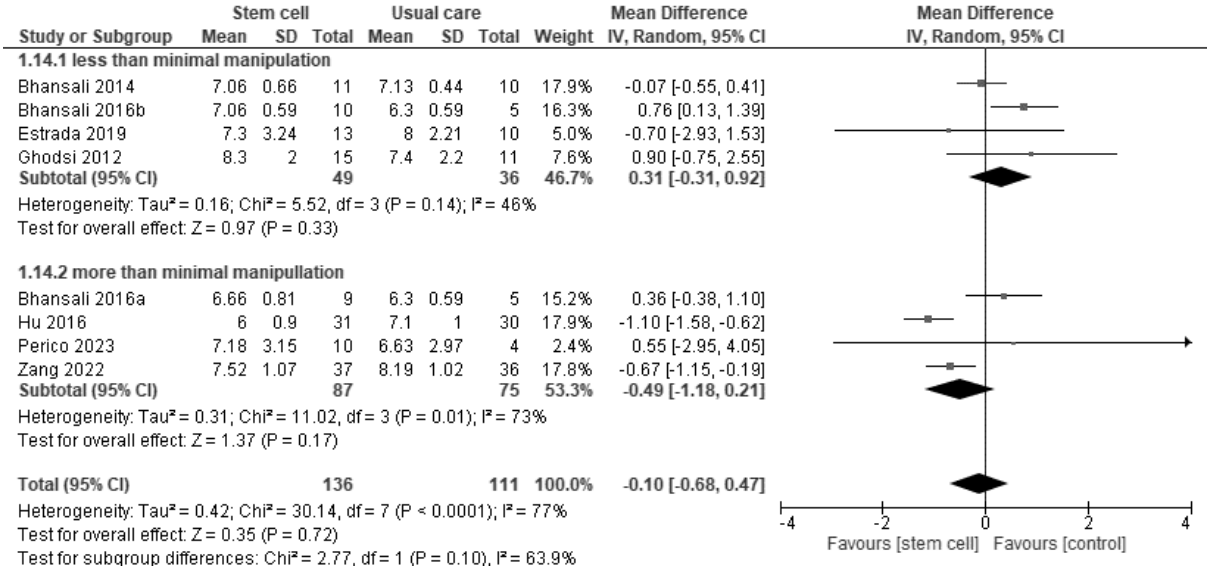


1.4. Forest plot of HbA1C percentage at 6 months based on cell type:

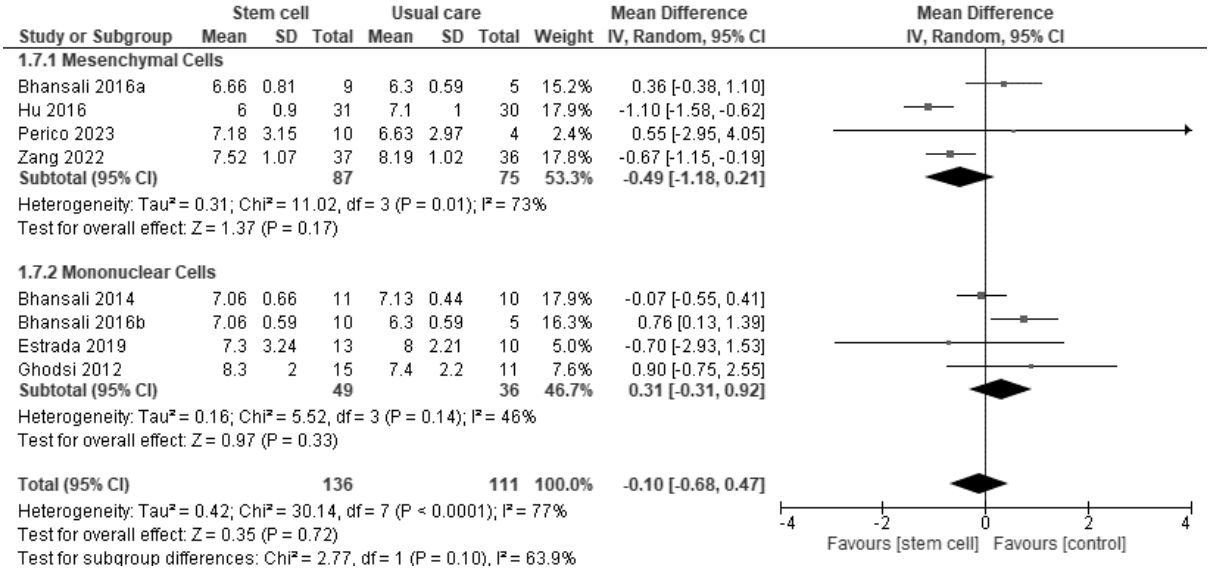


* BhansaliS_2016a – represents mesenchymal cells as intervention
BhansaliS_2016b – represents mononuclear cells as intervention

1.5. Forest plot of HbA1C percentage among type 2 DM at 12 months, **based on level of stem cell manipulation**:

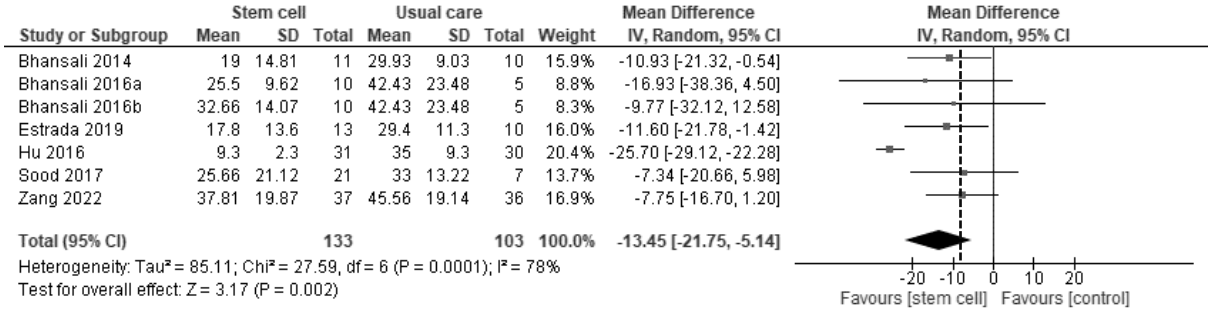


1.6. Forest plot of HbA1C percentage among type 2 DM at 12 months based on cell type:



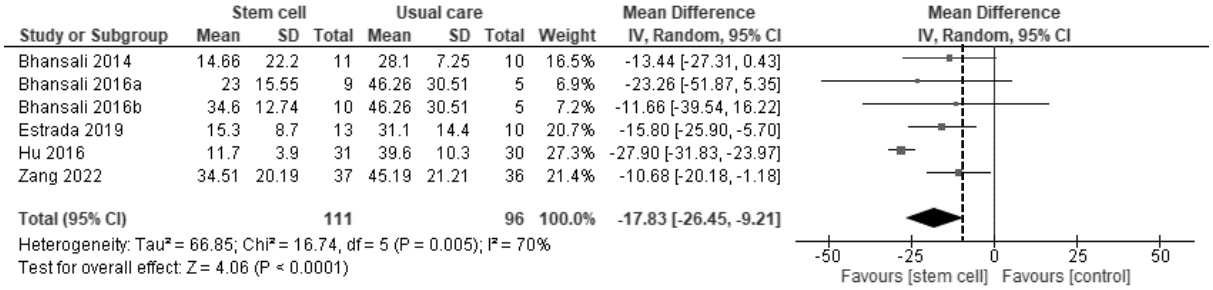
2. Insulin Requirement: Evidence from 6 trials with a total of 236 participants reporting the insulin requirement yielded a mean difference of -13.45 (95% CI: -21.75 to -5.14) IU/day at the end of six months between the stem cell arm and the usual care arm. Five trials with 207 participants showed a mean difference of -17.83 (95% CI: -26.45 to -9.21) IU/day at the end of twelve months. The differences at both the time points were statistically significant and more than MCID of 8 units, therefore, clinically important.

2.1. Forest plot of Insulin Requirement among type 2 DM at 6 months:



* BhansaliS_2016a – represents mesenchymal cells as intervention
BhansaliS_2016b – represents mononuclear cells as intervention

2.2. Forest plot of Insulin Requirement among type 2 DM at 12 months:

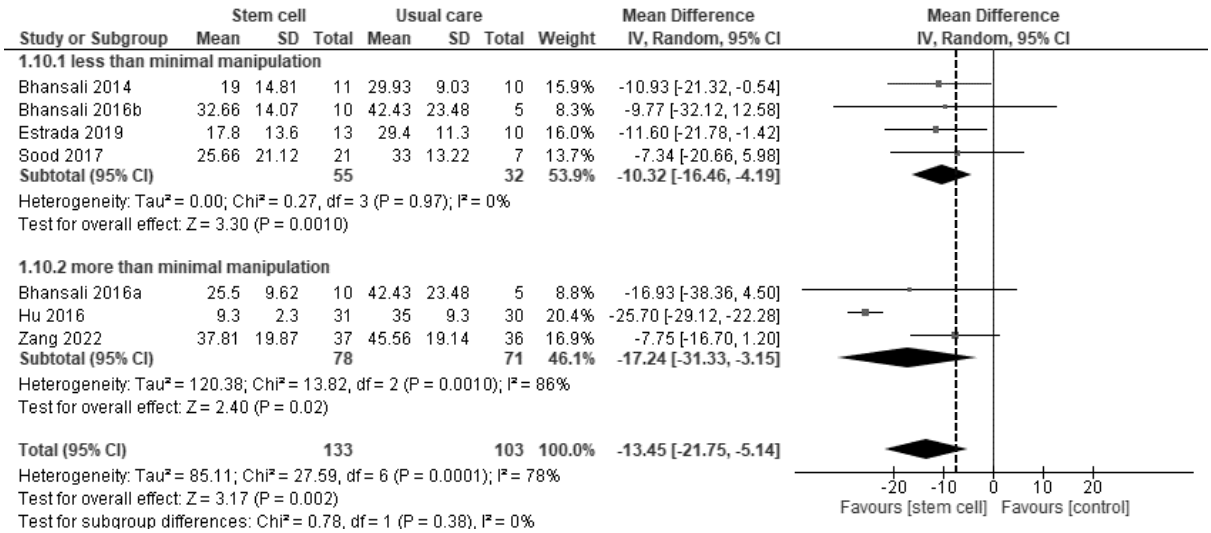


* BhansaliS_2016a – represents mesenchymal cells as intervention

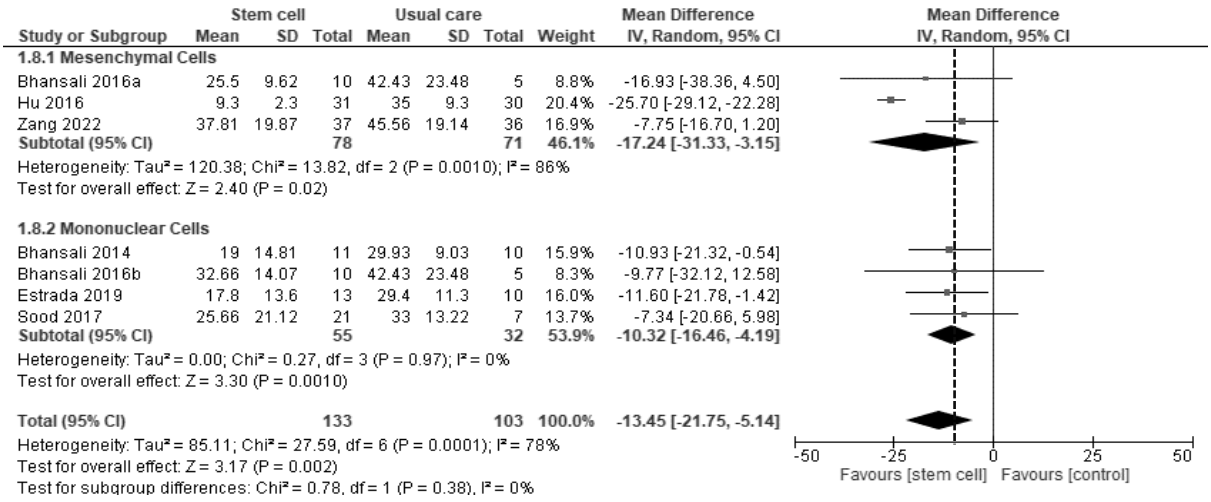
BhansaliS_2016b – represents mononuclear cells as intervention

<u>Subgroup analysis:</u>

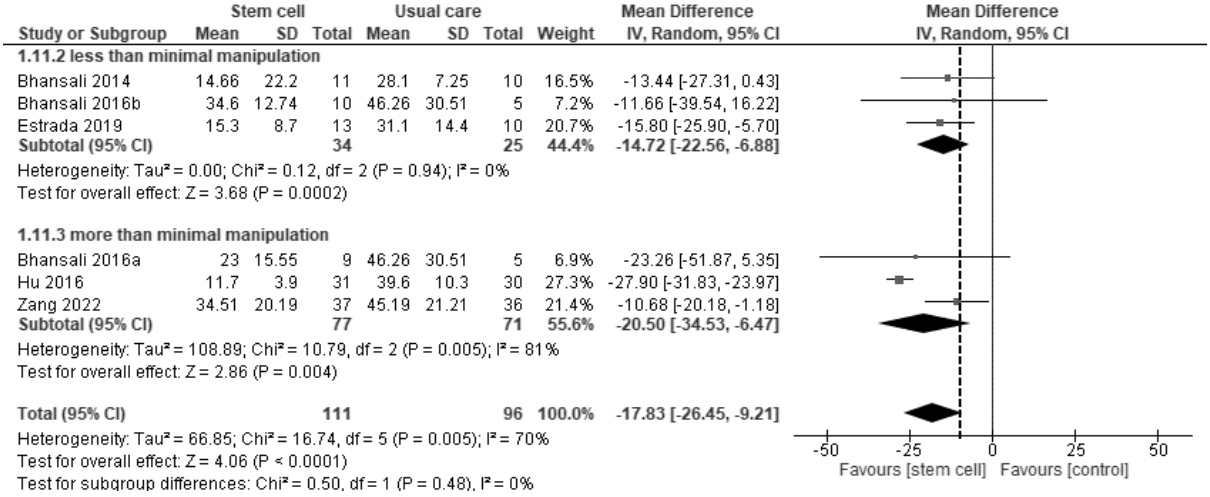
2.3. Forest plot of Insulin Requirement among type 2 DM at 6 months, **based on level of stem cell manipulation**:



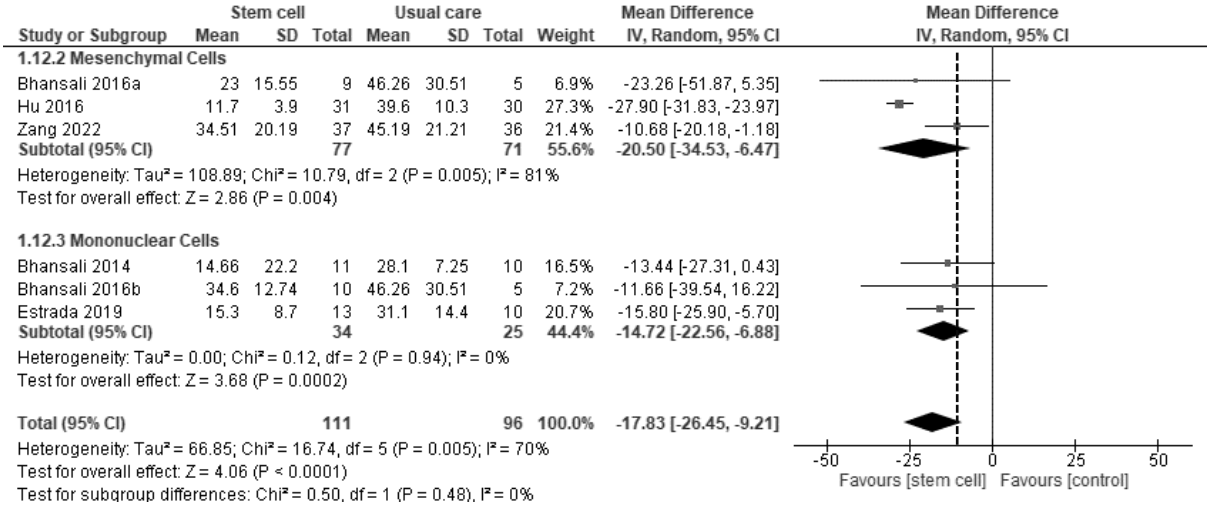
2.4. Forest plot of Insulin Requirement among type 2 DM at 6 months based on cell type:



2.5. Forest plot of Insulin Requirement among type 2 DM at 12 months, **based on level of stem cell manipulation:**



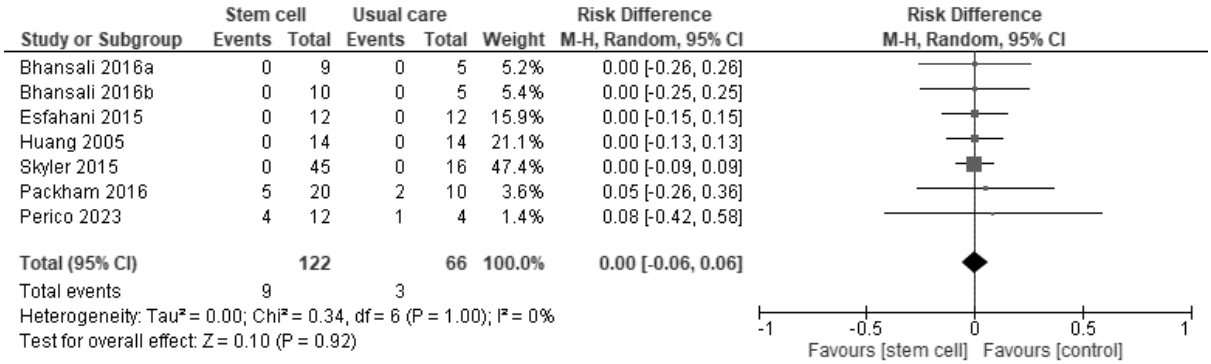
2.6. Forest plot of Insulin Requirement among type 2 DM at 12 months based on cell type:



Undesirable effects:

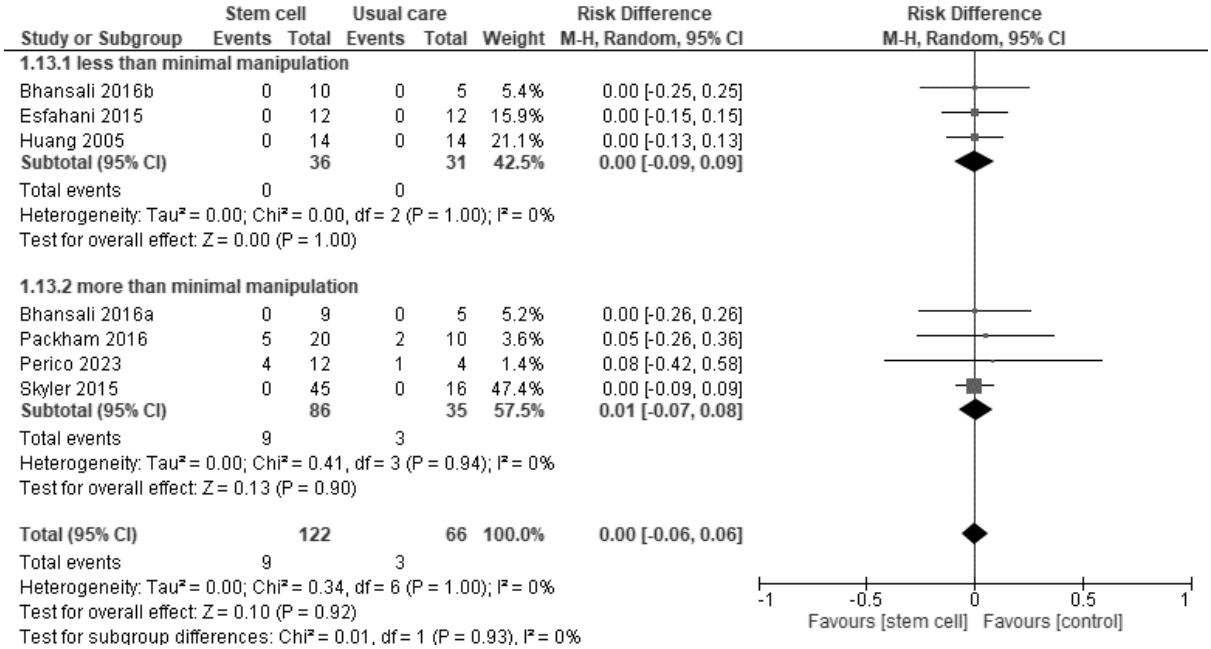
3. Serious adverse events: Six studies with 188 participants reported serious adverse events in a follow-up ranging between 3-36 months. There is no statistically significant difference in SAE [RD:0.00 95% CI (-0.06 to 0.06)] between the two groups.

Perico et al. 2023[2] and Packham et al. 2016[11] with 46 participants have reported SAEs. Study by Packham et al. reported adverse events such as acute myocardial infarction, anemia, asthma, congestive heart failure, syncope and upper gastrointestinal hemorrhage in usual care arm and atrial fibrillation, renal failure chronic, benign prostatic hyperplasia, gangrene and diverticulitis, in stem cell arm. Perico et al. 2023[2] reported bronchospasm in usual care arm while acute myocardial infarction, congestive heart failure, COVID-19 positive, anemia with increased dyspnea, left hip fracture, respiratory tract infection, complicated duodenal diverticulitis, respiratory failure, hyperkalemia, multiple myeloma and headache in stem cell arm.



* BhansaliS_2016a – represents mesenchymal cells as intervention
BhansaliS_2016b – represents mononuclear cells as intervention

3.1. Serious adverse events, **based on level of stem cell manipulation:**



Summary of findings:

Stem cell therapy compared to usual care for type 2 diabetes mellitus

Patient or population: Type 2 diabetes mellitus
Setting: Tertiary care
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**				
Insulin requirement in IU/day at 12 months	The mean insulin requirement in the usual care arm was 39.4 (range: 28.1 to 46.26 IU/day)	MD 17.83 IU/day lower (26.45 lower to 9.21 lower)	-	207 (5 RCTs)	⊕◯◯◯ Very low[a,b,c]	
HbA1C at 12 months	The mean HbA1C in the usual care arm was 7.13 % (range: 6.3% to 8.19 %	MD 0.10 % lower (0.68 lower to 0.47 higher)	-	247 (7 RCTs)	⊕◯◯◯ Very low[a,b,d]	
Serious adverse event (SAEs)	-	RD 0.00 (0.06 lower to 0.06 higher)	-	188 (6 RCTs)	⊕◯◯◯ Very low[a,d]	

***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; **RD:** Risk difference

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

Explanations
a. Downgraded two levels for risk of bias as more than 2/3 rd of studies (by wt.) were at high risk of bias.
b. Downgraded by one level for inconsistency as results are inconsistent across studies.
c. Downgraded by one level for imprecision as OIS not met.
d. Downgraded by one level for imprecision as CI crosses the line of null effect

Evidence profile:
Stem cell therapy compared to usual care for type 2 diabetes mellitus

Certainty assessment							Summary of findings				
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With [usual care]	With [Stem cell therapy]		Risk with [usual care]	Risk difference with [Stem cell therapy]
Insulin requirement in IU/day at 12 months											
207 (5 RCTs)	Very serious[a]	Serious[b]	Not serious	Serious[c]	None	⊕◯◯◯ Very low[a,b,c]	-	-	-	The mean insulin requirement in the usual care arm was 39.4 (range: 28.1 to 46.26 IU/day)	MD 17.83 IU/day lower (26.45 lower to 9.21 lower)
HbA1C at 12 months											
247 (7 RCTs)	Very serious[a]	Serious[b]	Not serious	Serious[d]	None	⊕◯◯◯ Very low[a,b,d]	-	-	-	The mean HbA1C in the usual care arm was 7.13 % (range: 6.3% to 8.19 %	MD 0.10 % lower (0.68 lower to 0.47 higher)
Serious Adverse Events (SAEs)											
188 (6 RCTs)	Very serious[a]	Not serious	Not serious	Serious[d]	None	⊕◯◯◯ Very low[a,d]	3/66	9/119	-	-	RD 0.00 (0.06 lower to 0.06 higher)

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

Explanations
a. Downgraded two levels for risk of bias as more than 2/3 rd of studies (by wt.) were at high risk of bias.
b. Downgraded by one level for inconsistency as results are inconsistent across studies.
c. Downgraded by one level for imprecision as OIS not met.
d. Downgraded by one level for imprecision as CI crosses the line of null effect.

D. SUMMARY OF JUDGEMENTS:

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

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

***** In patients with Type 1 Diabetes Mellitus, there was trivial improvement in insulin independence and quality of life. In patients with Type 2 Diabetes Mellitus, there was a small reduction in the insulin requirement in the stem cell group as compared to usual care. However, the reduction in HbA1C was statistically non-significant between the two groups. Hence, the committee decided to make the overall judgement of desirable effects as trivial.

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

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

E. CAVEATS IN EXISTING EVIDENCE:

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

1. Lack of sufficient number of RCTs with low risk of bias
2. Heterogeneity across trials in patient population and type of stem cell therapy, cell dosage, and route of administration
3. Lack of long term follow up of patients, thus providing insufficient evidence on the safety of this experimental therapy
4. 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 endocrinological conditions, priority areas for future research were identified and are as follows:

- Diabetes Mellitus

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

STEERING GROUP:

Dr. Rajiv Bahl, Secretary Department of Health Research (DHR) and DG, Indian Council of Medical Research (ICMR)- Chairman
Dr. Sunita Sharma, Director, Directorate General of Health Services (DGHS), New Delhi -Co-chairman
Dr. VG Somani, Joints Drug Controller, The Central Drugs Standard Control Organization (CDSCO), New Delhi
Dr. Annam Visala, Joint Drugs Controller, Central Drugs Standard Control Organization (CDSCO), New Delhi
Dr. Rajan Kapoor, Sr. Consultant, Army Hospital R&R, New Delhi
Dr. Kavita Gaur, Assistant Professor, Lady Hardinge Medical College (LHMC), New Delhi
Dr. Pramit Ghosh, Scientist-E, National Institute for Research in Bacterial Infections (NIRBI), Kolkata
Dr. Varsha Dalal, Scientist-E, DHR-ICMR, New Delhi
Dr. Siddharth Kapahtia, Scientist-D, DHR-ICMR, New Delhi
Dr. Hemlata, Scientist-D, Division of Basic Medical Sciences, ICMR Hqrs, New Delhi

GUIDELINE DEVELOPMENT GROUP:

Dr. Kameshwar Prasad, Fortis Flt Lt Rajan Dhall Hospital, Vasant Kunj, New Delhi-*Methodologist*
Dr. M. Jeeva Sankar, All India Institute of Medical Sciences (AIIMS), New Delhi-*Methodologist*
Dr. Rakesh Lodha, All India Institute of Medical Sciences, New Delhi-*Methodologis*t
Dr. Anil Gurtoo, Ex-Professor, Lady Hardinge Medical College (LHMC), New Delhi
Dr. Ranjan Das, National Centre for Disease Control (NCDC) Headquarters, Delhi
Dr. Shankar Prinja, Post Graduate Institute of Medical Education & Research, Chandigarh
Dr. Roli Mathur, Indian Council of Medical Research (ICMR) Headquarters, New Delhi
Dr. Vikram Gota, Advanced Centre for Treatment, Research and Education in Cancer (ACTREC), Mumbai
Dr. Rama Baru, Jawaharlal Nehru University, New Delhi
Dr. Priya Parmar, India Cancer Society, New Delhi
Ms. Manisha Bhattacharya, Mental Health Foundation, Kolkata

SUBJECT EXPERTS:

Stem cells:
Dr. Anurag Aggarwal, Trivedi School of Biosciences, Ashoka University, Sonipat, Haryana
Dr. Alok Srivastava, Christian Medical College, Vellore
Dr. Sujata Mohanty, All India Institute of Medical Sciences, New Delhi
Dr. Maneesha Inamdar, Institute for Stem Cell Science and Regenerative Medicine, Bengaluru
Dr. Anupam Kumar, Institute of Liver and Biliary Sciences, New Delhi
Dr. Naresh K, Sree Chitra Tirunal Institute for Medical Sciences and Technology (SCTIMST), Kerala

Endocrinology
Dr. V Mohan, Madras Diabetes Research Foundation, Chennai
Dr. Sujoy Ghosh, Institute of Post Graduate Medical Education & Research, Kolkata
Dr. Sanjay Bhadada, Post Graduate Institute of Medical Education & Research, Chandigarh
Dr. Nihal Thomas, Christian Medical College, Vellore
Dr. S.V Madhu, Universal College of Medical Sciences, New Delhi

SYSTEMATIC REVIEW TEAMS:

Diabetes Mellitus:

External team:

Dr. Jaivinder Yadav, Associate Professor, Pediatric Endocrinology Unit, Department of Pediatrics, PGIMER Chandigarh.
Dr. Jogender Kumar, Assistant Professor Neonatology Unit, Department of Pediatrics PGIMER Chandigarh.
Dr. Rakesh Kumar, Professor, Pediatric Endocrinology Unit, Department of Pediatrics PGIMER Chandigarh.
Dr. Bijaya Kumar Padhi, Department of Public Health PGIMER Chandigarh.
Dr. Jitendra Meena, Assistant Professor Department of Pediatrics, AIIMS New Delhi.
Dr. Lesa Dawman, Associate Professor, Pediatric Nephrology Unit, Department of Pediatrics PGIMER Chandigarh.
Dr. Lokesh Saini, Assistant Professor Department of Pediatrics, AIIMS Jodhpur.
Dr. Rimesh Pal, Assistant Professor Department of Endocrinology, PGIMER Chandigarh.

Internal team:

Dr. Manikandan Srinivasan, Assistant Professor, Epidemiology, JIPMER International School of Public Health, Puducherry
Dr. Roopa Hariprasad, Scientist F (Medical), Centre for Evidence for Guidelines, Department of Health Research, New Delhi
Dr. Bhavani Shankara Bagepally, Scientist E (Medical), ICMR-National Institute of Epidemiology, Chennai, Tamil Nadu

EXTERNAL REVIEW:

Dr. Belinda George, St John's Medical College Hospital, Bangalore, Karnataka
Dr. Jabbar Puthiyaveettil, Government Medical College, Thiruvananthapuram

ICMR-DHR SECRETARIAT:

Dr. Pramit Ghosh, Scientist-E, National Institute for Research in Bacterial Infections (NIRBI), Kolkata
Dr. Varsha Dalal, Scientist-E, DHR-ICMR, New Delhi
Dr. Siddharth Kapahtia, Scientist-D, DHR-ICMR, New Delhi
Dr. Hemlata, Scientist-D, Division of Basic Medical Sciences, ICMR Hqrs, New Delhi
Dr. Dimpi Vohra, Project Research Scientist-II, DHR
Dr.n Ritu Jain, Project Research Scientist-II, DHR

Annexure 3: DECLARATION OF INTEREST (DoI)

Name	Declaration of Interest (s)	Management of conflict (s) of interest
Dr. Sushama Nagarkar, Patient representative from Yash Charitable Trust	Declared that the outcome of the meeting or work may affect the interests of people with whom she has substantial personal/professional interests.	The steering group observed this as a potential conflict of interest and therefore decided against her inclusion in the GDG.
Dr. Kameshwar Prasad, Fortis Flt Lt RajanDhall Hospital, Vasant Kunj, New Delhi	None declared	Not applicable
Dr. M Jeeva Sankar, All India Institute of Medical Sciences (AIIMS), New Delhi	None declared	Not applicable
Dr. Rakesh Lodha, All India Institute of Medical Sciences, New Delhi	None declared	Not applicable
Dr. Anil Gurtoo, Ex-Professor, Lady Hardinge Medical College (LHMC), New Delhi	None declared	Not applicable
Dr. Ranjan Das, National Centre for Disease Control (NCDC) Headquarters, Delhi	None declared	Not applicable
Dr. Shankar Prinja, Post Graduate Institute of Medical Education & Research, Chandigarh	None declared	Not applicable
Dr. Roli Mathur, Indian Council of Medical Research (ICMR) Headquarters, New Delhi	None declared	Not applicable
Dr. Vikram Gota, Advanced Centre for Treatment, Research and Education in Cancer (ACTREC), Mumbai	None declared	Not applicable
Dr. Rama Baru, Jawaharlal Nehru University, New Delhi	None declared	Not applicable
Dr. Priya Parmar, India Cancer Society, New Delhi	None declared	Not applicable
Ms. Manisha Bhattacharya, Mental Health Foundation, Kolkata	None declared	Not applicable
Dr. Anurag Aggarwal, Trivedi School of Biosciences, Ashoka University, Sonipat, Haryana	None declared	Not applicable
Dr. Alok Srivastava, Christian Medical College, Vellore	None declared	Not applicable

Dr. Sujata Mohanty, All India Institute of Medical Sciences, New Delhi	She declared that she is a member of the Subject Expert Committees of CDSCO & NMC.	The Steering Group did not see it as a potential CoI.
Dr. Maneesha Inamdar, Institute for Stem Cell Science and Regenerative Medicine, Bengaluru	None declared	Not applicable
Dr. Anupam Kumar, Institute of Liver and Biliary Sciences, New Delhi	None declared	Not applicable
Dr. Naresh K, Sree Chitra Tirunal Institute for Medical Sciences and Technology (SCTIMST), Kerala	None declared	Not applicable
Dr. V Mohan, Madras Diabetes Research Foundation, Chennai	None declared	Not applicable
Dr. Sujoy Ghosh, Institute of Post Graduate Medical Education & Research, Kolkata	None declared	Not applicable
Dr. Sanjay Bhadada, Post Graduate Institute of Medical Education & Research, Chandigarh	None declared	Not applicable
Dr. Nihal Thomas, Christian Medical College, Vellore	None declared	Not applicable
Dr. S.V Madhu, Universal College of Medical Sciences, New Delhi	None declared	Not applicable
Dr.Belinda George, St John's Medical College Hospital, Bangalore, Karnataka	None declared	Not applicable
Dr. Jabbar Puthiyaveettil, Government Medical College, Thiruvananthapuram	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.

Our Team

Smt. Anu Nagar, Additional Secretary, DHR
Dr. Tushar Karmarkar, Deputy Secretary, DHR
Dr. Roopa Hariprasad, Scientist F
Dr. Chanchal Goyal, Scientist F
Dr. Vikas Dhikav, Scientist E
Dr. Varsha Dalal, Scientist E
Dr. Siddharth Kapahtia, Scientist D
Dr. Vikas Dhiman, Scientist D
Dr. Debjani Ram Purakayastha, Scientist D
Dr. Dimpi Vohra, Project Research Scientist-II
Dr. Ritu Jain, Project Research Scientist-II
Ms. Neeti Pandey, Project Research Scientist-II
Dr. Vikram Pal Gandhi, Project Research Scientist-II
Mr. Hitesh Tiwari, Project Research Scientist-II
Dr. Ruchi Baghel, Scientist C
Dr. Sabina Sultana, Young Professional
Mr. Ayush Raj Singh, Young Professional
Ms. Rozy Kumari, Young Professional
Ms. Ritu Panthri, Executive Assistant
Ms. Madhu Bala, Executive Assistant
Mr. Haris Chandra Sahoo, Executive Assistant
Mr. Lalit Kumar, Executive Assistant
Mr. Rohit Ratra, MTS
Mr. Gulshan Kumar, MTS
Mr. Mukul, MTS