National Institute for Health and Care Excellence

Diabetes in pregnancy: management from preconception to the postnatal period

[B] Technical appendices for managing type 1 diabetes using hybrid closed loop systems

NICE guideline NG3

Technical data underpinning evidence review [B]

June 2026

Draft

Contents

Appendix A - Review protocols

Review protocol for effectiveness review of managing type 1 diabetes using hybrid closed loop systems

Field	Content
Review title	Managing type 1 diabetes (T1D) using hybrid closed loop systems in people who are planning to become pregnant, are pregnant, or are in the postpartum period.
Review question	In people with type 1 diabetes, who are planning to become pregnant, are pregnant, or are in the postpartum period, what is the effectiveness and cost-effectiveness of hybrid closed loop systems to improve maternal and foetal/neonatal outcomes, compared to standard insulin therapy?
Objective	To determine the clinical and cost effectiveness of hybrid closed loop systems in improving maternal and foetal/neonatal outcomes in people with type 1 diabetes in the pre-conception, antenatal or postpartum period.
Searches	The following bibliographic databases will be searched: • Medline ALL (Ovid platform) • Embase (Ovid platform) • Cochrane Database of Systematic Reviews (Wiley platform) • Cochrane Central Register of Controlled Trials (CENTRAL, Wiley platform) • Epistemonikos (for systematic reviews-only) References to studies included in the previous NICE guideline NG3 and TA943 will be considered for inclusion in the updated review. Reference lists for any relevant systematic reviews identified will be checked for additional primary studies. The guideline committee or other stakeholders will be asked for details of any additional, relevant studies they may be aware of. The full search strategies for all databases will be published as an appendix to the final evidence review.

Condition or domain being studied	Managing type 1 diabetes (T1D) using hybrid closed loop systems.
Population	People with type 1 diabetes who are: • planning to become pregnant • pregnant • in the postpartum period (up to 6 months post childbirth)

Intervention/Exposure/Test	• Hybrid closed loop system
	
	Definitions:
	• Hybrid closed loop system (HCL): HCL systems use a mathematical algorithm to deliver insulin automatically in response to continuously monitored interstitial fluid glucose levels. They use a combination of real-time glucose monitoring from a continuous glucose monitor (CGM) device and a control algorithm to direct insulin delivery through continuous subcutaneous insulin infusion (CSII). Pregnancy-specific systems feature:
	  • a licence for use in pregnancy
	  • a glucose target of ≤5mmol/L
	  • evidence of a clinically relevant improvement in maternal glucose outcomes (>5% increased time in the pregnancy glucose target range of 3.5-7.8mmol/L compared to standard care with CGM and standard insulin delivery by multiple daily injections/pump).
	• Continuous subcutaneous insulin infusion: Also referred to as insulin pump therapy, CSII continuously delivers rapid-acting insulin via an infusion set inserted subcutaneously. The pump is battery operated, portable, and programmable.

Comparators	• Real time continuous glucose monitoring with multiple daily insulin injections • Intermittent capillary blood glucose monitoring with continuous subcutaneous insulin infusion • Continuous glucose monitoring with continuous subcutaneous insulin infusion (CSII)

	• Note: comparison group should be on the same insulin regimen as intervention group. (e.g., rapid acting, short acting, intermediate, long acting or mixed insulin). **Definitions:** • Real time continuous glucose monitoring: Consists of a subcutaneous sensor which measures the glucose levels in the interstitial fluid and sends data to a display device (a handheld monitor, smart phones or pump). The user can then analyse data and respond to changes in real-time or can make changes to insulin delivery, dose or timing based on retrospective data or trends. CGM models allow users to set alerts for high and low glucose levels, and rapid rate of change of glucose levels. • Intermittent capillary blood glucose monitoring: Conventional self-monitoring of blood glucose (SMBG) through 'finger prick' testing. Alternate sites may also be used for testing such as the palm, the upper forearm, the abdomen, the calf or the thigh.
Types of study to be included	Include published full-text papers: • Systematic reviews of RCTs • RCTs

Other exclusion criteria	• Exclude studies < 4 weeks duration
	• Studies with indirect, or mixed diabetes (type 1 diabetes and type 2 diabetes) populations will be excluded if:
	  • data has not been reported for the subgroup of type 1 diabetes patients OR,
	  • the population contains ≤70% of type 1 diabetes patients
	• Papers not published in the English language.
	• Preprints
	• Animal studies
	• Editorials, letters, news items and commentaries
	• Conference abstracts and posters
	• Registry entries for ongoing clinical trials or those that contain no results
	• Theses and dissertations
	• Date limits: pre 18/12/2019

Context	This review is part of an update of the NICE guideline on Diabetes in pregnancy: management from preconception to the postnatal period (NG3). https://www.nice.org.uk/guidance/ng3. This update covers hybrid closed loop systems in improving glycaemic control in people with type 1 diabetes, in the preconception, antenatal or postpartum period. This guideline will cover all settings where NHS healthcare is provided or commissioned.
Primary outcomes	**Maternal outcomes** 1. % time spent in the pregnancy-specific/postpartum* target glucose range: • Time spent within target glucose range • Time spent above target glucose range • Time spent below target glucose range • Overnight % time spent in range *Pregnancy specific target range: 3.5-7.8 mmol/L. Postpartum target range (same range as for pre-pregnancy): 3·9–10·0 mmol/L (Battelino T et al. Diabetes Care 2019;42:1593-1603). 2. Adverse events: • Hypoglycaemia (dichotomous or continuous outcome, depending how it is reported): ○ severe hypoglycaemia (defined as requiring third party assistance) ○ nocturnal hypoglycaemia • Diabetic ketoacidosis (DKA) 3. Quality of Life outcomes - measured using validated tools. For example: • Diabetes Distress Scale • Hypoglycaemia Fear Survey Questionnaire **Foetal/Neonatal outcomes** 4. Neonatal intensive care unit admissions longer than 24 hours 5. Adverse events: • Mortality:

	○ pregnancy loss (miscarriage, defined as <24weeks) ○ stillbirth, ≥24 weeks ○ neonatal loss, up to 28 days) • Neonatal hypoglycaemia • Preterm birth • Large/ small for gestational age (or however defined in the study, for example, using a customised measure based on gestational age and population norms; dichotomous data preferred).
Secondary outcomes	HCL device-related adverse events, including malfunctioning of device and user error.
Data extraction (selection and coding)	All references identified by the searches and from other sources will be uploaded into EPPI R5 and de-duplicated. Titles and abstracts of the retrieved citations will be screened to identify studies that potentially meet the inclusion criteria outlined in the review protocol. Dual sifting will be performed on at least 10% of records; 90% agreement is required. Disagreements will be resolved via discussion between the two reviewers, and consultation with senior staff if necessary. Full versions of the selected studies will be obtained for assessment. Studies that fail to meet the inclusion criteria once the full version has been checked will be excluded at this stage. Each study excluded after checking the full version will be listed, along with the reason for its exclusion. A standardised form will be used to extract data from studies. The following data will be extracted: study details (reference, country where study was carried out, type and dates), participant characteristics, inclusion and exclusion criteria, details of the interventions if relevant, setting and follow-up, relevant outcome data and source of funding. One reviewer will extract relevant data into a standardised form, and this will be quality assessed by a senior reviewer.
Risk of bias (quality) assessment	Quality assessment of individual studies will be performed using the following checklists: • ROBIS tool for systematic reviews

	• Cochrane RoB tool v.2 for RCTs The quality assessment will be performed by one reviewer and this will be quality assessed by a senior reviewer.
Strategy for data synthesis	**Intervention review:** Evidence will be stratified by type of hybrid closed loop system: • Standard • Pregnancy-specific Evidence will be stratified by the following stages: • Preconception • During pregnancy • Postnatal period Furthermore, outcomes in these categories will be grouped into the following time-points: • Pregnancy: • Pre 24 weeks' gestation • Post 24 weeks' gestation • Postnatal: • Day of delivery to 3 months postpartum • 4 to 6 months postpartum Depending on the availability of the evidence, the findings will be summarised narratively or quantitatively. Where possible, meta-analyses will be conducted using Cochrane Review Manager software. A fixed effect meta-analysis will be conducted and data will be presented as risk ratios or odds ratios for dichotomous outcomes, and mean differences or standardised mean differences for continuous outcomes. Heterogeneity in the effect estimates of the individual studies will be assessed using the I2 statistic. Alongside visual inspection of the point estimates and confidence intervals, the following criteria will be used to assess heterogeneity: no serious I2 = <40%; serious I2 = 40-60%; very serious I2 = >60%. Where I2 is 80% or above, the data will not be pooled. Heterogeneity will be explored as appropriate using sensitivity analyses and pre-specified subgroup analyses. If heterogeneity cannot be explained through

	subgroup analysis then a random effects model will be used for meta-analysis, or the data will not be pooled. Publication bias will be investigated using a funnel plot when there are 10 or more studies in an analysis. The confidence in the findings across all available evidence will be evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group: http://www.gradeworkinggroup.org/ Importance and imprecision of findings will be assessed against minimally important differences (MIDs). • Time in range (%): MID = 5% change in time in range	
Analysis of sub-groups	In case of between study heterogeneity evidence will be sub-grouped by: • Breastfeeding status: Any breastfeeding versus none. Where evidence is sub-grouped the committee will consider on a case by case basis if separate recommendations should be made for distinct groups. Separate recommendations may be made where there is evidence of a differential effect of interventions in distinct groups. If there is a lack of evidence in one group, the committee will consider, based on their experience, whether it is reasonable to extrapolate and assume the interventions will have similar effects in that group compared with others.	
Type and method of review	☒	Intervention
	☐	Diagnostic
	☐	Prognostic
	☐	Qualitative
	☐	Epidemiologic
	☐	Service Delivery
	☐	Other (please specify)
Language	English	
Country	England	

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<tr><td>Anticipated or actual start date</td><td colspan="3">2nd January 2026</td></tr>
<tr><td>Anticipated completion date</td><td colspan="3">26th August 2026</td></tr>
<tr><td rowspan="8">Stage of review at time of this submission</td><td>Review stage</td><td>Started</td><td>Completed</td></tr>
<tr><td>Preliminary searches</td><td>☐</td><td>☒</td></tr>
<tr><td>Piloting of the study selection process</td><td>☐</td><td>☒</td></tr>
<tr><td>Formal screening of search results against eligibility criteria</td><td>☐</td><td>☒</td></tr>
<tr><td>Data extraction</td><td>☐</td><td>☒</td></tr>
<tr><td>Risk of bias (quality) assessment</td><td>☐</td><td>☒</td></tr>
<tr><td>Data analysis</td><td>☐</td><td>☒</td></tr>
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5b Named contact e-mail
Diabetesinpregnancy@nice.org.uk

5e Organisational affiliation of the review
National Institute for Health and Care Excellence (NICE)</td></tr>
<tr><td>Review team members</td><td colspan="3">• Victoria Axe - Topic lead
• Rachel Woodcraft - Technical advisor
• Clare Wohlgemuth - Senior technical analyst
• Tayyaba Mumtaz - Technical analyst
• Paul Jacklin - Health economist
• Lina Gulhane - Information specialist
• Adam Okeefe - Project manager</td></tr>
<tr><td>Funding sources/sponsor</td><td colspan="3">This systematic review is being completed by NICE which receives funding from the Department of Health and Social Care.</td></tr>
<tr><td>Conflicts of interest</td><td colspan="3">All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each</td></tr>
</table>

	guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.	
Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: https://www.nice.org.uk/guidance/indevelopment/gid-ng10450	
Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.	
Keywords	Type 1 diabetes Preconception Pregnancy Postpartum Hybrid closed loop Automated insulin delivery Glycaemic control	
Details of existing review of same topic by same authors	None	
Current review status	☒	Ongoing
	☐	Completed but not published
	☐	Completed and published

	☐	Completed, published and being updated
	☐	Discontinued
Additional information	N/A	
Details of final publication	www.nice.org.uk	

Abbreviations: CGM: continuous glucose monitor; CSII: subcutaneous insulin infusion; Embase: Excerpta Medica dataBASE; DKA: diabetic ketoacidosis; EPPI: Evidence for Policy & Practice Information; GRADE: Grading of Recommendations Assessment, Development and Evaluation; HbA1c: Glycated Haemoglobin; HCL: hybrid closed loop system; Medline: Medical Literature Analysis and Retrieval System; MIDs: minimally important differences; NHS: National Health Service; NICE: National Institute for Health and Care Excellence; RCT: Randomized Controlled Trial; RoB: Risk of Bias; ROBIS: Risk of Bias in Systematic Reviews; SMBG: conventional self-monitoring of blood glucose.

Economic review protocol

ID	Field	Content
1.	Review title	In people with type 1 diabetes, who are planning to become pregnant, are pregnant, or are in the postpartum period, what is the effectiveness and cost-effectiveness of hybrid closed loop systems to improve maternal and foetal/neonatal outcomes, compared to standard insulin therapy?
2.	Objective	To identify economic studies on the cost-effectiveness of hybrid closed loop systems to improve maternal and foetal/neonatal outcomes compared to standard insulin therapy
3.	Inclusion criteria	People with type 1 diabetes who are: • planning to become pregnant • pregnant • in the postpartum period

		Intervention: hybrid closed loop system Comparator: Real time continuous glucose monitoring with multiple daily insulin injections Intermittent capillary blood glucose monitoring with continuous subcutaneous insulin infusion Continuous glucose monitoring with continuous subcutaneous insulin infusion (CSII) Relevant comparative economic study design: cost–utility analysis, cost–effectiveness analysis, cost–consequences analysis, comparative cost analysis Decision analytic model-based or within-trial economic analyses OECD countries Healthcare and personal social services cost perspective Studies published from 2019 – this cut off has been applied to restrict the review to more recent studies which will have more applicable resource use and costs. This is to reflect that the NG3 review on continuous glucose monitoring searched the period1946 to 17/12/19 High-quality studies in line with the NICE reference case (recent UK NHS/PSS cost-utility analyses using the QALY as the measure of outcome) are the most applicable to NICE decision making. Not all studies meeting the inclusion criteria will therefore necessarily be used in decision-making - see Review strategy below for details.

4.	Exclusion criteria	Conference posters or abstract only studies – these do not provide sufficient information for quality assessment. Studies published before 2019– this cut off has been applied to restrict the review to more recent studies which will have more applicable resource use and costs. This is to reflect that the NG3 review on continuous glucose monitoring searched 1946 to 17/12/19 Studies from non-OECD countries – these are considered unlikely to be applicable to the UK NHS setting due to substantial differences in healthcare delivery and unit costs. Non-comparative economic analyses including cost-of-illness studies. Letters, editorials or commentaries, study protocols or reviews of economic evaluations (recent reviews will be ordered and the bibliographies will be checked for relevant individual economic studies, which will then be ordered and checked for eligibility). Non-English language papers. Studies considering exclusively intervention costs, e.g. medicine acquisition costs, without considering wider healthcare costs associated with the management of type 1 diabetes. Studies comparing costs of branded vs generic forms of the same medicine. Studies only focussing on productivity losses or gains.

5.	Search approach	An economic study search will be undertaken using question-specific terms. The following bibliographic databases will be searched: • Medline ALL (Ovid platform) • Embase (Ovid platform) • INAHTA International HTA Database For search details see appendix B below.
6.	Review strategy	Studies meeting the inclusion and exclusion criteria will be assessed for applicability and methodological limitations using the NICE economic evaluation checklist in appendix H of Developing NICE guidelines: the manual. The NICE economic evaluation checklist assesses: Applicability to the NICE guideline decision making context with consideration of the NICE reference case relevant to the guideline. Recent UK studies that use the NICE reference case methods are the most applicable when considering cost effectiveness. Methodological limitations. The aim is to present the best available economic evidence to inform committee decision-making in the context of the guideline, the current UK NHS setting and NICE methods. Therefore, the health economist may not present all studies that meet inclusion criteria. Studies that are deemed not applicable or have very serious methodological limitations should not inform committee decision-making. If recent high quality, UK cost-utility analyses are available for a question, it is often not deemed informative to present studies that are less applicable or lower quality such as older UK analyses or analyses from other countries. A similar principle is deemed to apply more generally when

		considering applicability and methodological limitations. Some specific examples are given below: If multiple versions of a model are available for the UK and other countries it is usually reasonable to only present the UK version. If multiple versions of the same UK model are available, it is usually reasonable to present only the most recent. If there has been a NICE MTA or guideline model that informs current NHS practice it is usually reasonable not to present older studies, unless they address a different subpopulation or other specific issue. If a UK model that includes all interventions in the decision space is available it may be reasonable not to present studies that only include individual or fewer interventions, if the analysis is sufficiently applicable and of good methodological quality. Quality and relevance of effectiveness data used in the economic analysis: the more closely the clinical effectiveness data used in the economic analysis match with the outcomes of the studies included in the clinical review the more useful the analysis will be for decision-making in the guideline. Hierarchy of economic evaluation evidence based on quality assessment ‘Directly applicable’ and ‘Minor limitations’ (only recent UK CUAs can get this rating). Usually presented and used in decision-making.

		Directly or partially applicable combined with minor or potentially serious limitations (other than 1). Discretion over whether these are presented and used in decision-making, depending on the availability of more relevant evidence. 'Not applicable' or 'Very serious limitations'. Typically not presented and not used in decision-making. The health economist will make a decision based on the relative applicability and quality of the available evidence for each question, in discussion with the guideline committee if required. All decisions will be transparently reported in the evidence report. Studies that are presented to the committee and used in decision-making when formulating recommendations will be included in the summary tables and will have an evidence extraction. Other studies may not be presented to the committee in detail but will be listed, with the reason for not being presented to the committee and thus not used in decision-making being provided. Committee members can review and query the decision not to present studies with the health economist and will be provided with full details of these studies where requested.

Appendix B - Literature search strategies

Background and development

Search design and peer review

A NICE Senior Information Specialist (SIS) conducted the literature searches. The MEDLINE strategies below were quality assured (QA) by another NICE

SIS. All translated search strategies were peer reviewed to ensure their accuracy. Both procedures were adapted from the Peer Review of Electronic Search Strategies Guideline Statement (for further details see: McGowan J et al. PRESS 2015 Guideline Statement. *Journal of Clinical Epidemiology*, 75, 40-46).

The principal search strategies were developed in MEDLINE (Ovid interface) and adapted, as appropriate, for use in the other sources listed in the protocol, taking into account their size, search functionality and subject coverage.

This search report is based on the requirements of the PRISMA Statement for Reporting Literature Searches in Systematic Reviews (for further details see: Rethlefsen M et al. PRISMA-S. *Systematic Reviews*, 10(1), 39).

Review management

The search results were managed in EPPI-Reviewer v5. Duplicates were removed in EPPI-R5 using a two-step process. First, automated deduplication is performed using a high-value algorithm. Second, manual deduplication is used to assess "low-probability" matches. All decisions made for the review can be accessed via the deduplication history.

Prior work

Elements from two sources were consulted to select terms and construct the strategy:

Diabetes in pregnancy: Management of diabetes and its complications

Asgharzadeh A., Patel M., Connok M., Dmery S., Ghosh I., Court R., Jordan M, Momanyi K, Freeman K., Brown A., Baldwin S., Ogunlayi F., Stinton C., Cummins E., Al-Khudairy L. Hybrid closed loop systems for managing blood glucose levels in type 1 diabetes. 2022.

Search limits and other restrictions

Formats

Limits were applied in adherence to standard NICE practice (as set out in the Identifying the evidence chapter of the manual) and the eligibility criteria listed in the review protocol to exclude:

- Animal studies
- Editorials, letters, news items and commentaries
- Conference abstracts and posters
- Registry entries for ongoing clinical trials or those that contain no results
- Theses and dissertations
- Papers not published in the English language.

The limit to remove animal studies in the searches was the standard NICE practice, which has been adapted from:

Dickersin K, Scherer R & Lefebvre C. (1994) Systematic reviews: identifying relevant studies for systematic reviews. *BMJ*, 309 (6964), 1286.

Date limits

A date limit of 1 January 2019 to 22 December 2025 was applied, as stated in the review protocol.

Search filters and classifiers

Applying was the standard NICE practice the following filter and limits were applied:

- The limit to remove animal studies, which has been adapted from:

  Dickersin, K., Scherer, R., & Lefebvre, C. (1994). Systematic Reviews: Identifying relevant studies for systematic reviews. *BMJ*, 309(6964), 1286.

- English language limits were applied in adherence to the review protocol.

Cost effectiveness searches

In line with the review protocol, the sensitive version of the validated NICE cost utility filter was used in the MEDLINE and Embase strategies without amendment.

> Hubbard W et al. (2022) Development and validation of paired MEDLINE and Embase search filters for cost-utility studies. *BMC Medical Research Methodology*, 22(1), 310.

The following search filters were applied to the search strategies in MEDLINE and Embase to identify cost-effectiveness studies:

> Glanville J et al. (2009) Development and Testing of Search Filters to Identify Economic Evaluations in MEDLINE and EMBASE. Alberta: Canadian Agency for Drugs and Technologies in Health (CADTH)

Note: Several modifications have been made to these filters over the years that are standard NICE practice.

Key decisions

Searches were adapted to suit different database functionality.

Clinical searches

Database results

Database	Date searched	Database Platform	Database segment or version	No. of results downloaded
MEDLINE ALL	22/12/2025	Ovid	1946 to December 19, 2025	611
Embase	22/12/2025	Ovid	1974 to 2025 December 18	847
Cochrane Central Register of Controlled Trials (CENTRAL)	22/12/2025	Wiley	Issue 11 of 12, November 2025	81
Cochrane Database of Systematic Reviews (CDSR)	22/12/2025	Wiley	Issue 12 of 12, December 2025	1
Epistemonikos	22/12/2025	Epistemonikos	22/12/2026	359

Search strategy history

Database name: Medline

Searches		
1	Diabetes mellitus, type 1/	92430
2	((diabet* or DM) adj3 ("type 1" or type1 or "type I" or typei or "type one")).ti,ab.	74628
3	(T1D or T1DM or T1 DM or DM1 or DM 1 or DMT1 or DM T1 or IDDM).ti,ab.	34062
4	or/1-3	123104
5	Pregnancy/	1056465
6	Pregnant People/	17286
7	pregnan*.ti,ab.	663479
8	pre?pregnan*.ti,ab.	4959
9	Family Planning Services/	27366
10	(family adj plan*).ti,ab.	26525
11	((plan* or try*) adj3 (conceiv* or conception* or child*)).ti,ab.	6194
12	Preconception Care/	2993

Searches	
13	pre?conception.ti,ab. 6773
14	(pre adj conception).ti,ab. 991
15	peri?conception*.ti,ab. 2443
16	(peri adj conception*).ti,ab. 226
17	Prenatal care/ 35316
18	(pre?natal* or ante?natal*).ti,ab. 180024
19	(pre adj natal*).ti,ab. 1598
20	(ante adj natal*).ti,ab. 697
21	Perinatal care/ 5870
22	peri?natal.ti,ab. 97463
23	(peri adj natal).ti,ab. 220
24	Peripartum Period/ 2085
25	peri?partum.ti,ab. 7506
26	(peri adj partum).ti,ab. 268
27	puerperium.ti,ab. 6846
28	Postpartum Period/ 34702
29	post?natal*.ti,ab. 137758
30	(post adj natal*).ti,ab. 9360
31	post?partum*.ti,ab. 81594
32	(post adj partum*).ti,ab. 14525
33	or/5-32 1427255
34	4 and 33 6284
35	Pregnancy in Diabetics/ 11351
36	34 or 35 14845
37	Insulin Infusion Systems/ 7225
38	(insulin adj (pump* or deliver* or dose* or dosing or infusi*)).ti,ab. 19103
39	Pancreas, Artificial/ 1094
40	((artificial or bionic) adj2 pancreas).ti,ab. 1751
41	(artificial adj2 beta cell*).ti,ab. 156
42	(glucose adj (monitor* or control*)).ti,ab. 25795
43	(glyc?emic adj control*).ti,ab. 48327
44	(CGM or CGMs or CBGM or "Flash GM" or FGM or FGMs or iCGM or iCGMs or rtCGM or rtCGMS).ti,ab. 8608
45	closed loop*.ti,ab. 18069
46	(HCL or AHCL).ti,ab. 41401
47	(Ominipod* or "Dana i" or "Medtronic 780g" or Tslim or YpsoPump).ti,ab. 110
48	or/37-47 142556
49	36 and 48 2096
50	animals/ 7802864

Searches	
51	exp Animals, Laboratory/ 1020003
52	exp Animal Experimentation/ 10813
53	exp Models, Animal/ 701159
54	exp Rodentia/ 3774771
55	(rat or rats or mouse or mice or rodent*).ti. 1549409
56	or/50-55 7940587
57	56 not humans/ 5502549
58	49 not 57 2069
59	letter/ 1320514
60	editorial/ 744142
61	news/ 233437
62	exp historical article/ 418217
63	Anecdotes as Topic/ 4748
64	comment/ 1059233
65	(letter or comment*).ti. 223789
66	or/59-65 3067296
67	randomized controlled trial/ or random*.ti,ab. 1837925
68	66 not 67 3038881
69	58 not 68 1993
70	limit 69 to english language 1837
71	limit 70 to yr="2019 -Current" 611

1 **Database name: EMBASE**

Searches	
1	insulin dependent diabetes mellitus/ 169243
2	((diabet* or DM) adj3 ("type 1" or type1 or "type I" or typei or "type one")).ti,ab. 123797
3	(T1D or T1DM or T1 DM or DM1 or DM 1 or DMT1 or DM T1 or IDDM).ti,ab. 62091
4	or/1-3 204476
5	pregnancy/ 773735
6	pregnant person/ 776
7	pregnan*.ti,ab. 891357
8	pre?pregnan*.ti,ab. 6536
9	family planning/ 42206
10	(family adj plan*).ti,ab. 25559
11	((plan* or try*) adj3 (conceiv* or conception or child*)).ti,ab. 9124
12	prepregnancy care/ 3940
13	pre?conception.ti,ab. 9933

Searches		
14	(pre adj conception).ti,ab.	1928
15	peri?conception*.ti,ab.	3227
16	(peri adj conception*).ti,ab.	350
17	prenatal care/	60943
18	(pre?natal* or ante?natal*).ti,ab.	242077
19	(pre adj natal*).ti,ab.	2115
20	(ante adj natal*).ti,ab.	1057
21	perinatal care/	17770
22	peri?natal.ti,ab.	134776
23	(peri adj natal).ti,ab.	441
24	perinatal period/	47794
25	peri?partum.ti,ab.	11628
26	(peri adj partum).ti,ab.	620
27	puerperium.ti,ab.	7271
28	puerperium/	58627
29	post?natal*.ti,ab.	177865
30	(post adj natal*).ti,ab.	14773
31	post?partum*.ti,ab.	111103
32	(post adj partum*).ti,ab.	22534
33	or/5-32	1540313
34	4 and 33	10351
35	*maternal diabetes mellitus/	2920
36	pregnancy in diabetics/	132
37	34 or 35 or 36	12824
38	insulin infusion/	11261
39	insulin pump/	13848
40	insulin delivery device/	1175
41	(insulin adj (pump* or deliver* or dose* or dosing or infusi*)).ti,ab.	36133
42	artificial pancreas/	3260
43	((artificial or bionic) adj2 pancreas).ti,ab.	3133
44	(artificial adj2 beta cell*).ti,ab.	203
45	(glucose adj (monitor* or control*)).ti,ab.	46584
46	(glyc?emic adj control*).ti,ab.	84051
47	(CGM or CGMs or CBGM or "Flash GM" or FGM or FGMs or iCGM or iCGMs or rtCGM or rtCGMS).ti,ab.	18425
48	closed loop*.ti,ab.	24277
49	(HCL or AHCL).ti,ab.	53252
50	(Ominipod* or "Dana i" or "Medtronic 780g" or Tslim or YpsoPump).ti,ab.	364
51	or/38-50	223055

Searches		
52	37 and 51	3350
53	animal/	1744160
54	nonhuman/	8435642
55	exp Animal Experiment/	3479475
56	exp Experimental Animal/	927279
57	animal model/	2006193
58	exp Rodent/	4439367
59	(rat or rats or mouse or mice or rodent*).ti.	1747926
60	or/53-59	11076182
61	60 not human/	7797263
62	52 not 61	3317
63	letter.pt. or letter/	1412993
64	note.pt.	1030836
65	editorial.pt.	856374
66	(letter or comment*).ti.	268329
67	or/63-66	3364663
68	randomized controlled trial/ or random*.ti,ab.	2695310
69	67 not 68	3326206
70	62 not 69	3216
71	conference*.db,pt,su.	6582375
72	70 not 71	2085
73	limit 72 to english language	1937
74	limit 73 to yr="2019 -Current"	847

Database name: The Cochrane Library: Central Register of Controlled Trials (CENTRAL) and Cochrane Database of Systematic Reviews (CDSR)

Searches		
#1	[mh ^“Diabetes mellitus, type 1”]	7858
#2	((diabet* or DM) NEAR/3 (“type 1” or type1 or “type I” or typei or “type one”)):ti,ab	11448
#3	(T1D or T1DM or T1 DM or DM1 or DM 1 or DMT1 or DM T1 or IDDM):ti,ab	9738
#4	{OR #1-#3}	18902
#5	[mh ^“Pregnancy”]	33514
#6	[mh ^“Pregnant People”]	1088
#7	pregnan*:ti,ab	79772
#8	pre?pregnan*:ti,ab	1067
#9	[mh ^“Family Planning Services”]	445

Searches	
#10	(family NEXT plan*):ti,ab 1533
#11	((plan* or try*) NEAR/3 (conceiv* or conception or child*)):ti,ab 989
#12	[mh ^“Preconception Care”] 201
#13	pre?conception:ti,ab 685
#14	(pre NEXT conception):ti,ab 81
#15	peri?conception*:ti,ab 207
#16	(peri NEXT conception*):ti,ab 32
#17	[mh ^“Prenatal care”] 2388
#18	(pre?natal* or ante?natal*):ti,ab 11887
#19	(pre NEXT natal*):ti,ab 77
#20	(ante NEXT natal*):ti,ab 86
#21	[mh ^“Perinatal care”] 257
#22	peri?natal:ti,ab 7115
#23	(peri NEXT natal):ti,ab 11
#24	[mh ^“Peripartum Period”] 44
#25	peri?partum:ti,ab 432
#26	(peri NEXT partum):ti,ab 19
#27	puerperium:ti,ab 1232
#28	[mh ^“Postpartum Period”] 2130
#29	post?natal*:ti,ab 6544
#30	(post NEXT natal*):ti,ab 560
#31	post?partum*:ti,ab 15239
#32	(post NEXT partum*):ti,ab 2233
#33	{OR #5-#32} 106386
#34	#4 and #33 892
#35	[mh ^“Pregnancy in Diabetics”] 341
#36	#34 or #35 1097
#37	[mh ^“Insulin Infusion Systems”] 1032
#38	(insulin NEXT (pump* or deliver* or dose* or dosing or infusi*)):ti,ab 6600
#39	[mh ^“Pancreas, Artificial”] 118
#40	((artificial or bionic) NEAR/2 pancreas):ti,ab 476
#41	(artificial NEAR/2 beta cell*):ti,ab 4
#42	(glucose NEXT (monitor* or control*)):ti,ab 9365
#43	(glyc?emic NEXT control*):ti,ab 16859
#44	(CGM or CGMs or CBGM or “Flash GM” or FGM or FGMs or iCGM or iCGMs or rtCGM or rtCGMS):ti,ab 3769
#45	closed loop*:ti,ab 2272
#46	(HCL or AHCL):ti,ab 3641

Searches	
#47	(Ominipod* or "Dana i" or "Medtronic 780g" or Tslim or YpsoPump):ti,ab 67
#48	{OR #37-#47} 32101
#49	#36 and #48 416
#50	((clinicaltrials or trialsearch* or trial-registry or trials-registry or clinicalstudies or trialsregister* or trialregister* or trial-number* or studyregister* or study-register* or controlled-trials-com or current-controlled-trial or AMCTR or ANZCTR or ChiCTR* or CRiS or CTIS or CTRI* or DRKS* or EU-CTR* or EUCTR* or EUDRACT* or ICTRP or IRCT* or JAPIC* or JMCTR* or JRCT or ISRCTN* or LBCTR* or NTR* or ReBec* or REPEC* or RPCEC* or SLCTR or TCTR* or UMIN*):so or (ctgov or ictrp)):an 603888
#51	#49 not #50 248
#52	conference:pt 271969
#53	#51 not #52 with Cochrane Library publication date Between Jan 2019 and Dec 2025 82

1 **Database name: Epistemonikos**

Searches
(advanced_title_en:((diabet* OR dm) AND ("type 1" OR type1 OR "type i" OR typei OR "type one") OR (t1d OR t1dm OR t1 dm OR dm1 OR dm 1 OR dmt1 OR dm t1 OR iddm)) OR advanced_abstract_en:((diabet* OR dm) AND ("type 1" OR type1 OR "type i" OR typei OR "type one") OR (t1d OR t1dm OR t1 dm OR dm1 OR dm 1 OR dmt1 OR dm t1 OR iddm))) AND (advanced_title_en:(pregnan* OR prepregnan* OR pre pregnan* OR (family AND plan*) OR ((plan* OR try*) AND (conceiv* OR conception OR pregnan* OR child*)) OR preconception OR (pre AND conception) OR periconception* OR (peri AND conception*) OR prenatal* OR antenatal* OR (pre AND natal*) OR (ante AND natal*) OR perinatal OR (peri AND natal) OR peripartum OR (peri AND partum) OR puerperium OR postnatal* OR (post AND natal*) OR postpartum* OR (post AND partum*)) OR advanced_abstract_en:(pregnan* OR prepregnan* OR pre pregnan* OR (family AND plan*) OR ((plan* OR try*) AND (conceiv* OR conception OR pregnan* OR child*)) OR preconception OR (pre AND conception) OR periconception* OR (peri AND conception*) OR prenatal* OR antenatal* OR (pre AND natal*) OR (ante AND natal*) OR perinatal OR (peri AND natal) OR peripartum OR (peri AND partum) OR puerperium OR postnatal* OR (post AND natal*) OR postpartum* OR (post AND partum*))) AND (advanced_title_en:((advanced_title_en:((insulin AND (pump* OR deliver* OR dose* OR dosing OR infusi*)) OR ((artificial OR bionic) AND pancreas) OR (artificial AND beta cell*) OR (glucose AND (monitor* OR control*)) OR ((glycemic OR glycaemic) AND control*) OR (cgm OR cgms OR cbgm OR "flash gm" OR fgm OR fgms OR icgm OR icgms OR rtcgm OR rtcgms) OR (closed loop*) OR ("hcl" OR "ahcl") OR ("ominipod 5" OR "dana i" OR "medtronic 780g" OR "tandem tslim" OR "mylife ypsopump")) OR advanced_abstract_en:((insulin AND (pump* OR deliver* OR dose* OR dosing OR infusi*)) OR ((artificial OR bionic) AND pancreas) OR (artificial AND beta cell*) OR (glucose AND (monitor* OR control*)) OR ((glycemic OR glycaemic) AND control*) OR (cgm OR cgms OR cbgm OR "flash gm" OR fgm OR fgms OR icgm OR icgms OR rtcgm OR rtcgms) OR (closed loop*) OR ("hcl" OR "ahcl") OR (Ominipod* OR "Dana i" OR "Medtronic 780g" OR Tslim OR YpsoPump)))) OR

Searches
advanced_abstract_en:((advanced_title_en:((insulin AND (pump* OR deliver* OR dose* OR dosing OR infusi*)) OR ((artificial OR bionic) AND pancreas) OR (artificial AND beta cell*) OR (glucose AND (monitor* OR control*)) OR ((glycemic OR glycaemic) AND control*) OR (cgm OR cgms OR cbgm OR "flash gm" OR fgm OR fgms OR icgm OR icgms OR rtcgm OR rtcgms) OR (closed loop*) OR ("hcl" OR "ahcl") OR ("ominipod 5" OR "dana i" OR "medtronic 780g" OR "tandem tslim" OR "mylife ypsopump")) OR advanced_abstract_en:((insulin AND (pump* OR deliver* OR dose* OR dosing OR infusi*)) OR ((artificial OR bionic) AND pancreas) OR (artificial AND beta cell*) OR (glucose AND (monitor* OR control*)) OR ((glycemic OR glycaemic) AND control*) OR (cgm OR cgms OR cbgm OR "flash gm" OR fgm OR fgms OR icgm OR icgms OR rtcgm OR rtcgms) OR (closed loop*) OR ("hcl" OR "ahcl") OR (Ominipod* OR "Dana i" OR "Medtronic 780g" OR Tslim OR YpsoPump))))) [Filters: classification=systematic-review, protocol=no, min_year=2019, max_year=2025] Total: 359

Cost-effectiveness searches

Database results – Economic Evaluations

Databases	Date searched	Database platform	Database segment or version	No. of results downloaded
MEDLINE ALL	08/01/26	Ovid	1946 to January 07, 2026	27
Embase	08/01/26	Ovid	1974 to 2026 January 06	30
International HTA Database	08/01/26	INAHTA	08/01/2026	24

Search strategy history

Database name: Medline

Searches		
1	Diabetes mellitus, type 1/	92479
2	((diabet* or DM) adj3 ("type 1" or type1 or "type I" or typei or "type one")).ti,ab.	74789
3	(T1D or T1DM or T1 DM or DM1 or DM 1 or DMT1 or DM T1 or IDDM).ti,ab.	34166
4	or/1-3	123294
5	Pregnancy/	1057559
6	Pregnant People/	17313

Searches		
7	pregnan*.ti,ab.	664756
8	pre?pregnan*.ti,ab.	4963
9	Family Planning Services/	27384
10	(family adj plan*).ti,ab.	26575
11	((plan* or try*) adj3 (conceiv* or conception* or child*)).ti,ab.	6215
12	Preconception Care/	2999
13	pre?conception.ti,ab.	6803
14	(pre adj conception).ti,ab.	996
15	peri?conception*.ti,ab.	2447
16	(peri adj conception*).ti,ab.	226
17	Prenatal care/	35356
18	(pre?natal* or ante?natal*).ti,ab.	180447
19	(pre adj natal*).ti,ab.	1600
20	(ante adj natal*).ti,ab.	698
21	Perinatal care/	5877
22	peri?natal.ti,ab.	97725
23	(peri adj natal).ti,ab.	220
24	Peripartum Period/	2090
25	peri?partum.ti,ab.	7527
26	(peri adj partum).ti,ab.	267
27	puerperium.ti,ab.	6847
28	Postpartum Period/	34755
29	post?natal*.ti,ab.	137975
30	(post adj natal*).ti,ab.	9369
31	post?partum*.ti,ab.	81888
32	(post adj partum*).ti,ab.	14538
33	or/5-32	1429363
34	4 and 33	6293
35	Pregnancy in Diabetics/	11355
36	34 or 35	14857
37	Insulin Infusion Systems/	7225
38	(insulin adj (pump* or deliver* or dose* or dosing or infusi*)).ti,ab.	19135
39	Pancreas, Artificial/	1096
40	((artificial or bionic) adj2 pancreas).ti,ab.	1752
41	(artificial adj2 beta cell*).ti,ab.	156
42	(glucose adj (monitor* or control*)).ti,ab.	25886
43	(glyc?emic adj control*).ti,ab.	48510
44	(CGM or CGMs or CBGM or "Flash GM" or FGM or FGMs or iCGM or iCGMs or rtCGM or rtCGMS).ti,ab.	8654
45	closed loop*.ti,ab.	18225

Searches
46 (HCL or AHCL).ti,ab. 41456
47 (Ominipod* or "Dana i" or "Medtronic 780g" or Tslim or YpsoPump).ti,ab. 112
48 or/37-47 143037
49 36 and 48 2099
50 animals/ 7810844
51 exp Animals, Laboratory/ 1021464
52 exp Animal Experimentation/ 10816
53 exp Models, Animal/ 702732
54 exp Rodentia/ 3778843
55 (rat or rats or mouse or mice or rodent*).ti. 1550667
56 or/50-55 7949127
57 56 not humans/ 5506666
58 49 not 57 2072
59 letter/ 1322325
60 editorial/ 745287
61 news/ 233576
62 exp historical article/ 418370
63 Anecdotes as Topic/ 4748
64 comment/ 1059675
65 (letter or comment*).ti. 224478
66 or/59-65 3070915
67 randomized controlled trial/ or random*.ti,ab. 1843574
68 66 not 67 3042415
69 58 not 68 1996
70 limit 69 to english language 1840
71 limit 70 to yr="2019 -Current" 614
72 Cost-Benefit Analysis/ 99964
73 Quality-Adjusted Life Years/ 18804
74 Markov Chains/ 17694
75 exp Models, Economic/ 17130
76 cost*.ti. 162804
77 (cost* adj2 utilit*).tw. 9186
78 (cost* adj2 (effective* or assess* or evaluat* or analys* or model* or benefit* or threshold* or quality or expens* or saving* or reduc*)).tw. 341882
79 (economic* adj2 (evaluat* or assess* or analys* or model* or outcome* or benefit* or threshold* or expens* or saving* or reduc*)).tw. 57504
80 (qualit* adj2 adjust* adj2 life*).tw. 21359
81 QALY*.tw. 17447
82 (incremental* adj2 cost*).tw. 20772

Searches		
83	ICER.tw.	7744
84	utilities.tw.	10892
85	markov*.tw.	37367
86	(dollar* or USD or cents or pound or pounds or GBP or sterling* or pence or euro or euros or yen or JPY).tw.	61515
87	((utility or effective*) adj2 analys*).tw.	30346
88	(willing* adj2 pay*).tw.	12396
89	(EQ5D* or EQ-5D*).tw.	17348
90	((euroqol or euro-qol or euroquol or euro-quol or eurocol or euro-col) adj3 ("5" or five)).tw.	5248
91	(european* adj2 quality adj3 ("5" or five)).tw.	927
92	or/72-91	596610
93	71 and 92	27

1 **Database name: Embase**

Searches		
1	insulin dependent diabetes mellitus/	169729
2	((diabet* or DM) adj3 ("type 1" or type1 or "type I" or typei or "type one")).ti,ab.	124211
3	(T1D or T1DM or T1 DM or DM1 or DM 1 or DMT1 or DM T1 or IDDM).ti,ab.	62371
4	or/1-3	205060
5	pregnancy/	775659
6	pregnant person/	808
7	pregnan*.ti,ab.	894048
8	pre?pregnan*.ti,ab.	6546
9	family planning/	42262
10	(family adj plan*).ti,ab.	25625
11	((plan* or try*) adj3 (conceiv* or conception or child*)).ti,ab.	9150
12	prepregnancy care/	3965
13	pre?conception.ti,ab.	9977
14	(pre adj conception).ti,ab.	1941
15	peri?conception*.ti,ab.	3231
16	(peri adj conception*).ti,ab.	351
17	prenatal care/	61130
18	(pre?natal* or ante?natal*).ti,ab.	242661
19	(pre adj natal*).ti,ab.	2114
20	(ante adj natal*).ti,ab.	1060
21	perinatal care/	17804
22	peri?natal.ti,ab.	135297

Searches	
23	(peri adj natal).ti,ab. 444
24	perinatal period/ 47901
25	peri?partum.ti,ab. 11682
26	(peri adj partum).ti,ab. 624
27	puerperium.ti,ab. 7285
28	puerperium/ 58826
29	post?natal*.ti,ab. 178209
30	(post adj natal*).ti,ab. 14799
31	post?partum*.ti,ab. 111650
32	(post adj partum*).ti,ab. 22615
33	or/5-32 1544127
34	4 and 33 10400
35	*maternal diabetes mellitus/ 2933
36	pregnancy in diabetics/ 136
37	34 or 35 or 36 12884
38	insulin infusion/ 11279
39	insulin pump/ 13900
40	insulin delivery device/ 1194
41	(insulin adj (pump* or deliver* or dose* or dosing or infusi*)).ti,ab. 36240
42	artificial pancreas/ 3258
43	((artificial or bionic) adj2 pancreas).ti,ab. 3135
44	(artificial adj2 beta cell*).ti,ab. 203
45	(glucose adj (monitor* or control*)).ti,ab. 46872
46	(glyc?emic adj control*).ti,ab. 84568
47	(CGM or CGMs or CBGM or "Flash GM" or FGM or FGMs or iCGM or iCGMs or rtCGM or rtCGMS).ti,ab. 18559
48	closed loop*.ti,ab. 24483
49	(HCL or AHCL).ti,ab. 53339
50	(Ominipod* or "Dana i" or "Medtronic 780g" or Tslim or YpsoPump).ti,ab. 369
51	or/38-50 224119
52	37 and 51 3366
53	animal/ 1746311
54	nonhuman/ 8457144
55	exp Animal Experiment/ 3488092
56	exp Experimental Animal/ 930291
57	animal model/ 2012496
58	exp Rodent/ 4447795
59	(rat or rats or mouse or mice or rodent*).ti. 1749729
60	or/53-59 11100557

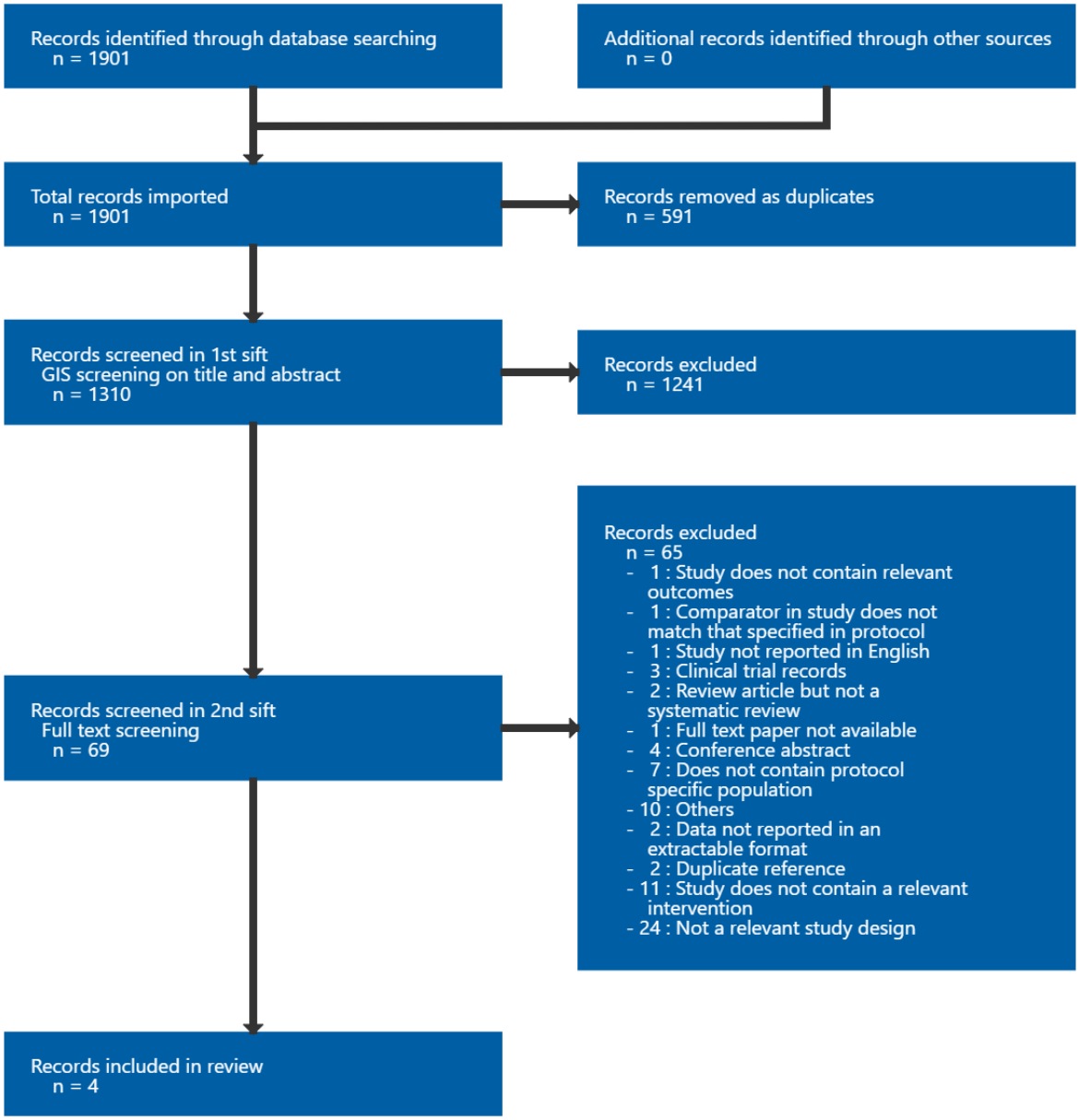
Searches		
61	60 not human/	7810663
62	52 not 61	3333
63	letter.pt. or letter/	1415735
64	note.pt.	1031964
65	editorial.pt.	857934
66	(letter or comment*).ti.	269114
67	or/63-66	3370312
68	randomized controlled trial/ or random*.ti,ab.	2707070
69	67 not 68	3331750
70	62 not 69	3232
71	conference*.db,pt,su.	6623409
72	70 not 71	2092
73	limit 72 to yr="2019 -Current"	885
74	cost utility analysis/	14888
75	quality adjusted life year/	43388
76	cost*.ti.	220474
77	(cost* adj2 utilit*).tw.	15483
78	(cost* adj2 (effective* or assess* or evaluat* or analys* or model* or benefit* or threshold* or quality or expens* or saving* or reduc*)).tw.	479188
79	(economic* adj2 (evaluat* or assess* or analys* or model* or outcome* or benefit* or threshold* or expens* or saving* or reduc*)).tw.	82376
80	(qualit* adj2 adjust* adj2 life*).tw.	32983
81	QALY*.tw.	32469
82	(incremental* adj2 cost*).tw.	34346
83	ICER.tw.	16243
84	utilities.tw.	17610
85	markov*.tw.	47325
86	(dollar* or USD or cents or pound or pounds or GBP or sterling* or pence or euro or euros or yen or JPY).tw.	85673
87	((utility or effective*) adj2 analys*).tw.	46530
88	(willing* adj2 pay*).tw.	18346
89	(EQ5D* or EQ-5D*).tw.	34851
90	((euroqol or euro-qol or euroquol or euro-quol or eurocol or euro-col) adj3 ("5" or five)).tw.	7163
91	(european* adj2 quality adj3 ("5" or five)).tw.	1333
92	or/74-91	772206
93	73 and 92	30

Database name: INAHTA

Searches
(closed loop) or HCL or AHCL or * (artificial pancreas) or (bionic pancreas) or (artificial beta cell*) or Ominipod* or "Dana i" or "Medtronic 780g" or Tslim or YpsoPump or CGM or CGMs or CBGM or “Flash GM” or FGM or FGMs or iCGM or iCGMs or rtCGM or rtCGMS or (insulin and (pump* or deliver* or dose* or dosing or infusi*) or (glucose and (monitor* or control*) Total: 24 As retrieval was low only the intervention was used for this search

Appendix C - Study selection – effectiveness evidence

Figure 1 Effectiveness evidence study selection



Appendix D - Effectiveness evidence tables

Benhalima, 2024

Bibliographic Reference	Benhalima, Katrien; Beunen, Kaat; Van Wilder, Nancy; Ballaux, Dominique; Vanhaverbeke, Gerd; Taes, Youri; Aers, Xavier-Philippe; Nobels, Frank; Marlier, Joke; Lee, Dahae; Cuypers, Joke; Preumont, Vanessa; Siegelaar, Sarah E; Painter, Rebecca C; Laenen, Annouschka; Gillard, Pieter; Mathieu, Chantal; Comparing advanced hybrid closed loop therapy and standard insulin therapy in pregnant women with type 1 diabetes (CRISTAL): a parallel-group, open-label, randomised controlled trial.; The lancet. Diabetes & endocrinology; 2024; vol. 12 (no. 6); 390-403

Study details

Secondary publication of another included study- see primary study for details	NA
Other publications associated with this study included in review	Beunen 2024 - reports intrapartum and postpartum outcomes for the population of original trial
Trial name / registration number	CRISTAL trial / NCT04520971
Study type	Randomised controlled trial (RCT)
Study location	Secondary and tertiary specialist endocrinology centres across two countries: • Belgium – 11 hospitals

	• The Netherlands – 1 hospital
Study setting	Secondary and tertiary specialist hospital based endocrine and diabetes in pregnancy clinics-based endocrine and diabetes-in-pregnancy clinics
Study dates	Participants were recruited between 15 January 2021 and 30 September 2022 and followed from early pregnancy until delivery.
Sources of funding	Trial funding was provided by the Diabetes Liga Research Fund, and Medtronic provided devices and an unrestricted grant for academic research

Inclusion criteria	• Pregnant women with a diagnosis of type 1 diabetes
	• Diagnosis duration ≥ 1 year prior to recruitment
	• 18 to 45 years at the time of enrolment
	• Singleton pregnancy
	• Pregnancy confirmed by:
	  ○ Ultrasound or
	  ○ Positive hCG blood test
	• Gestational age ≤ 11 weeks + 6 days at recruitment
	• Receiving intensive insulin therapy, defined as:
	• Multiple daily insulin injections (MDI), or
	• Insulin pump therapy (CSII)
	• HbA_1c ≤ 10.0% (≤ 86 mmol/mol) at screening
	• Use of continuous glucose monitoring (CGM)

Exclusion criteria	• Use of an advanced hybrid closed loop (AHCL) system in closed loop mode at screening • Multiple pregnancy (e.g. twins or higher order multiples) • Gestational age > 11 weeks + 6 days at recruitment • Medications known to interfere with glucose metabolism • Total daily insulin dose ≥ 1.5 units/kg/day • known allergy to adhesives for infusion set or CGM (or both)

	• Inability to comply with study procedures or protocol requirement

Recruitment / selection of participants	Women were screened early in pregnancy, before 11 weeks + 6 days' gestation, following confirmation of a viable pregnancy (ultrasound or serum hCG).
	
	Participants were screened based on the study's inclusion criteria.
	
	• Eligible women entered a 10day CGM run-in phase before randomisation.
	• Purpose of the run-in phase:
	  ○ To standardise baseline glycaemic assessment
	  ○ To confirm compliance with CGM use
	• A masked Guardian 3 CGM was used if participants were not already using a compatible CGM system.

Intervention(s)	Randomisation occurred before 14 weeks' gestation. After completion of the run-in phase, participants were randomised 1:1. Intervention: Advanced hybrid closed loop (AHCL) therapy (MiniMed™ 780G) N= 46 Participants received structured training on the MiniMed 780G within a week of randomisation and then switched to AHCL therapy. The system uses proportional–integral–derivative technology with insulin feedback (SmartGuard), consisting of the 780G pump and the AccuChek Guide Link glucometer with either the Guardian 3 or 4 CGM. As the Guardian 4 became available during the trial, participants were transitioned from Guardian 3 to Guardian 4, and new participants used Guardian 4 from the outset.

	The Guardian 4 sensor uses an updated calibration algorithm but is otherwise similar to Guardian 3, aiming to reduce or remove the need for calibrations. The sensor hardware is identical, and the Guardian 4 transmitter is equivalent to the Guardian Connect transmitter with the added G Algorithm. No major bias is expected from switching between Guardian 3 and 4 within the intervention.
Population subgroups	NA
Comparator	Randomisation occurred before 14 weeks' gestation. After completion of the run-in phase, participants were randomised 1:1. Comparator: Standard insulin therapy (Standard Care); could use multiple daily injections/ CSII without automation; all participants used CGM N= 49 Participants in the standard care group continued with usual insulin therapy, either multiple daily injections or pump therapy (with standalone or sensor augmented pumps) using any CGM. For those not using a Guardian 3 or 4 CGM, a masked Guardian 3 was applied at set timepoints (14 - 17, 20 - 23, 26 - 29, and 33 - 36 weeks' gestation) to assess glycaemic assessment.

Number of participants	• 187 pregnant women with type 1 diabetes assessed for eligibility
	• 101 women screened
	• 95 women randomised:
	  ○ 46 to AHCL therapy
	  ○ 49 to standard insulin therapy

Duration of follow-up	From early pregnancy (first trimester) until delivery Participants were randomised at a median gestational age of ~10 weeks

	Follow-up continued through: • Mid-pregnancy • Late pregnancy • End of pregnancy (delivery) Repeated CGM assessments were conducted at: • 14–17 weeks • 20–23 weeks • 26–29 weeks • 33–36 weeks of gestation
Indirectness	None
Method of analysis	ITT
Additional comments	*Primary analysis was carried out using ITT for primary and secondary outcomes.*

Study arms

Hybrid Closed-loop system (N = 46)
Advanced hybrid closed loop insulin therapy using the MiniMed™ 780G system 46 participants were recruited, 43 completed the study

Standard insulin therapy (N = 49)
Participants continued their usual non-closed-loop insulin therapy. 49 participants were randomised and 46 completed the study

Characteristics

Arm-level characteristics

Characteristic	Hybrid Closed-loop system (N = 46)	Standard insulin therapy (N = 49)
% Female Sample size	n = 46; % = 100	n = 49; % = 100
Mean age (SD) (Years (mean, SD)) Mean (SD)	30.8 (4.6)	30.3 (3.8)
Ethnicity Sample size	n = NR; % = NR	n = NR; % = NR
Comorbidities - Diabetic retinopathy Intervention: 12/44, Comparator 10/47 Sample size	n = 12; % = 27.3	n = 10; % = 21.3
Comorbidities - Microalbuminuria (pre-gestational) intervention: 6/44, comparator: 8/40 Sample size	n = 6; % = 13.6	n = 8; % = 20
Comorbidities - Neuropathy intervention: 2/45, comparator: 4/48 Sample size	n = 2; % = 4.4	n = 3; % = 6.2

Characteristic	Hybrid Closed-loop system (N = 46)	Standard insulin therapy (N = 49)
Comorbidities - Macrovascular diabetes complications intervention: 1/46, comparator: 0/49 Sample size	n = 1; % = 2.2	n = 0; % = 0
Comorbidities - Chronic hypertension intervention: 1/46, comparator: 1/49 Sample size	n = 1; % = 2.2	n = 1; % = 2.0
Gestational age - At recruitment Median (IQR)	8.2 (7 to 10.1)	8.6 (6.9 to 10)
Gestational age - At randomisation Median (IQR)	10.3 (8.9 to 11.9)	10.1 (8.5 to 11.6)
Gestational age - At the start of HCL therapy Median (IQR)	10.7 (8.9 to 12.6)	NR (NR to NR)
HbA1c - <6% Sample size	n = 6; % = 13	n = 9; % = 18.4
HbA1c - 6·0 to <7·0% Sample size	n = 30; % = 65.2	n = 29; % = 59.2
HbA1c - 7·0 to <8·0% Sample size	n = 9; % = 19.6	n = 9; % = 18.4

Characteristic	Hybrid Closed-loop system (N = 46)	Standard insulin therapy (N = 49)
HbA1c - ≥8·0% Sample size	n = 1; % = 2.2	n = 2; % = 4.1
HbA1c (%) Mean (SD)	6.5 (0.6)	6.5 (0.7)
Diabetes therapy - Continuous glucose monitor using Medtronic Sample size	n = 41; % = 89.1	n = 40; % = 81.6
Diabetes therapy - Continuous glucose monitor using Dexcom Sample size	n = 4; % = 8.7	n = 5; % = 10.2
Diabetes therapy - Continuous glucose monitor using Abbott FreeStyle Libre Sample size	n = 1; % = 2.2	n = 4; % = 18.4
Insulin delivery via multiple daily injections Sample size	n = 2; % = 4.3	n = 2; % = 4.1
Insulin delivery via pump Sample size	n = 44; % = 95.7	n = 47; % = 95.9
Insulin delivery via pump - Continuous subcutaneous insulin infusion with standalone continuous glucose monitor (CSII) Sample size	n = 3/44; % = 6.8	n = 7/47; % = 14.9

Characteristic	Hybrid Closed-loop system (N = 46)	Standard insulin therapy (N = 49)
Insulin delivery via pump - Sensor-augmented pump Sample size	n = 37/44; % = 84.1	n = 38/47; % = 80.8
Insulin delivery via pump - Advanced hybrid closed loop therapy Sample size	n = 4/44; % = 9.1	n = 2/47; % = 4.3
Time spent in the pregnancy-specific glucose target range (%) Mean (SD)	60.5 (14.2)	57.6 (13.7)
BMI (kg/m²) Mean (SD)	26 (3.6)	26.9 (5.4)
Duration of diabetes (years (mean)) Mean (SD)	17 (9.2)	30.3 (3.8)

Outcomes

Maternal Outcomes

Outcome	Hybrid Closed-loop system, N = 46	Standard insulin therapy, N = 49
% time spent in the pregnancy-specific target glucose range - Time spent above target glucose range (>7.8 mmol/L) Mean (SD)	30.9 (10.6)	32.8 (13.1)
% time spent in the pregnancy-specific target glucose range - Time spent below target glucose range (<3.5 mmol/L) Mean (SD)	2.5 (2.8)	4.1 (3.4)
% time spent in the pregnancy-specific target glucose range - Overnight % time spent in range (00:00–06:00; 3.5–7.8 mmol/L) Mean (SD)	75.1 (13.1)	67.2 (14.6)
% time spent in the pregnancy-specific target glucose range - Overall time spent in target glucose range 3.5-7.8mmol/L Mean (SD)	66.5 (10)	63.2 (12.4)
Adverse events - Severe hypoglycaemia No of events	n = 6; % = 13	n = 5; % = 10.2
Adverse events - Diabetic ketoacidosis No of events	n = 1; % = 0.022	n = 1; % = 0.02

1 Adverse events - Polarity - Lower values are better

Foetal/Neonatal outcomes

Outcome	Hybrid Closed-loop system, N =	Standard insulin therapy, N =
Neonatal intensive care unit admissions longer than 24 hours Hybrid closed-loop = 42, Standard insulin therapy = 45 No of events	n = 14; % = 33.3	n = 11; % = 24.4
Pregnancy loss (miscarriage < 20 weeks) Hybrid closed-loop = 45, Standard insulin therapy = 47 No of events	n = 2; % = 4.4	n = 1; % = 2.1
Stillbirth (≥20 weeks) Hybrid closed-loop = 45, Standard insulin therapy = 47 No of events	n = 1; % = 2.2	n = 0; % = 0
Neonatal loss (≤28 days) Hybrid closed-loop = 42, Standard insulin therapy = 46 No of events	n = 0; % = 0	n = 0; % = 0
Neonatal hypoglycaemia (<40 mg/dL) Hybrid closed-loop = 38, Standard insulin therapy = 42 No of events	n = 12; % = 31.6	n = 19; % = 45.2
Preterm birth (<37 weeks) Hybrid closed-loop = 43, Standard insulin therapy = 46 Sample size	n = 12; % = 27.9	n = 9; % = 19.6

Outcome	Hybrid Closed-loop system, N =	Standard insulin therapy, N =
Large for gestational age Hybrid closed-loop = 43, Standard insulin therapy = 46 No of events	n = 24; % = 55.8	n = 31; % = 67.4
small for gestational age Hybrid closed-loop = 43, Standard insulin therapy = 46 No of events	n = 0; % = 0	n = 0; % = 0

Device-related adverse events

Outcome	Hybrid closed loop, N = 61	Standard Care, N = 63
Hybrid closed loop system No of events	n = 1	n = NA
Continuous glucose monitor No of events	n = 1	n = 3

Critical Appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low *(Randomisation & concealment is appropriate; baseline balanced; Deviations: open label but high adherence and objective outcomes; ITT and per protocol consistent Missing data: minimal; handled appropriately Outcome measurement: objective CGM with harmonised assessment Selective reporting: prespecified and complete)*

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable *(The study's population, interventions, comparators, clinically meaningful outcomes, and real world settings all directly address the clinical question of AHCL use in pregnant women with type 1 diabetes. There are no serious concerns regarding indirectness.)*

Beunen, 2024

Bibliographic Reference	Beunen, Kaat; Gillard, Pieter; Van Wilder, Nancy; Ballaux, Dominique; Vanhaverbeke, Gerd; Taes, Youri; Aers, Xavier-Philippe; Nobels, Frank; Van Huffel, Liesbeth; Marlier, Joke; Lee, Dahae; Cuypers, Joke; Preumont, Vanessa; Siegelaar, Sarah E; Painter, Rebecca C; Laenen, Annouschka; Mathieu, Chantal; Benhalima, Katrien; Advanced Hybrid Closed-Loop Therapy Compared With Standard Insulin Therapy Intrapartum and Early Postpartum in Women With Type 1 Diabetes: A Secondary Observational Analysis From the CRISTAL Randomized Controlled Trial.; Diabetes care; 2024; vol. 47 (no. 11); 2002-2011

Study details

Secondary publication of another included study- see primary study for details	Benhalima 2024
Other publications associated with this study included in review	Benhalima 2024
Trial name / registration number	CRISTAL trial / NCT04520971

Study location	Secondary and tertiary specialist endocrinology centres across two countries: • Belgium – 11 hospitals • The Netherlands – 1 hospital
Study setting	Secondary and tertiary specialist hospital based endocrine and diabetes in pregnancy clinics
Study dates	Participants were recruited between 15 January 2021 and 30 September 2022
Sources of funding	Trial funding was provided by the Diabetes Liga Research Fund, and Medtronic provided devices and an unrestricted grant for academic research

Inclusion criteria	• Pregnant women with a diagnosis of type 1 diabetes
	• Diagnosis duration ≥ 1 year prior to recruitment
	• 18 to 45 years at the time of enrolment
	• Singleton pregnancy
	• Pregnancy confirmed by:
	  ○ Ultrasound or
	  ○ Positive hCG blood test
	• Gestational age ≤ 11 weeks + 6 days at recruitment
	• Receiving intensive insulin therapy, defined as:
	• Multiple daily insulin injections (MDI), or
	• Insulin pump therapy (CSII)
	• HbA_1c ≤ 10.0% (≤ 86 mmol/mol) at screening
	• Use of continuous glucose monitoring (CGM)

Exclusion criteria	• Use of an advanced hybrid closed loop (AHCL) system in closed loop mode at screening • Multiple pregnancy (e.g. twins or higher order multiples) • Gestational age > 11 weeks + 6 days at recruitment • Medications known to interfere with glucose metabolism • Total daily insulin dose ≥ 1.5 units/kg/day • known allergy to adhesives for infusion set or CGM (or both)

	• Inability to comply with study procedures or protocol requirement

Recruitment / selection of participants	This paper was a prespecified, secondary observational analysis focusing on labour & delivery (intrapartum) and early postpartum (day after delivery until hospital discharge; median 4 days) among women already randomized in CRISTAL. Participants were not rerandomized; rather, they were grouped by the actual therapy used during the period of interest.
	
	Selection into the intrapartum and early postpartum groups:
	
	• Of those who completed the pregnancy follow-up (43 in the AHCL arm; 46 in the standard arm):
	  ○ Intrapartum
	  ▪ From the original AHCL arm: 27/43 (62.8%) continued AHCL during labour & delivery (used 95.4% of the time on the day of delivery).
	  ▪ From the original standard arm: 45/46 (97.8%) continued standard insulin therapy intrapartum (2 had missing CGM metrics for the delivery day, so n=43 for CGM based intrapartum comparisons).
	  ▪ Some participants temporarily used IV insulin infusion or sensor augmented pump per treating clinician; Beunen also presents comparisons by actual intrapartum therapy (AHCL n=28, standard n=26, IV insulin n=33), irrespective of original allocation.
	  ○ Early postpartum (to discharge; median 4 days)
	  ▪ From the original AHCL arm: 37/43 (86.0%) continued AHCL (median AHCL use 77.3% of the time).
	  ▪ From the original standard arm: 34/46 (73.9%) continued standard insulin therapy;10/46 (22.7%) started AHCL postpartum (not used for the primary between group early postpartum comparison of “AHCL vs standard”).

Intervention(s)	Intervention: Advanced hybrid closed-loop (AHCL) therapy (MiniMed™ 780G)
Population subgroups	Population from the original trial that completed the pregnancy follow-up
Comparator	Comparator: Standard insulin therapy (Standard Care); could use multiple daily injections/ CSII without automation; all participants used CGM

Number of participants	Of those who completed the pregnancy follow-up (43 in the AHCL arm; 46 in the standard arm):
	• Intrapartum:
	  ○ Intervention = 27
	  ○ Comparator = 43
	• Early postpartum (to discharge; median 4 days)
	  ○ Intervention = 37
	  ○ Comparator = 34

Duration of follow-up	Intrapartum: During labour Postpartum: Until discharge - median 4 days
Method of analysis	ITT

Study arms

Hybrid Closed-loop system (N = 46)
Advanced hybrid closed loop insulin therapy using the MiniMed™ 780G system. 46 participants were recruited, 43 completed the study

Standard insulin therapy (N = 49)
Participants continued their usual non-closed loop insulin therapy. 49 participants were randomised and 46 completed the study

Outcomes

Intrapartum (day of delivery)

Outcome	Hybrid Closed-loop system, N = 27	Standard insulin therapy, N = 43
% time spent in the pregnancy-specific target glucose range - Time spent above target glucose range (>7.8 mmol/L) Mean (SD)	27.3 (17.4)	35.3 (17.5)
% time spent in the pregnancy-specific target glucose range - Time spent below target glucose range (<3.5 mmol/L) Mean (SD)	1.1 (2.4)	1.5 (2.3)
% time spent in the pregnancy-specific target glucose range - Overnight % time spent in range (00:00–06:00; 3.5–7.8 mmol/L) Mean (SD)	83.7 (23.7)	79.3 (26.4)
% time spent in the pregnancy-specific target glucose range - Overall time spent in target glucose range 3.5-7.8mmol/L Mean (SD)	71.5 (17.7)	63.1 (17)

Early Postpartum

Outcome	Hybrid Closed-loop system, N = 37	Standard insulin therapy, N = 34
% time spent in the non-pregnancy-specific target glucose range - Time spent above target glucose range (>10.0 mmol/L))	8.0 (6.2)	8.6 (8.5)

Outcome	Hybrid Closed-loop system, N = 37	Standard insulin therapy, N = 34
Mean (SD)		
% time spent in the pregnancy-specific target glucose range - Time spent below target glucose range (<3.9 mmol/L) Mean (SD)	5.2 (3.3)	7.6 (6.3)
% time spent in the pregnancy-specific target glucose range - % time spent in the pregnancy-specific target glucose range - Overnight % time spent in range (00:00–06:00; 3.5–7.8 mmol/L) Mean (SD)	81.5 (13.7)	80.2 (18.3)
% time spent in the pregnancy-specific target glucose range - Overall time spent in target glucose range 3.9-10.0mmol/L Mean (SD)	86.8 (6.7)	83.8 (8.1)

1 **Critical Appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT**

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Participants randomised at pregnancy phase were carried forward during intrapartum and postnatal periods. They were offered to change their intervention and were only excluded from final analysis if they decided to change intervention. The randomisation was lost; study lacks details of baseline data between arms; per protocol consistent Missing data: minimal; handled appropriately; Outcome measurement: objective CGM with harmonised assessment Selective reporting: prespecified and complete)*
Overall bias and Directness	Overall Directness	Directly applicable

2

Lee, 2023

Bibliographic Reference	Lee, Tara T M; Collett, Corinne; Bergford, Simon; Hartnell, Sara; Scott, Eleanor M; Lindsay, Robert S; Hunt, Katharine F; McCance, David R; Barnard-Kelly, Katharine; Rankin, David; Lawton, Julia; Reynolds, Rebecca M; Flanagan, Emma; Hammond, Matthew; Shepstone, Lee; Wilinska, Malgorzata E; Sibayan, Judy; Kollman, Craig; Beck, Roy; Hovorka, Roman; Murphy, Helen R; Automated Insulin Delivery in Women with Pregnancy Complicated by Type 1 Diabetes.; The New England journal of medicine; 2023; vol. 389 (no. 17); 1566-1578

Study details

Other publications associated with this study included in review	Lee et al. 2025.
Trial name / registration number	AiDAPT trial/ ISRCTN56898625
Study type	Randomised controlled trial (RCT)
Study location	United Kingdom
Study setting	Nine National Health Service (NHS) antenatal hospital clinics in England, Scotland, and Northern Ireland.
Study dates	September 2019 to May 2022
Sources of funding	Non-industry funding (the trial was funded by the National Institute for Health and Care Research (NIHR) Efficacy and Mechanism Evaluation (EME) programme (NIHR award ref: 16/35/01); continuous glucose monitoring devices were supplied by Dexcom at a discounted cost).
Inclusion criteria	• Pregnant women aged 18 - 45 years, • confirmed viable pregnancy by ultrasound, up to 13 weeks and 6 days gestation, • gestational age <14 weeks at recruitment, • diagnosis of type 1 diabetes for at least 12 months,

	• using intensive insulin therapy (≥3 daily injections or insulin pump); this includes sensor augmented insulin pumps and hybrid closed loop systems other than CamAPS FX,augmented insulin pumps and hybrid closed loop systems other than CamAPS FX,-augmented insulin pumps and hybrid closed loop-loop systems other than CamAPS FX, • HbA1c ≥48 mmol/mol (≥6.5%) in early pregnancy (at booking), • HbA1c ≤86 mmol/mol (≤10%) at randomisation, • provide informed consent, • has access to email.
Exclusion criteria	• Non-type 1 diabetes, • any physical or psychological condition likely to interfere with study conduct or interpretation (investigator judgement), • current use of medication that affects glucose metabolism (e.g. high dose corticosteroids), • known or suspected insulin allergy, • advanced nephropathy (eGFR <45), severe autonomic neuropathy, uncontrolled gastroparesis, or severe proliferative retinopathy (investigator judgement), • target glycaemia or very high HbA1c: first antenatal HbA1c <48 mmol/mol (<6.5%) or HbA1c >86 mmol/mol (>10%). Participants with HbA1c >86 mmol/mol (>10%) may take part if reduced to ≤86 mmol/mol (≤10%) before randomisation, • total daily insulin dose 1.5 units/kg, • severe visual or hearing impairment. • inability to speak and understand English.
Recruitment / selection of participants	Participants received study information at least a week before recruitment, and trained staff obtained written consent once a viable pregnancy had been confirmed by ultrasound (up to 13 weeks 6 days). Baseline history, current diabetes management and a brief physical examination were completed. Participants wore a study continuous glucose monitoring (CGM) to confirm tolerance and establish baseline glycaemia before randomisation. Personal glucose targets were user set, with recommended levels of 5.5 mmol/L in early pregnancy and 4.5 – 5.0 mmol/L from 16 – 20 weeks' gestation onward. Set, with recommended levels of 5.5 mmol/L in early pregnancy and

	4.5 – 5.0 mmol/L from 16 – 20 weeks' gestation onward. Set, with recommended levels of 5.5 mmol/L in early pregnancy and 4.5 – 5.0 mmol/L from 16 – 20 weeks'- gestation onward.
Intervention(s)	Automated hybrid closed-loop insulin delivery (CamAPS FX (CamDiab, Cambridge, UK)), an app running on an unlocked Android smartphone (Samsung Galaxy S8–12). The phone communicated via Bluetooth with the insulin pump (Dana Diabecare RS, Sooil, South Korea) and the continuous glucose monitor (Dexcom G6, Dexcom, CA, USA). The algorithm calculated a glucose responsive basal rate, delivered by the pump as extended boluses every 8 – 12 minutes. responsive basal rate, delivered by the pump as extended boluses every 8 – 12 minutes, -responsive basal rate, delivered by the pump as extended boluses every 8 – 12 minutes. At initiation, the participant’s weight and total daily insulin dose were entered into the system, and their insulin to carbohydrate ratios and insulin sensitivity factors were programmed into the pump’s bolus calculator. For existing pump users, their previous basal profile was stored for use if Auto Mode became unavailable (e.g. loss of communication, missing glucose data for more than 30 minutes, sensor warmup, or smartphone power loss), in which case the pump reverted to Manual Mode. For those previously on multiple daily injections, the total daily insulin dose was standardised to 70±10% of their injection dose, with a flat basal rate set at half of that dose evenly distributed over 24 hours. Participants were trained to use the closed loop system by the research educator or local teams. They set their own glucose targets, with a recommended target of 100 mg/dL (5.5 mmol/L) in early pregnancy, reduced to 81 – 90 mg/dL (4.5 – 5.0 mmol/L) from 16 – 20 weeks’ gestation and maintained at this lower range until delivery. Participants using closed loop were advised to adjust the maternal weight setting each trimester to reflect gestational weight gain to carbohydrate ratios and insulin sensitivity factors were programmed into the pump’s bolus calculator. For existing pump users, their previous basal profile was stored for use if Auto Mode became unavailable (e.g. loss of communication, missing glucose data for more than 30 minutes, sensor warmup, or smartphone power loss), in which case the pump reverted to Manual Mode. For those previously on multiple daily injections, the total daily insulin dose was standardised to 70±10% of their injection dose, with a flat basal rate set at half of that dose evenly distributed over 24 hours. Participants were trained to use the closed loop system by the research educator or local teams. They set their own glucose targets, with a recommended target of 100 mg/dL (5.5 mmol/L) in early pregnancy, reduced to 81 – 90 mg/dL (4.5 – 5.0 mmol/L) from 16 – 20 weeks’ gestation and maintained at this lower range until delivery. Participants using closed loop were advised to adjust the maternal weight setting each trimester to reflect gestational weight gain to carbohydrate ratios and insulin sensitivity factors were programmed into the pump’s bolus calculator. For existing pump users, their previous basal profile was stored for use if Auto Mode became unavailable (e.g. loss of communication, missing glucose data for more than 30 minutes, sensor warmup, or smartphone power loss), in which case the pump

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	mg/dL (4.5 – 5.0 mmol/L) from 16 – 20 weeks' gestation and maintained at this lower range until delivery. Participants using closed-loop were advised to adjust the maternal weight setting each trimester to reflect gestational weight gain.
Population subgroups	Subgroup analyses by breastfeeding status not available, loop system and by breastfeeding status are not available.-loop system and by breastfeeding status are not available.
Comparator	Standard care. Participants continued multiple daily injections or insulin pump therapy, with insulin doses adjusted by their local teams to meet standard glucose targets (63 – 100 mg/dL before meals and <140 mg/dL one hour after meals). Local teams also provided training in continuous glucose monitoring and insulin dose adjustment. After randomisation, participants attended in person or virtual (telephone or video) visits every 4 weeks, with additional contacts as clinically required. HbA1c was measured locally at 24 and 36 weeks, and follow-up questionnaires were completed at 34 – 36 weeks' gestation. Pump therapy, with insulin doses adjusted by their local teams to meet standard glucose targets (63 – 100 mg/dL before meals and <140 mg/dL one hour after meals). Local teams also provided training in continuous glucose monitoring and insulin dose adjustment. After randomisation, participants attended in person or virtual (telephone or video) visits every 4 weeks, with additional contacts as clinically required. HbA1c was measured locally at 24 and 36 weeks, and follow-up questionnaires were completed at 34 – 36 weeks' gestation. ump therapy, with insulin doses adjusted by their local teams to meet standard glucose targets (63 – 100 mg/dL before meals and <140 mg/dL one hour after meals). Local teams also provided training in continuous glucose monitoring and insulindose adjustment. After randomisation, participants attended inperson or virtual (telephone or video) visits every 4 weeks, with additional contacts as clinically required. HbA1c was measured locally at 24 and 36 weeks, and followup questionnaires were completed at 34 – 36 weeks' gestation. Pump therapy, with insulin doses adjusted by their local teams to meet standard glucose targets (63 – 100 mg/dL before meals and <140 mg/dL one hour after meals). Local teams also provided training in continuous glucose monitoring and insulin dose adjustment. After randomisation, participants attended in person or virtual (telephone or video) visits every 4 weeks, with additional contacts as clinically required. HbA1c was measured locally at 24 and 36 weeks, and follow-up questionnaires were completed at 34 – 36 weeks' gestation. Pump therapy, with insulin doses adjusted by their local teams to meet standard glucose targets (63 – 100 mg/dL before meals and <140 mg/dL one hour after meals). Local teams also provided training in continuous glucose monitoring and insulin dose adjustment. After randomisation, participants attended in person or virtual (telephone or video) visits every 4 weeks, with additional contacts as clinically required. HbA1c was measured locally at 24 and 36 weeks, and follow-up questionnaires were completed at 34 – 36 weeks' gestation. Pump therapy, with insulin doses adjusted by their local teams to meet standard glucose targets (63 – 100 mg/dL before meals and <140 mg/dL one hour after meals). Local teams also provided training in continuous glucose monitoring and insulin dose adjustment. After randomisation, participants attended in person or virtual (telephone or video) visits every 4 weeks, with additional contacts as clinically required.

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Number of participants	N = 124 Hybrid closed loop group n = 61 Standard care group n = 63
Duration of follow-up	From 16 weeks gestation until delivery.
Indirectness	Directly applicable.
Method of analysis	ITT
Additional comments	Statistical analyses followed an ITT approach and included all participants who had at least 96 hours of glucose sensor data from 16 weeks' gestation to delivery.

1

Study arms

Hybrid closed loop (N = 61)
An app hosted on an Android smartphone which runs the algorithm (CamAPS® FX, CamDiab Ltd, Cambridge, UK) that adjusts insulin delivery via an insulin pump (Dana Diabecare RS, Advanced Therapeutics UK Ltd., Warwick, UK) according to continuous glucose measurements (Dexcom G6).

Standard Care (N = 63)
CGM (Dexcom G6 CGM; Dexcom, Inc., San Diego, CA, USA) alongside standard care insulin delivery, which was either multiple daily injections or insulin pump therapy.

Characteristics

Arm-level characteristics

Characteristic	Hybrid closed loop (N = 61)	Standard Care (N = 63)
Mean age (SD) (years) Mean (SD)	32 (5)	30.2 (5.5)
Ethnicity - white No of events	n = 58; % = 95	n = 57; % = 90
Ethnicity - Black No of events	n = 1; % = 2	n = 3; % = 5
Ethnicity - Asian No of events	n = 1; % = 2	n = 2; % = 3
Ethnicity - Other/mixed race	n = 1; % = 2	n = 1; % = 2

Characteristic	Hybrid closed loop (N = 61)	Standard Care (N = 63)
No of events		
Diabetes complications No of events	n = 35; % = 57	n = 35; % = 56
Retinopathy No of events	n = 35; % = 57	n = 34; % = 54
Nephropathy No of events	n = 4; % = 7	n = 5; % = 8
Neuropathy No of events	n = 4; % = 7	n = 2; % = 3
Comorbidities - Previous diabetic ketoacidosis No of events	n = 1; % = 2	n = 10; % = 16
Comorbidities - Previous severe hypoglycaemia No of events	n = 4; % = 7	n = 5; % = 8
Comorbidities - Chronic hypertension No of events	n = 4; % = 7	n = 2; % = 3
Duration of diabetes (years) Mean (SD)	18 (8)	16 (7)

Characteristic	Hybrid closed loop (N = 61)	Standard Care (N = 63)
Week of gestation at recruitment (Median (IQR)) Median (IQR)	10.3 (8 to 11.7)	10 (8.4 to 11.3)
Pregnancy history - No previous births No of events	n = 21; % = 34	n = 38; % = 60
Pregnancy history - Previous pregnancy loss No of events	n = 21; % = 34	n = 20; % = 32
HbA1c (%) during early pregnancy (Mean (SD)) Mean (SD)	7.6 (1.1)	7.9 (1.3)
HbA1c (%) during early pregnancy - 6.0 to <7.0% No of events	n = 23; % = 38	n = 13; % = 21
HbA1c (%) during early pregnancy - 7.0 to <8.0% No of events	n = 21; % = 34	n = 24; % = 38
HbA1c (%) during early pregnancy - ≥8.0% No of events	n = 17; % = 28	n = 26; % = 41
Continuous glucose monitor No of events	n = 59; % = 97	n = 62; % = 98
Continuous glucose monitor - Abbott FreeStyle Libre	n = 43; % = 73	n = 47; % = 76

Characteristic	Hybrid closed loop (N = 61)	Standard Care (N = 63)
No of events		
Continuous glucose monitor - Dexcom No of events	n = 12; % = 20	n = 14; % = 23
Continuous glucose monitor - Medtronic No of events	n = 4; % = 7	n = 1; % = 2
Insulin delivery - Insulin pump No of events	n = 32; % = 52	n = 25; % = 40
Insulin delivery - Multiple daily injections No of events	n = 27; % = 44	n = 37; % = 59
Insulin delivery - Automated insulin delivery Participants using alternative hybrid closed loop systems were eligible. No of events	n = 2; % = 3	n = 1; % = 2
BMI Mean (SD)	27.9 (5.9)	26.9 (4.8)

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Outcomes

Maternal outcomes: percentage of time spent in the target glucose range

Outcome	Hybrid closed loop, N = 59	Standard Care, N = 61
>140 mg/dl - Time spent above target glucose range Mean (SD)	29.2 (10.6)	41.4 (13.2)
63–140 mg/dl – Overall time spent in target glucose range Mean (SD)	68.2 (10.5)	55.6 (12.5)
>180 mg/dl - Time spent above target glucose range Mean (SD)	10.8 (8.5)	17.3 (10.5)
Overnight time spent in range (63–140 mg/dl) (11 p.m. to 7 a.m.) Mean (SD)	70.8 (11.2)	56.7 (13.6)

Maternal outcomes: adverse events

Outcome	Hybrid closed loop, N = 59	Standard Care, N = 61
Severe hypoglycaemia No of events	n = 6	n = 5
Diabetic ketoacidosis No of events	n = 1	n = 1

Maternal outcomes: percentage of time spent in the >140 mg/dL glucose range per trimester

Outcome	Hybrid closed loop, N =	Standard Care, N =
First trimester Closed loop n = 40 Standard care n = 44 Mean (SD)	38 (15.5)	43.5 (13.9)
Second trimester Closed loop n = 60 Standard care n = 61 Mean (SD)	31.6 (10.6)	44.2 (13.4)
Third trimester Closed loop n = 57 Standard care n = 58 Mean (SD)	26.2 (9)	37.5 (13.3)

Maternal outcomes: percentage of time spent in the <63 mg/dL glucose range per trimester

Outcome	Hybrid closed loop, N =	Standard Care, N =
First trimester Closed loop n = 40 Standard care n = 44 Median (IQR)	2.2 (1.1 to 4)	2.1 (1.2 to 3.6)
Second trimester Closed loop n = 60 Standard care n = 61 Median (IQR)	2.2 (1.6 to 3.6)	2.1 (1.3 to 4.8)
Third trimester Closed loop n = 57 Standard care n = 58 Median (IQR)	2.2 (1.4 to 3.3)	2.7 (1.2 to 3.9)

Foetal/Neonatal outcomes: neonatal intensive care unit admissions longer than 24 hours

Outcome	Hybrid closed loop, N = 59	Standard Care, N = 60
Neonatal intensive care unit stay ≥1 day No of events	n = 13; % = 22	n = 15; % = 25

Foetal/Neonatal outcomes: adverse events

Outcome	Hybrid closed loop, N = 59	Standard Care, N = 60
Pregnancy loss at <20 wk No of events	n = 1; % = 1.6	n = 1; % = 1.6
Neonatal death No of events	n = 0	n = 1; % = 1.6
Hypoglycaemia treated with intravenous or oral glucose No of events	n = 26; % = 44	n = 25; % = 42
Preterm birth, at <37 wk Closed loop n = 60 Standard care n = 63 No of events	n = 27; % = 45	n = 14; % = 22
Birth weight - Small for gestational age No of events	n = 3 ; % = 5	n = 1 ; % = 2
Birth weight - Large for gestational age No of events	n = 23 ; % = 39	n = 30 ; % = 50

Outcome	Hybrid closed loop, N = 59	Standard Care, N = 60
Birth weight - Extremely large for gestational age No of events	n = 13 ; % = 22	n = 19 ; % = 32
Birth weight - Macrosomia >4.0 kg No of events	n = 4 ; % = 7	n = 9 ; % = 15

1 Device-related adverse events

Outcome	Hybrid closed loop, N = 61	Standard Care, N = 63
Hybrid closed loop system No of events	n = 7	n = NA
Continuous glucose monitor No of events	n = NA	n = 9

2 Maternal outcomes: Quality of Life outcomes

Outcome	Hybrid closed loop, N =	Standard Care, N =
Diabetes Distress Scale (DDS) Total; Closed loop n = 34 Standard care n = 43 Mean (SD)	1.5 (0.5)	1.5 (0.4)

3 Diabetes Distress Scale (DDS) - Polarity - Lower values are better

4

Critical Appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Moderate *(Randomisation appropriate & no information about concealment; baseline balanced; Deviations: open label but high adherence and objective outcomes; ITT analysis consistent Missing data: minimal; handled appropriately Outcome measurement: objective CGM with harmonised assessment Selective reporting: prespecified and complete)*
Overall bias and Directness	Overall Directness	Directly applicable

Lee, 2025

Bibliographic Reference	Lee, Tara T M; Collett, Corinne; Bergford, Simon; Hartnell, Sara; Scott, Eleanor M; Lindsay, Robert S; Hunt, Katharine F; McCance, David R; Reynolds, Rebecca M; Wilinska, Malgorzata E; Sibayan, Judy; Kollman, Craig; Hovorka, Roman; Murphy, Helen R; Automated insulin delivery during the first 6 months postpartum (AiDAPT): a prespecified extension study.; The lancet. Diabetes & endocrinology; 2025; vol. 13 (no. 3); 210-220

Study details

Secondary publication of another included study- see primary study for details	Extension of Lee et al. 2023 study.
Other publications associated with	Lee et al. 2023

this study included in review	
Trial name / registration number	ISRCTN56898625 (extension).
Study type	Randomised controlled trial (RCT)
Study location	United Kingdom
Study setting	As per Lee et al. 2023 study.
Study dates	November 2021 to May 2023
Sources of funding	As per Lee et al. 2023 study.
Inclusion criteria	Participants recruited to AiDAPT study after the postpartum protocol amendment (12 Nov 2021) were eligible if they were: • still pregnant, or • within 6 months postpartum, and • still using CGM or hybrid closed loop therapy from pregnancy.
Exclusion criteria	As per Lee et al. 2023 study.
Recruitment / selection of participants	As per Lee et al. 2023 study. Eligible participants who were still pregnant or within 6 months postpartum with available CGM data were approached after the postpartum protocol amendment. Those recruited after the protocol amendment were consented alongside AiDAPT trial enrolment. After delivery, all participants received usual clinical care. Participants remained in their originally randomised groups, although continuation into the postnatal phase required participants to opt in rather than undergo new randomisation. Six participants discontinued HCL did so for reasons unrelated to adverse events or poor glucose control, and baseline characteristics remained balanced between groups.

Intervention(s)	Participants used the HCL system as in the AiDAPT trial, comprising the CamAPS FX app on an Android smartphone, a Dana Diabecare RS insulin pump, and a Dexcom G6 CGM, all linked via Bluetooth (as per Lee et al. 2023 study). Postnatal pump and HCL settings were agreed with the diabetes antenatal team and documented before delivery. Women were advised to switch to the recommended starting postpartum settings immediately before caesarean section or once the placenta was delivered. Initial postpartum settings included a glucose target of 6.0 mmol/L and insulin to carbohydrate ratios of 1:12g – 1:15g, depending on infant feeding status. While in hospital, participants adjusted their glucose targets, insulin to carbohydrate ratios, and premeal boluses to meet CGM time in range goals (70% time between 3·9 – 10·0 mmol/L and <5% time below 3·9 mmol/L), and were encouraged to use boost and ease off features for 2 – 4 hours when other setting adjustments were not acting quickly enough to address rising or falling glucose levels. They continued self titration after discharge, with access to their usual NHS diabetes support services for guidance.
Population subgroups	Subgroup analyses by breastfeeding status - exclusive breast feeding and exclusive formula feeding.
Comparator	Participants continued their usual insulin therapy, either multiple daily injections or pump therapy, with support from their local clinical teams. Postpartum, insulin doses were adjusted to meet CGM targets (70% time between 3·9 – 10·0 mmol/L [70–180 mg/dL]). Follow up by telephone reviews at 8 - 12 weeks and 24 weeks postpartum assessed CGM data, insulin dosing and delivery method, safety outcomes, and infant feeding. Diabetes management was reviewed and dosing adjusted as needed.
Number of participants	N = 57 Hybrid closed loop group n = 28 Standard care group n = 29
Duration of follow-up	6 months postpartum.
Indirectness	Directly applicable.
Additional comments	Per protocol analyses was used.

1

Study arms

Hybrid closed loop (N = 28)
CamAPS FX app on an Android smartphone, a Dana Diabecare RS insulin pump, and a Dexcom G6 CGM, all linked via Bluetooth.

Standard Care (N = 29)
CGM alongside standard care insulin delivery, which was either multiple daily injections or insulin pump therapy.

Characteristics

Arm-level characteristics

Characteristic	Hybrid closed loop (N = 28)	Standard Care (N = 29)
Mean age (SD) years Mean (SD)	32 (4)	30 (4)
Ethnicity - White No of events	n = 25; % = 89	n = 25; % = 86
Ethnicity - Asian No of events	n = 1; % = 4	n = 1; % = 3
Ethnicity - Black or African No of events	n = 1; % = 4	n = 2; % = 7
Ethnicity - Multiple races	n = 1; % = 4	n = 1; % = 3

Characteristic	Hybrid closed loop (N = 28)	Standard Care (N = 29)
No of events		
Duration of diabetes Years Mean (SD)	17 (8)	16 (7)
Diabetes complications No of events	n = 15; % = 54	n = 17; % = 59
Pregnancy history - No previous births No of events	n = 7; % = 25	n = 16; % = 55
Early pregnancy insulin modality - Pump No of events	n = 15; % = 54	n = 11; % = 38
Early pregnancy insulin modality - Multiple dose injections No of events	n = 12; % = 43	n = 17; % = 59
Early pregnancy insulin modality - Automated insulin delivery Participants using alternative hybrid closed loop systems were eligible No of events	n = 1; % = 4	n = 1; % = 3
Adverse events in previous 12 months pre-pregnancy - Pre-pregnancy DKA, participants No of events	n = 0	n = 3; % = 10

Characteristic	Hybrid closed loop (N = 28)	Standard Care (N = 29)
Adverse events in previous 12 months pre-pregnancy - Previous severe hypoglycaemia Hypoglycaemia was considered severe if the event required third-party assistance No of events	n = 1; % = 4	n = 2; % = 7
Number of adverse events during pregnancy - Severe hypoglycaemia during pregnancy Hypoglycaemia was considered severe if the event required third-party assistance. No of events	n = 5	n = 1
Number of adverse events during pregnancy - DKA during pregnancy No of events	n = 1	n = 1
BMI Mean (SD)	28.6 (4.5)	25.8 (3.9)
HbA1c (%) Mean (SD)	7.6 (1.1)	7.6 (0.9)

Outcomes

Maternal outcomes: percentage of time spent in the target glucose range, measured from delivery until 24 weeks postpartum

Outcome	Hybrid closed loop, N = 28	Standard Care, N = 29
3·9–10·0 mmol/L	72 (12)	54 (17)

Outcome	Hybrid closed loop, N = 28	Standard Care, N = 29
Mean (SD)		
3·9–10·0 mmol/L - From 0 to 3 months Hybrid closed loop n = 26/28 Standard care n = 27/29 Mean (SD)	75 (12)	57 (16)
3·9–10·0 mmol/L - 3 to 6 months Hybrid closed loop n = 25/28 Standard care n = 24/29 Mean (SD)	70 (9)	50 (19)
>10·0 mmol/L - Time spent above target glucose range Mean (SD)	26 (12)	42 (18)
>10·0 mmol/L - From 0 to 3 months Hybrid closed loop n = 26/28 Standard care n = 27/29 Mean (SD)	22 (13)	39 (17)
>10·0 mmol/L - 3 to 6 months Hybrid closed loop n = 25/28 Standard care n = 24/29 Mean (SD)	28 (10)	47 (21)

Maternal outcomes: adverse events

Outcome	Hybrid closed loop, N = 28	Standard Care, N = 29
Severe hypoglycaemia No of events	n = 0	n = 1

Outcome	Hybrid closed loop, N = 28	Standard Care, N = 29
Diabetic ketoacidosis No of events	n = 0	n = 0

1 Postnatal outcomes by infant feeding method

Outcome	Hybrid closed loop, N = 28	Standard Care, N = 29
3·9–10·0 mmol/L - 3 to 6 months Exclusive breastfeeding Hybrid closed loop n = 8 Standard care n = 10 Mean (SD)	69 (11)	60 (16)
3·9–10·0 mmol/L - 3 to 6 months Exclusive formula feeding Hybrid closed loop n = 16 Standard care n = 11 Mean (SD)	69 (8)	44 (20)
>10·0 mmol/L - 3 to 6 months Exclusive breastfeeding Hybrid closed loop n = 8 Standard care n = 10 Mean (SD)	28 (11)	35 (17)

Outcome	Hybrid closed loop, N = 28	Standard Care, N = 29
>10·0 mmol/L - 3 to 6 months Exclusive formula feeding Hybrid closed loop n = 8 Standard care n = 10 Mean (SD)	29 (9)	53 (21)

Device-related adverse events

Outcome	Hybrid closed loop, N = 28	Standard Care, N = 29
Hybrid closed loop system No of events	n = 1	n = 0
Continuous glucose monitor No of events	n = 0	n = 0

Critical Appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Moderate *(Participants randomised at pregnancy phase were carried forward during intrapartum and postnatal periods. They were offered to change their intervention and were only excluded from final analysis if they decided to change intervention. The randomisation was lost; but baseline data between arms is balanced; ITT consistent Missing data: minimal; handled appropriately; Outcome measurement: objective CGM with harmonised assessment Selective reporting: prespecified and complete)*

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

1

Appendix E - Forest plots

Preconception period

No evidence was found for the preconception period when pregnancy-specific hybrid closed loop system was compared with standard insulin therapy.

During pregnancy

Maternal outcomes during pregnancy

Figure 2 Overall % time spent in the pregnancy-specific target glucose range of 3.5-7.8mmol/L during pregnancy when hybrid close loop system is compared with standard insulin therapy (higher is better)

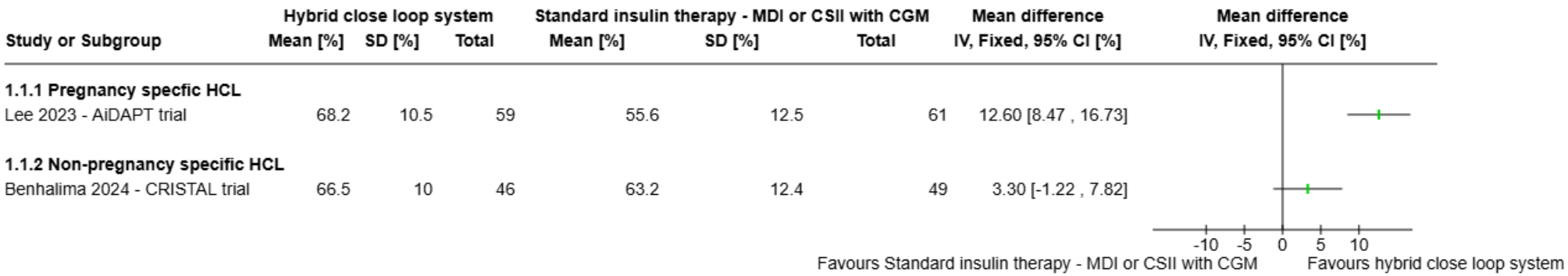


Figure 2 % time spent above the pregnancy-specific target glucose range of 7.8mmol/L during pregnancy period when hybrid close loop system is compared with standard insulin therapy (lower is better)

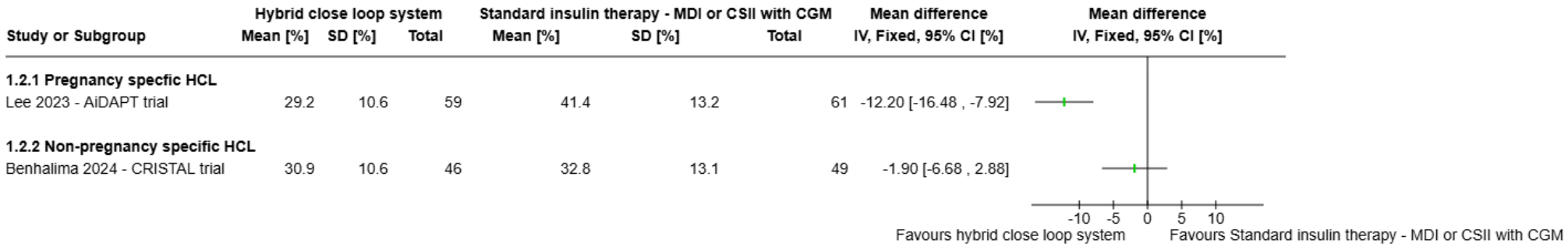


Figure 3 % time spent below the pregnancy-specific target glucose range of 3.5 mmol/L during pregnancy period when hybrid close loop system is compared with standard insulin therapy (lower is better)

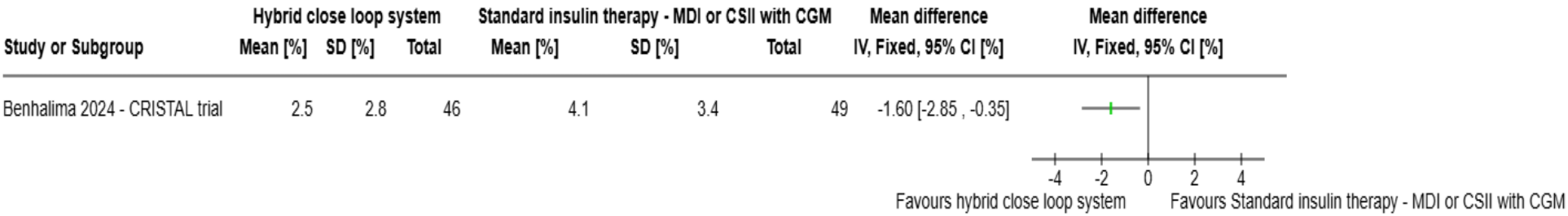
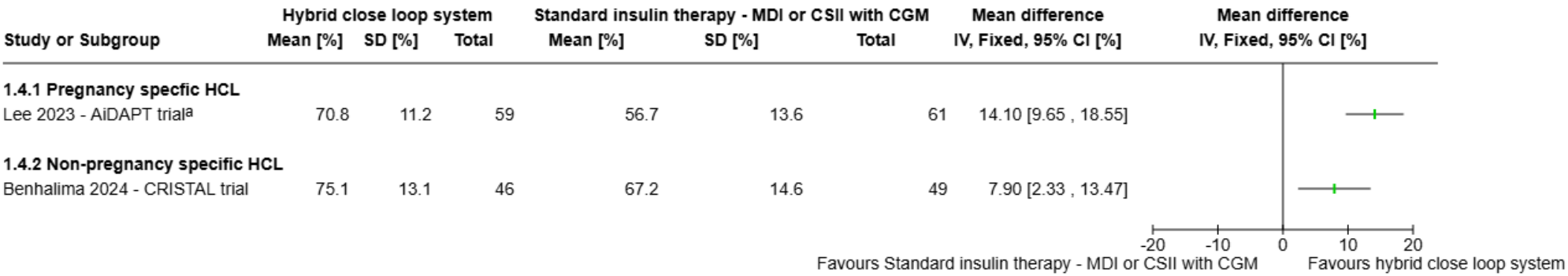


Figure 4 Overnight % time spent in the pregnancy-specific target glucose range of 3.5-7.8mmol/L during pregnancy period when hybrid close loop system is compared with standard insulin therapy (higher is better)



Footnotes

[a]11 p.m. to 7 a.m

Figure 5 Maternal Severe hypoglycaemia during pregnancy when hybrid close loop system is compared with standard insulin therapy (lower is better)

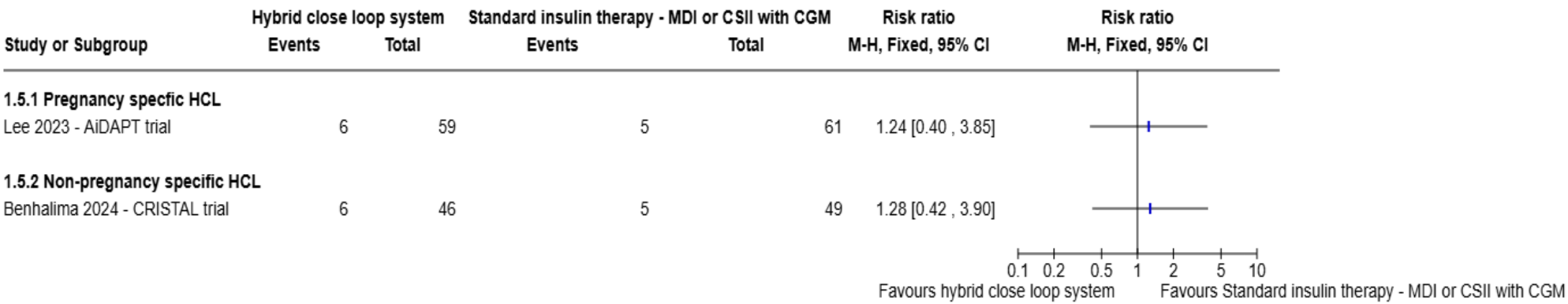


Figure 6 Diabetic ketoacidosis during pregnancy when hybrid close loop system is compared with standard insulin therapy (lower is better)

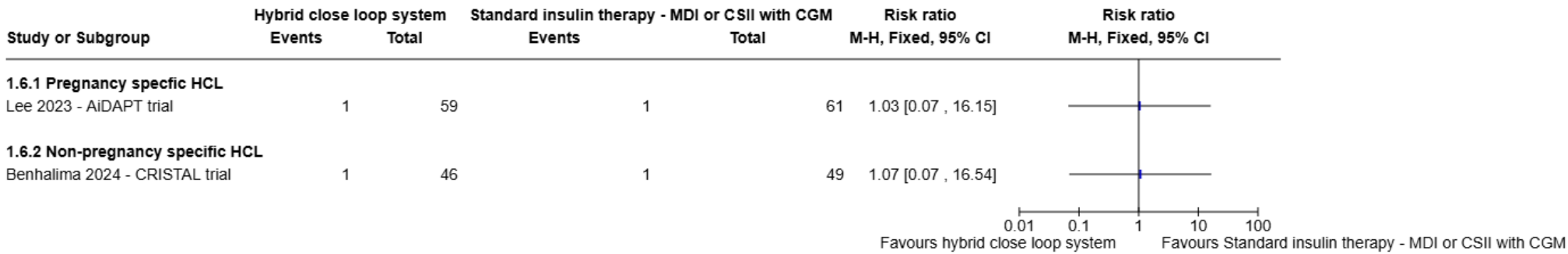
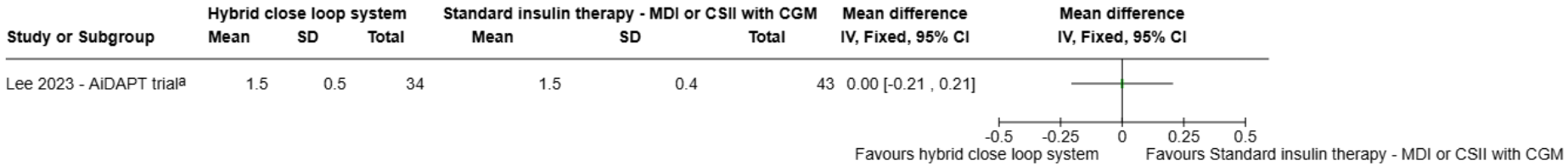


Figure 7 Quality of Life outcomes assessed by Diabetes Distress Scale overall scores during pregnancy when pregnancy-specific hybrid close loop system is compared with standard insulin therapy (lower is better)



Footnotes

[a]Each item is rated between 1-6, average indicates overall scores. Overall rating is <2, 2-2.9 or >3

Neonatal outcomes during pregnancy

Figure 8 Neonatal intensive care unit admissions longer than 24 hours when hybrid close loop system is compared with standard insulin therapy (lower is better)

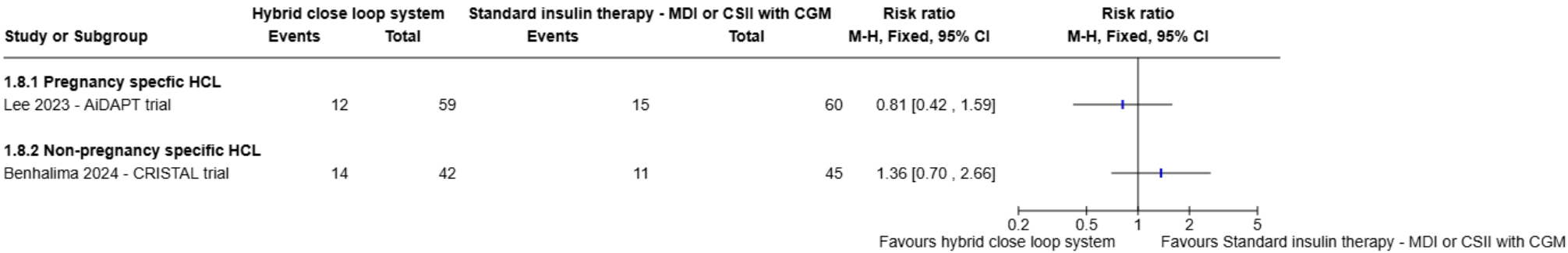


Figure 9 Mortality - Pregnancy loss (miscarriage, defined as <24weeks) when hybrid close loop system is compared with standard insulin therapy (lower is better)

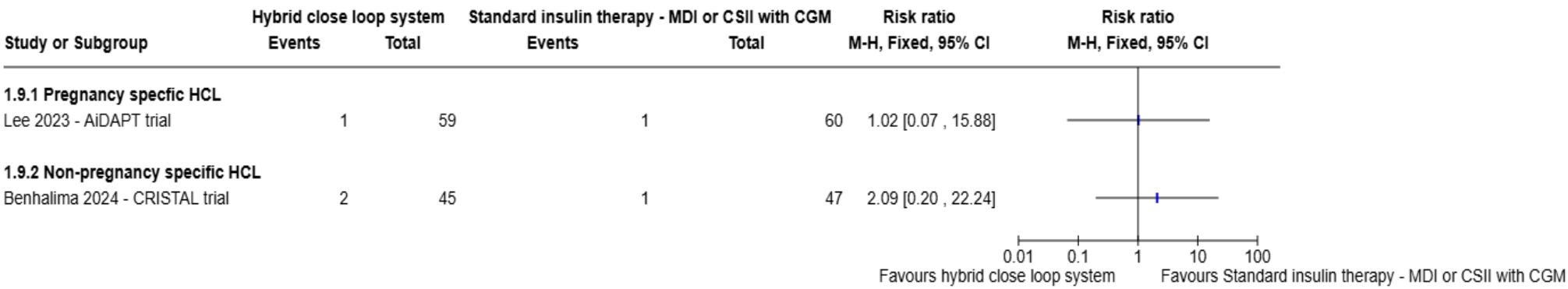


Figure 10 Mortality – stillbirth, ≥24 weeks when hybrid close loop system is compared with standard insulin therapy (lower is better)

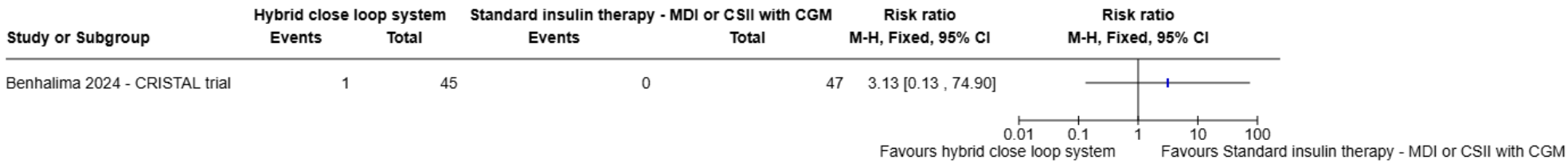


Figure 11 Mortality - neonatal loss, up to 28 days when hybrid close loop system is compared with standard insulin therapy (lower is better)

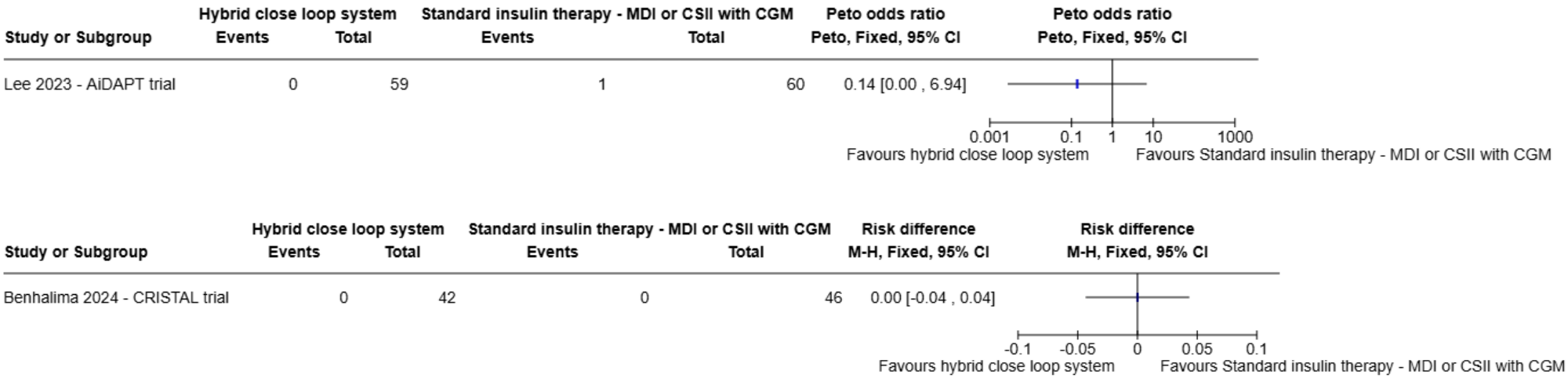


Figure 12 Neonatal hypoglycaemia when hybrid close loop system is compared with standard insulin therapy (lower is better)

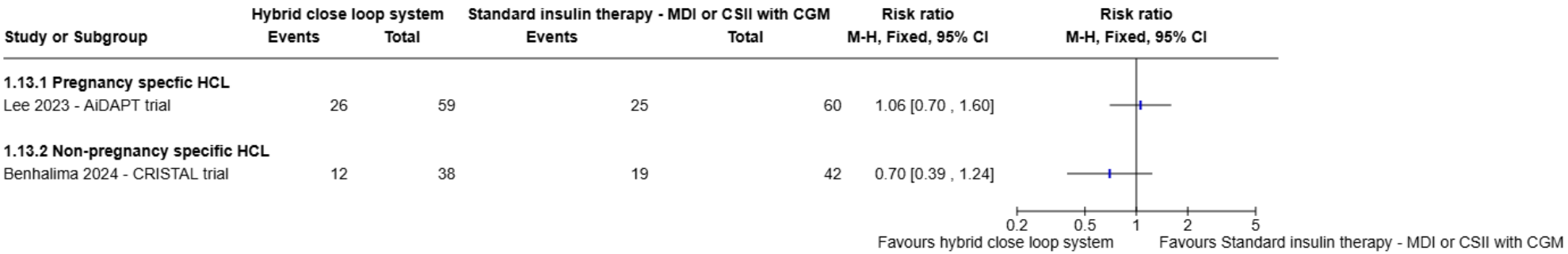


Figure 13 Preterm birth when hybrid close loop system is compared with standard insulin therapy (lower is better)

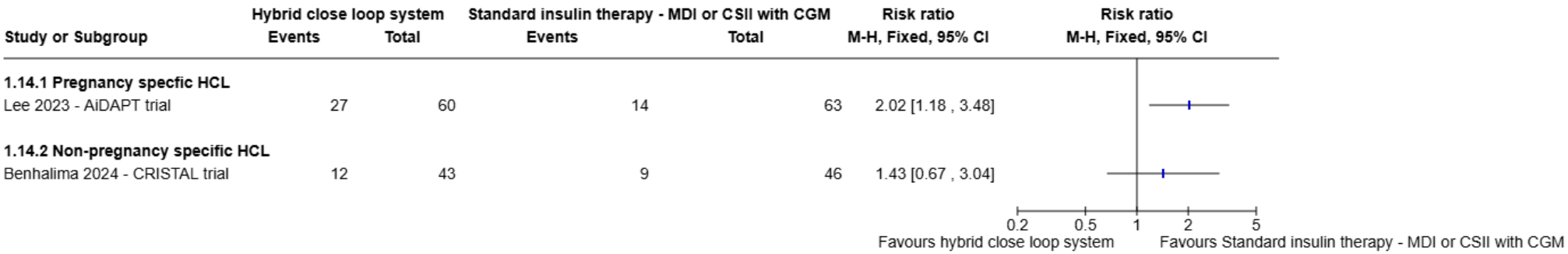


Figure 14 Large for gestational age when hybrid close loop system is compared with standard insulin therapy (lower is better)

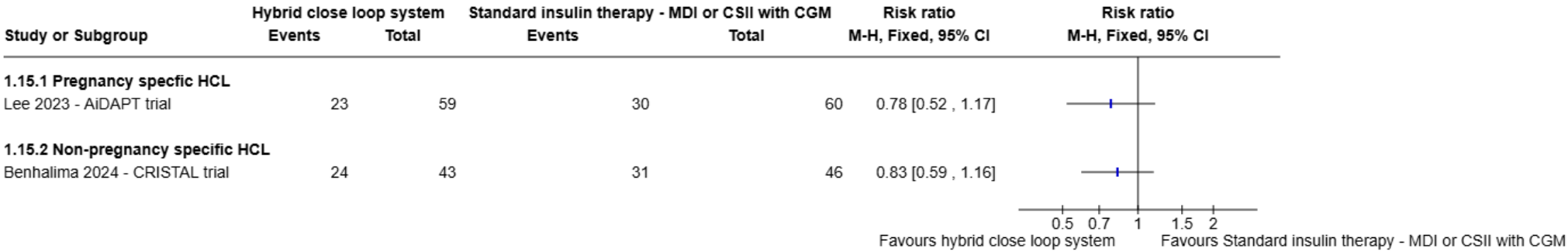
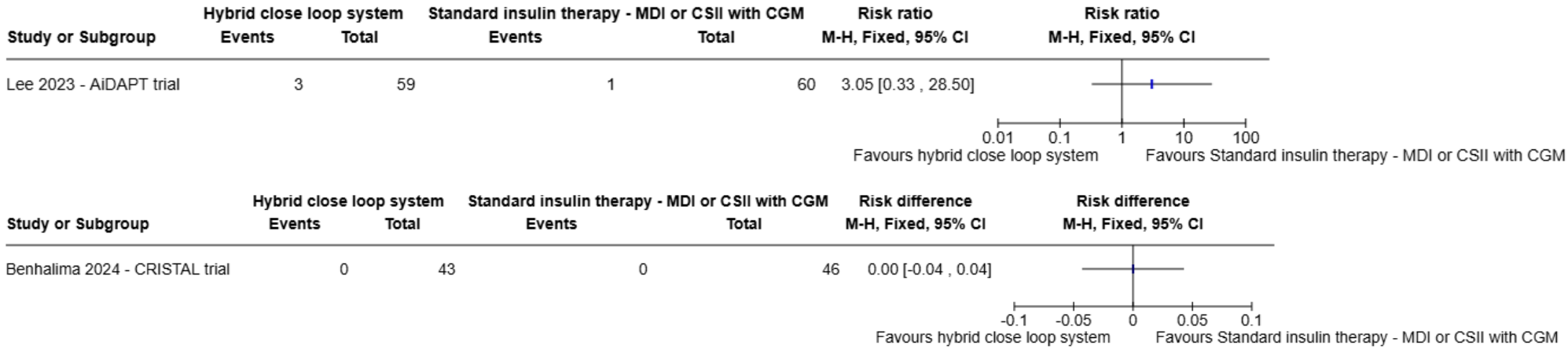


Figure 15 Small for gestational age when hybrid close loop system is compared with standard insulin therapy (lower is better)



Intrapartum period (defined as day of delivery)

Maternal outcomes

Figure 16 Overall % time spent in the pregnancy specific target glucose range of 3.5-7.8mmol/L during intrapartum period when non-pregnancy specific hybrid close loop system is compared with standard insulin therapy (higher is better)

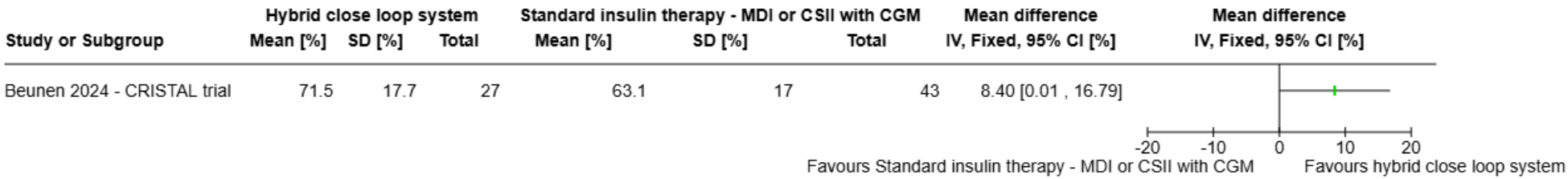


Figure 17 % time spent above pregnancy specific target glucose range of 7.8 mmol/L during intrapartum period when non-pregnancy specific hybrid close loop system is compared with standard insulin therapy (lower is better)

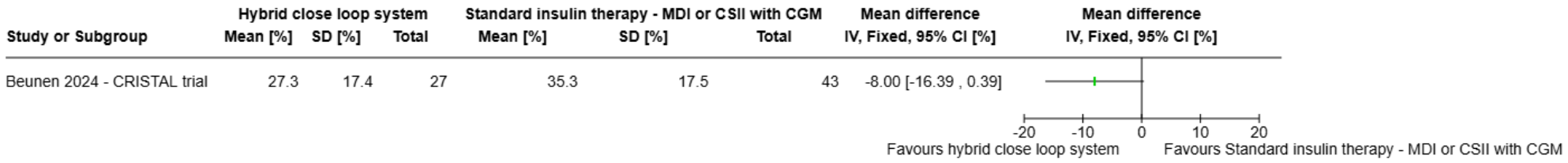


Figure 18 % time spent below the pregnancy-specific target glucose range of 3.5 mmol/L during intrapartum period when non-pregnancy specific hybrid close loop system is compared with standard insulin therapy (lower is better)

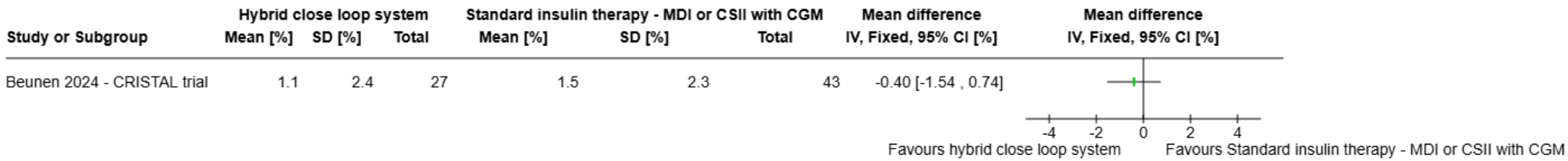
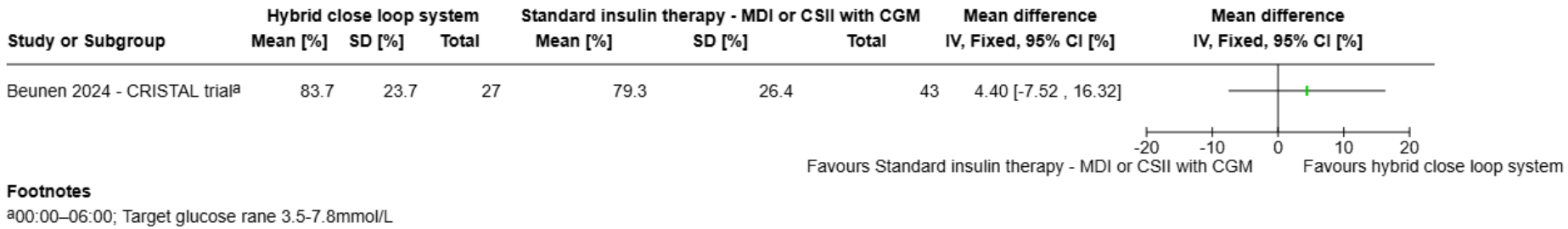


Figure 19 Overnight % time spent in the pregnancy-specific target glucose range of 3.5-7.8mmol/L during intrapartum period when non-pregnancy specific hybrid close loop system is compared with standard insulin therapy (higher is better)



Footnotes

[a]00:00–06:00; Target glucose rane 3.5-7.8mmol/L

Postnatal period

Maternal outcomes

Figure 20 Overall % time spent in the specific target glucose range of 3.9-10.0 mmol/L during postnatal period when hybrid close loop system is compared with standard insulin therapy (higher is better)

Study or Subgroup	Hybrid close loop system Mean [%]	SD [%]	Total	Standard insulin therapy - MDI or CSII with CGM Mean [%]	SD [%]	Total	Mean difference IV, Fixed, 95% CI [%]
3.1.1 Pregnancy specific HCL							
Lee 2025 - AiDAPT trial	72	12	28	54	17	29	18.00 [10.38 , 25.62]
3.1.2 Non-pregnancy specific HCL							
Beunen 2024 - Postnatal CRISTAL trial	86.8	6.7	37	83.8	8.1	34	3.00 [-0.47 , 6.47]

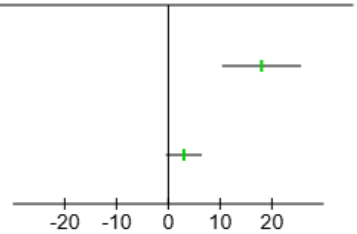
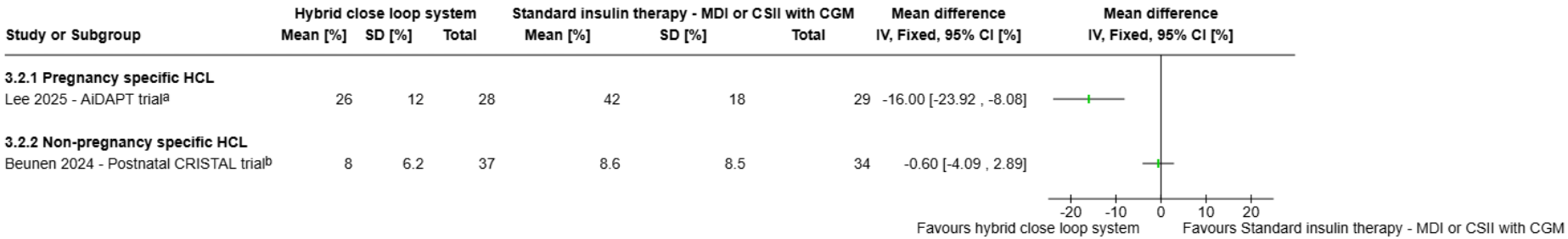


Figure 21 % time spent above specific target glucose range of 10.0 mmol/L during postnatal period when hybrid close loop system is compared with standard insulin therapy (lower is better)



Footnotes

[a]>10·0 mmol/L

[b]>10.0mmol/L

Figure 22 % time spent below specific target glucose range of 3.9 mmol/L during postnatal period when non-pregnancy specific hybrid close loop system is compared with standard insulin therapy (lower is better)

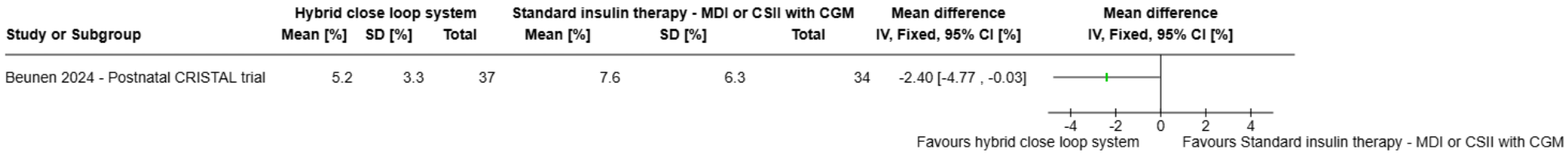
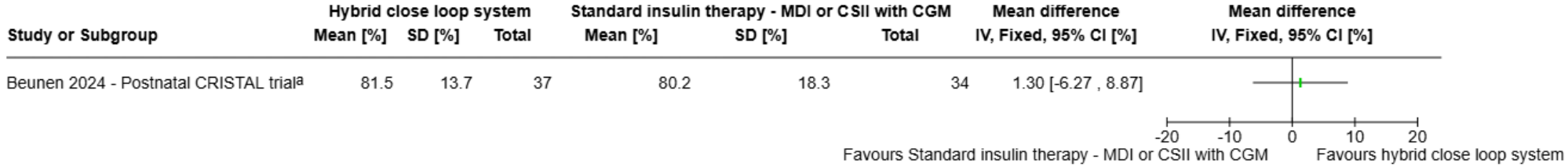


Figure 23 Overnight % time spent in the specific target glucose range during postnatal period when non-pregnancy specific hybrid close loop system is compared with standard insulin therapy (higher is better)



Footnotes

[a]00:00–06:00; 3.5-7.8mmol/L

Figure 24 Maternal severe hypoglycaemia during postnatal period when pregnancy-specific hybrid close loop system is compared with standard insulin therapy (lower is better)

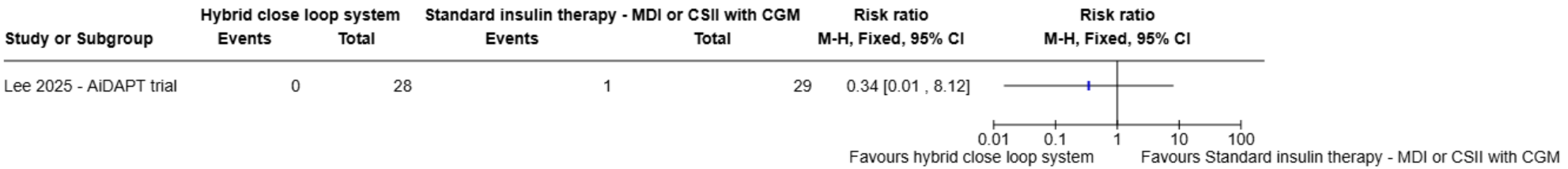


Figure 25 Diabetic ketoacidosis during postnatal period when pregnancy-specific hybrid close loop system is compared with standard insulin therapy (lower is better)

Appendix F - GRADE summary

Table 1 Effectiveness evidence summary: Hybrid closed loop system vs Multiple daily injections or continuous subcutaneous insulin infusion with continuous glucose monitoring during pregnancy period.

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Absolute effects	
				Risk with standard insulin therapy - MDI or CSII with CGM	Risk difference with hybrid close loop system
Overall % time spent in the pregnancy-specific target glucose range - **Pregnancy specific HCL**	120 (1 RCT)[a]	Low[b,c] **EV. OF BENEFIT**	-	The mean overall % time spent in the pregnancy-specific target glucose range - Pregnancy specific HCL was **0** %	MD **12.6 % higher** (8.47 higher to 16.37 higher)
Overall % time spent in the pregnancy-specific target glucose range - **Non-pregnancy specific HCL**	95 (1 RCT)[d]	Low[c,e] **UN. EFFECT**	-	The mean overall % time spent in the pregnancy-specific target glucose range - Non-pregnancy specific HCL was **0** %	MD **3.3 % higher** (1.22 lower to 7.82 higher)
% time spent above the pregnancy-specific target glucose range during pregnancy period - **Pregnancy specific HCL**	120 (1 RCT)[a]	Low[b,c] **EV. OF BENEFIT**	-	The mean % time spent above the pregnancy-specific target glucose range during pregnancy period - Pregnancy specific HCL was **0** %	MD **12.2 % lower** (16.48 lower to 7.92 lower)

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Absolute effects	
				Risk with standard insulin therapy - MDI or CSII with CGM	Risk difference with hybrid close loop system
% time spent above the pregnancy-specific target glucose range during pregnancy period - **Non-pregnancy specific HCL**	95 (1 RCT)[d]	Low[c,e] **UN. EFFECT**	-	The mean % time spent above the pregnancy-specific target glucose range during pregnancy period - Non-pregnancy specific HCL was **0** %	MD **1.9 % lower** (6.68 lower to 2.88 higher)
% time spent below the pregnancy-specific target glucose during pregnancy period - **non-pregnancy-specific HCL**	95 (1 RCT)[d]	Moderate[c] **EV. OF NO EFFECT**	-	The mean % time spent below the pregnancy-specific target glucose during pregnancy period was **0** %	MD **1.6 % lower** (2.85 lower to 0.35 lower)
Overnight % time spent in the pregnancy-specific target glucose during pregnancy period - **Pregnancy specific HCL**	120 (1 RCT)[a]	Low[b,c] **EV. OF BENEFIT**	-	The mean overnight % time spent in the pregnancy-specific target glucose during pregnancy period - Pregnancy specific HCL was **0** %	MD **14.1 % higher** (9.65 higher to 18.55 higher)
Overnight % time spent in the pregnancy-specific target glucose during pregnancy period - **Non-pregnancy specific HCL**	95 (1 RCT)[d]	Low[c,e] **EV. OF BENEFIT**	-	The mean overnight % time spent in the pregnancy-specific target glucose during pregnancy period - Non-pregnancy specific HCL was **0** %	MD **7.9 % higher** (2.33 higher to 13.47 higher)

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Absolute effects	
				Risk with standard insulin therapy - MDI or CSII with CGM	Risk difference with hybrid close loop system
Maternal Severe hypoglycaemia - **Pregnancy specific HCL**	120 (1 RCT)[a]	Very low[b,c,f] **UN. EFFECT**	**RR 1.24** (0.40 to 3.85)	82 per 1,000	**20 more per 1,000** (49 fewer to 234 more)
Maternal Severe hypoglycaemia - **Non-pregnancy specific HCL**	95 (1 RCT)[d]	Very low[c,f] **UN. EFFECT**	**RR 1.28** (0.42 to 3.90)	102 per 1,000	**29 more per 1,000** (59 fewer to 296 more)
Diabetic ketoacidosis - **Pregnancy specific HCL**	120 (1 RCT)[a]	Very low[b,c,f] **UN. EFFECT**	**RR 1.03** (0.07 to 16.15)	16 per 1,000	**0 fewer per 1,000** (15 fewer to 248 more)
Diabetic ketoacidosis **- Non-pregnancy specific HCL**	95 (1 RCT)[d]	Very low[c,f] **UN. EFFECT**	**RR 1.07** (0.07 to 16.54)	20 per 1,000	**1 more per 1,000** (19 fewer to 317 more)
Quality of Life outcomes - Diabetes Distress Scale – **Pregnancy-specific HCL**	77 (1 RCT)[a]	Low[b,c] **Ev. OF NO EFFECT**	-	The mean quality of Life outcomes - Diabetes Distress Scale was **0**	MD **0** (0.21 lower to 0.21 higher)

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Absolute effects	
				Risk with standard insulin therapy - MDI or CSII with CGM	Risk difference with hybrid close loop system
Neonatal intensive care unit admissions longer than 24 hours - **Pregnancy specific HCL**	119 (1 RCT)[a]	Very low[b,c,f] UN. EFFECT	**RR 0.81** (0.42 to 1.59)	250 per 1,000	**47 fewer per 1,000** (145 fewer to 148 more)
Neonatal intensive care unit admissions longer than 24 hours - **Non-pregnancy specific HCL**	87 (1 RCT)[d]	Very low[c,f] UN. EFFECT	**RR 1.36** (0.70 to 2.66)	244 per 1,000	**88 more per 1,000** (73 fewer to 406 more)
Mortality - Pregnancy loss (miscarriage, defined as <24weeks) - **Pregnancy specific HCL**	119 (1 RCT)[a]	Very low[b,c,f] UN. EFFECT	**RR 1.02** (0.07 to 15.88)	17 per 1,000	**0 fewer per 1,000** (15 fewer to 248 more)
Mortality - Pregnancy loss (miscarriage, defined as <24weeks) - **Non-pregnancy specific HCL**	92 (1 RCT)[d]	Very low[c,f] UN. EFFECT	**RR 2.09** (0.20 to 22.24)	21 per 1,000	**23 more per 1,000** (17 fewer to 452 more)
Mortality - stillbirth, ≥24 weeks – **Non-pregnancy-specific HCL**	92 (1 RCT)[d]	Very low[c,f] UN. EFFECT	**RR 3.13** (0.13 to 74.90)	0 per 1,000	**0 fewer per 1,000** (0 fewer to 0 fewer)

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Absolute effects	
				Risk with standard insulin therapy - MDI or CSII with CGM	Risk difference with hybrid close loop system
Mortality - neonatal loss, up to 28 days **- Pregnancy specific HCL**	119 (1 RCT)[a]	Very low[b,c,g] UN. EFFECT	**POR 0.14** (0.00 to 6.94)	17 per 1,000	**14 fewer per 1,000** (17 fewer to 99 more)
Mortality - neonatal loss, up to 28 days - **Non-pregnancy specific HCL**	88 (1 RCT)[d]	Very low[c,h] UN. EFFECT	**Risk Difference 0.00** (-0.04 to 0.04)	0 per 1,000	**0 fewer per 1,000** (0 fewer to 0 fewer)
Neonatal hypoglycaemia- **Pregnancy specific HCL**	119 (1 RCT)[a]	Very low[b,c,i] UN. EFFECT	**RR 1.06** (0.70 to 1.60)	417 per 1,000	**25 more per 1,000** (125 fewer to 250 more)
Neonatal hypoglycaemia - **Non-pregnancy specific HCL**	80 (1 RCT)[d]	Very low[c,f] UN. EFFECT	**RR 0.70** (0.39 to 1.24)	452 per 1,000	**136 fewer per 1,000** (276 fewer to 109 more)
Preterm birth **- Pregnancy specific HCL**	123 (1 RCT)[a]	Very low[b,c,f] EV. OF DISBENEFIT	**RR 2.03** (1.18 to 3.48)	222 per 1,000	**229 more per 1,000** (40 more to 551 more)

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Absolute effects	
				Risk with standard insulin therapy - MDI or CSII with CGM	Risk difference with hybrid close loop system
Preterm birth **- Non-pregnancy specific HCL**	89 (1 RCT)[d]	Very low[c,f] **EV. OF DISBENEFIT**	**RR 1.43** (0.67 to 3.04)	196 per 1,000	**84 more per 1,000** (65 fewer to 399 more)
Large for gestational age - **Pregnancy specific HCL**	119 (1 RCT)[a]	Very low[b,c,j] **UN. EFFECT**	**RR 0.78** (0.52 to 1.17)	500 per 1,000	**110 fewer per 1,000** (240 fewer to 85 more)
Large for gestational age - **Non-pregnancy specific HCL**	89 (1 RCT)[d]	Low[c,k] **UN. EFFECT**	**RR 0.83** (0.59 to 1.16)	674 per 1,000	**115 fewer per 1,000** (276 fewer to 108 more)
Small for gestational age - **Pregnancy specific HCL**	119 (1 RCT)[a]	Very low[b,c,f] **UN. EFFECT**	**RR 3.05** (0.33 to 28.50)	17 per 1,000	**34 more per 1,000** (11 fewer to 458 more)
Small for gestational age - **Non-pregnancy specific HCL**	89 (1 RCT)[d]	Very low[c,l] **EV. OF NO EFFECT**	**Risk Difference 0.00** (-0.04 to 0.04)	0 per 1,000	**0 fewer per 1,000** (0 fewer to 0 fewer)

Abbreviation: CI: confidence interval; **MD:** mean difference; **RR:** risk ratio **EV. OF BENEFIT:** evidence of benefit; **UN. Effect:** uncertain effect; **EV. OF NO EFFECT:** evidence of no effect

Explanations

a) Lee 2023
b) Serious risk of bias in the evidence contributing to the outcome. The evidence came from a study at moderate risk of bias as per RoB 2.0 tool
c) Single study- downgraded once for inconsistency, as single study outcomes may otherwise receive favorable ratings for inconsistency by default.
d) Benhalima 2024
e) Serious imprecision because 95% CI crosses 1 decision making threshold (5%)
f) Very serious imprecision because the ratio of the upper to lower boundary of the confidence interval is ≥3 for risk ratio
g) Serious imprecision because N<OIS (1,444)
h) Very serious imprecision because N<30% of OIS (774)
i) Serious imprecision because N<OIS (13,314)
j) Serious imprecision because N<OIS (630)
k) Serious imprecision because N<OIS (546)
l) Very serious imprecision because N<30% of OIS (774)

Table 2 Effectiveness evidence summary: Hybrid closed loop system vs Multiple daily injections or continuous subcutaneous insulin infusion with continuous glucose monitoring during intrapartum period.

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with standard insulin therapy - MDI or CSII with CGM	Risk difference with hybrid close loop system
Overall % time spent in the pregnancy-specific target glucose range – **non-pregnancy-specific HCL**	70 (1 RCT)[a]	Very low[b,c,d] UN. EFFECT	-	The mean overall % time spent in the pregnancy-specific target glucose range was **0** %	MD **8.4 higher** (0.01 higher to 16.79 higher)
% time spent above the pregnancy-specific target glucose range during intrapartum period - **non-pregnancy-specific HCL**	70 (1 RCT)[a]	Very low[b,c,d] UN. EFFECT	-	The mean % time spent above the pregnancy-specific target glucose range during intrapartum period was **0** %	MD **8 lower** (16.39 lower to 0.39 higher)
% time spent below the specific target glucose during intrapartum period - **non-pregnancy-specific HCL**	70 (1 RCT)[a]	Low[b,c] UN. EFFECT	-	The mean % time spent below the specific target glucose during intrapartum period was **0** %	MD **0.4 lower** (1.54 lower to 0.74 higher)
Overnight % time spent in the pregnancy-specific target glucose during intrapartum period - **non-pregnancy-specific HCL**	70 (1 RCT)[a]	Very low[b,c,e] UN. EFFECT	-	The mean overnight % time spent in the pregnancy-specific target glucose during intrapartum period was **0** %	MD **4.4 % higher** (7.52 lower to 16.32 higher)

Abbreviation: CI: confidence interval; **MD:** mean difference; **RR:** risk ratio; **UN. Effect:** uncertain effect

Explanations

a) Beunen 2024

b) Serious risk of bias in the evidence contributing to the outcome. The evidence came from a study at moderate risk of bias as per RoB 2.0 tool

c) Single study- downgraded once for inconsistency, as single study outcomes may otherwise receive favourable ratings for inconsistency by default.

d) Serious imprecision because 95%CI crosses 1 MID (5%)

e) Very serious imprecision because 95%CI crosses 2 MIDs (5%)

Table 3 Effectiveness evidence summary: Hybrid closed loop system vs Multiple daily injections or continuous subcutaneous insulin infusion with continuous glucose monitoring during postnatal period.

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Absolute effects	
				Risk with standard insulin therapy - MDI or CSII with CGM	Risk difference with hybrid close loop system
Overall % time spent in the non-pregnancy specific target glucose range - **Pregnancy specific HCL**	57 (1 RCT)[a]	Low[b,c] **EV. OF BENEFIT**	-	The mean overall % time spent in the non-pregnancy specific target glucose range - Pregnancy specific HCL was **0** %	MD **18 % higher** (10.38 higher to 25.62 higher)
Overall % time spent in the non-pregnancy specific target glucose range - **Non-pregnancy specific HCL**	71 (1 RCT)[d]	Very low[b,c,e] **UN. EFFECT**	-	The mean overall % time spent in the non-pregnancy specific target glucose range - Non-pregnancy specific HCL was **0** %	MD **3 % higher** (0.47 lower to 6.47 higher)
% time spent above the specific target glucose during postnatal period - **Pregnancy specific HCL**	57 (1 RCT)[a]	Low[b,c] **EV. OF BENEFIT**	-	The mean % time spent above the specific target glucose during postnatal period - Pregnancy specific HCL was **0** %	MD **16 % lower** (23.92 lower to 8.08 lower)
% time spent above the specific target glucose during postnatal period - **Non-pregnancy specific HCL**	71 (1 RCT)[d]	Low[b,c] **UN. EFFECT**	-	The mean % time spent above the specific target glucose during postnatal period - Non-pregnancy specific HCL was **0** %	MD **0.6 % lower** (4.09 lower to 2.89 higher)

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Absolute effects	
				Risk with standard insulin therapy - MDI or CSII with CGM	**Risk difference with hybrid close loop system**
% time spent below specific target glucose during postnatal period - **Non-pregnancy specific HCL**	71 (1 RCT)[d]	Low[b,c] **UN. EFFECT**	-	The mean % time spent below specific target glucose during postnatal period was **0** %	MD **2.4 % lower** (4.77 lower to 0.03 lower)
Overnight % time spent in the specific target glucose during postnatal period - **Non-pregnancy specific HCL**	71 (1 RCT)[d]	Very low[b,c,f] **UN. EFFECT**	-	The mean overnight % time spent in the specific target glucose during postnatal period was **0** %	MD **1.3 % higher** (6.27 lower to 8.87 higher)
Maternal Severe hypoglycaemia- **Pregnancy-specific HCL**	57 (1 RCT)[a]	Very low[b,c,g] **UN. EFFECT**	**RR 0.34** (0.01 to 8.12)	34 per 1,000	**23 fewer per 1,000** (34 fewer to 246 more)
Diabetic ketoacidosis- **Pregnancy-specific HCL**	57 (1 RCT)[a]	Very low[b,c,h] **EV. OF NO EFFECT**	**Risk Difference 0.00** (-0.07 to 0.07)	0 per 1,000	**0 fewer per 1,000** (0 fewer to 0 fewer)

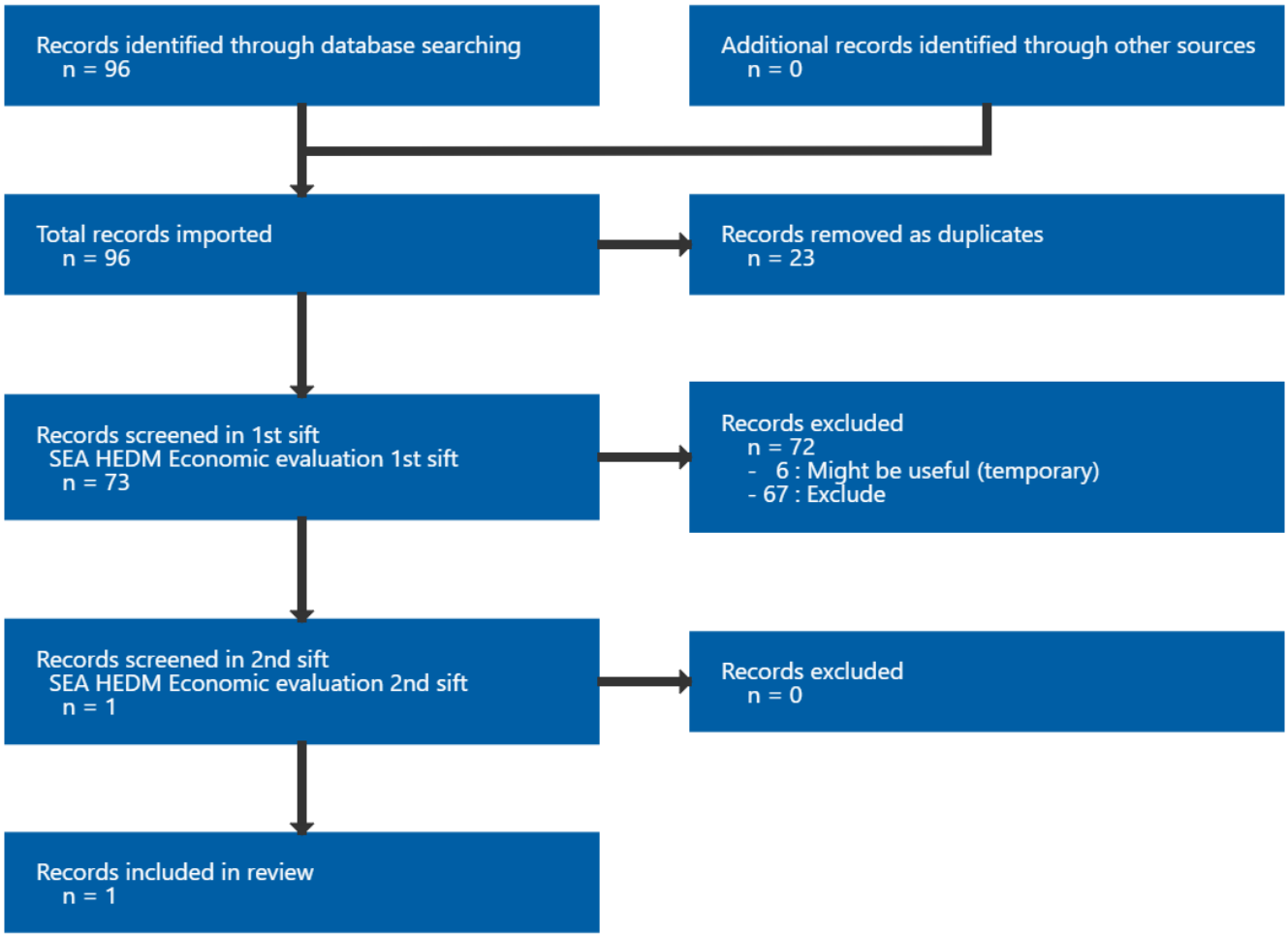
Explanations

a) Lee 2025

b) Serious risk of bias in the evidence contributing to the outcome. The evidence came from a study at moderate risk of bias as per RoB 2.0 tool
c) Single study- downgraded once for inconsistency, as single study outcomes may otherwise receive favourable ratings for inconsistency by default.
d) Beunen 2024
e) Serious imprecision because 95%CI crosses 1 MID (5%)
f) Very serious imprecision because 95%CI crosses 2 MIDs (5%)
g) Very serious imprecision because the ratio of the upper to lower boundary of the confidence interval is ≥3 for risk ratio
h) Very serious imprecision because N< OIS (108)

Appendix G - Economic evidence study selection

Figure 3: Economic evidence study selection flow chart



Appendix H - Economic evidence tables

Azahaf, 2025

Section	Details for Azahaf, 2025
Study details	**Economic analysis type:** Cost-effectiveness/Cost-consequences **Analysis design:** Decision analytic model **Country setting:** Belgium **Perspective:** Healthcare **Time horizon/Follow-up:** 28 weeks **Treatment duration:** 28 weeks **Discount rate per year:** NA (time horizon < 1 year)
Interventions	**Intervention 1:** Standard care (insulin injections, standalone insulin pump or sensor augmented pump therapy) **Intervention 2:** the MiniMed™ 780G AHCL (Advanced Hybrid Closed Loop) therapy system
Population	**Population:** Pregnant population with type 1 diabetes and with a gestational age of <12 weeks **Baseline characteristics** Sample size (if trial or cohort study): 49 standard care; 46 AHCL Mean age: 30.3 years standard care; 30.8 years AHCL
Costs included	**Original currency & cost year:** 2024 Euros **Cost components incorporated:** AHCL technology (pump, sensor transmitter), Standard care technology (pump sensor and transmitter), Miscarriage, Treatment with hospitalisation, Treatment without hospitalisation, Birth, NICU admission, Brachial plexus injury
Outcomes included	**Primary health outcome(s) in economic analysis:** Time in range, Time below range **Key events modelled /analysed:** See cost components
Data Sources	**Effectiveness data:** CRISTAL trial (Benhalima 2024) **Baseline / epidemiological data:** Benhalima 2024 (RCT), Murphy 2021 (cohort), Feig 2017 (RCT) **Quality-of-life weights:** SF-36 (not used in economic analysis) **Costs and/or resource use:** MyDiabetesCare website, University Hospital Leuven (2023), Benhalima 2024, Belgian NIHDI data (2021), Neyt 2014, Chevalier 2016, Murphy 2019
Results: costs	**Total costs (per patient):** Standard care: £12,230 AHCL: £12,030 Incremental: -£200 (95% CI: -£917, £255; p=NR) Converted to pound sterling using IMF Purchasing Power Parities: https://eppi.ioe.ac.uk/costconversion/default.aspx
Results: health outcomes	**Time in range (per patient):** Incremental: AHCL 24 minutes more in range (95% CI: 8 minutes, 30 minutes; p=NR)

Section	Details for Azahaf, 2025
	Time below range (per patient): Incremental: AHCL 19 minutes less below range (95% CI: -32 minutes, -7 minutes; p=NR)
Results: cost effectiveness	**Incremental cost-effectiveness ratios:** AHCL dominates standard care
Results: Uncertainty	**Deterministic:** *Scenario 1:* Included hospitalisations that are typically related to diabetes but were excluded from the base case as attribution to intervention was uncertain. *Scenario 2:* Like the base-case analysis it was limited to hospitalisations directly related to diabetes management. It differed from the base case as it relied solely on trial data for model outcomes. *Scenario 3:* This included additional hospitalisations with an ambiguous link to diabetes management but using CRISTAL trial data. The scenario analyses only had an impact on cost outcomes, but AHCL had the lowest mean cost per patient in each of the scenarios. **Probabilistic:** Probability Intervention AHCL dominates: Base case: 73% Scenario 1: 59% Scenario 2: 80% Scenario 3: 79%
Health inequalities assessment	NR
Comments	**Source of funding:** Diabetes Liga Research Fund, Medtronic **Other:** Analysis was limited to short term outcomes and departed from protocol due to non-significant difference in the primary outcome in the CRISTAL trial and because that study was not powered to detect differences in primary outcome. So rather than the planned long-term analysis a 28 week time horizon was adopted, reflecting duration of the intervention
Rating: Applicability	Partially applicable A non-NHS setting and standard care control group were all on pumps which may not be representative of UK populations. Analysis does not use QALYs despite the CRISTAL trial including health related quality of life outcomes.
Rating: Quality/ limitations	Potentially serious limitations Departures from pre-specified protocol and limited effectiveness to short term outcomes. PSA was undertaken but some concerns about arbitrary rules used for parameterisation (e.g. Standard errors are assumed to be 20% for all parameters and across all scenarios).

Abbreviations: AHCL = advanced hybrid closed loop; CI= confidence interval; PSA=probabilistic sensitivity analysis; NA=not applicable; NR=not reported; QALY=quality-adjusted life-year; RCT=randomised controlled trial;

Appendix I - Excluded studies

Effectiveness

Table 2 Studies excluded from the effectiveness review

Study	Code [Reason]
Akabane, M.A.C.C., Yu, M.Y., Coelho, H. et al. (2024) Impact Of Automated Insulin Delivery On Fear Of Hypoglycemia In Pregnant And Puerperal Women With Type 1 Diabetes: A Systematic Review And Meta-Analysis. Journal of the Endocrine Society 8: A421-A422	- Conference abstract
Al Nofal, A., Nduwimana, M.-J., Mohammad, A.-K. et al. (2025) The Utilization of Hybrid Closed Loop System in Management of Type I Diabetes in Pregnant Women: A Systematic Review and Meta-Analysis. ENDO 2025 9: A624-None	- Conference abstract
Al Nofal, Alaa, Benkhadra, Khalid, Abbas, Alzhraa et al. (2025) A Systematic Review Supporting the Clinical Practice Guidelines on the Management of Preexisting Diabetes and Pregnancy. The Journal of clinical endocrinology and metabolism 110(9): e2811-e2832	- Others *Question 8 of the SR is relevant to our protocol Only 2 out of 5 included RCTs uses a licenced HCL device. These two are already part of the review*
Anonymous. (2021) Randomized Clinical Trial to Assess the Efficacy of the System Insulclock 360 for Insulin Treatment Management in Type 1 Diabetes Patients With Insufficient Glycemic Control. clinicaltrials.gov	- Clinical trial records - Does not contain protocol specific population *excludes pregnant population*
Anonymous. (2024) Commercial or Open Source Closed Loop Impact on Pregnancy (COSCLIP) Study. clinicaltrials.gov	- Clinical trial records *Clinical trials record of a already included study*
Anonymous. (2021) Automated Insulin Delivery Amongst Pregnant Women With Type 1 Diabetes. clinicaltrials.gov	- Not a relevant study design *Study protocol.*
Anonymous. (2021) Feasibility Study of the Pancreas4ALL Closed-loop Automated Glycemic Control System in Patients With Type 1 Diabetes Mellitus: Pancreas4ALL Project - Good News Study - Phase I. clinicaltrials.gov	- Not a relevant study design *Study protocol.*
Anonymous. (2025) Automated Insulin for Management of Intrapartum Glycemia	- Not a relevant study design *Study protocol.*

Study	Code [Reason]
(AIMING): a Randomized Clinical Trial. clinicaltrials.gov	
Anonymous. (2021) Closed-loop Insulin Delivery by Glucose Responsive Computer Algorithms In Type 1 Diabetes Pregnancies (CIRCUIT). clinicaltrials.gov	- Not a relevant study design *Study protocol.*
Anonymous. (2020) Closed-loop Insulin Delivery in Pregnant Women With Type 1 Diabetes: a Randomized Controlled Trial: the CRISTAL Study. clinicaltrials.gov	- Not a relevant study design *Study protocol.*
Anonymous. (2020) Closed-Loop Insulin Delivery Postpartum in Mothers With Type 1 Diabetes and Their Babies' Feeding Practices. clinicaltrials.gov	- Not a relevant study design *Study protocol.*
Anonymous. (2020) Intravenous Insulin Versus Subcutaneous Insulin Infusion in Intrapartum Management of Pregnant Women With Type 1 Diabetes Mellitus: A Randomized Trial. clinicaltrials.gov	- Clinical trial records *compares CSII vs. IV infusion of insulin* - Study does not contain a relevant intervention *compares CSII vs. IV infusion of insulin*
Anonymous. (2021) Comparison of Conventional Mode and Combined Digitalized Mode of Management for Gestational Diabetes Mellitus in China. clinicaltrials.gov	- Does not contain protocol specific population *Population is women diagnosed with gestational diabetes.*
Asgharzadeh, Asra, Patel, Mubarak, Connock, Martin et al. (2024) Hybrid closed-loop systems for managing blood glucose levels in type 1 diabetes: a systematic review and economic modelling. Health technology assessment (Winchester, England) 28(80): 1-190	- Others *12 RCTs are included in this SR, out of which 11 rcts recruits non-pregnant/ very young population. Remaining 1 RCT - Stewart et al., that doesn't use HCL licensed for pregnancy*
Azahaf, Salima, Beunen, Kaat, Van Wilder, Nancy et al. (2025) Cost-effectiveness of advanced hybrid closed loop therapy compared to standard insulin therapy for type 1 diabetes in pregnancy: an economic evaluation of the CRISTAL trial. EClinicalMedicine 81: 103106	- Others *Cost effective analysis of CRISTAL trial*
Benhalima, Katrien, van Nes, Falco, Laenen, Annouschka et al. (2021) Risk for ketonaemia in type 1 diabetes pregnancies with sensor-augmented pump therapy with predictive low glucose suspend compared with low glucose suspend: a crossover RCT. Diabetologia 64(12): 2725-2730	- Study does not contain a relevant intervention *Study intervention is SAP. It compares SAP at two different modes of insulin delivery*
Benhalima, Katrien and Yamamoto, Jennifer M (2024) Use of continuous	- Not a relevant study design

Study	Code [Reason]
glucose monitoring and hybrid closed-loop therapy in pregnancy. Diabetes, obesity & metabolism 26suppl7: 74-91	*Narrative review of the current evidence on the use of continuous glucose monitoring and advanced hybrid closed-loop therapy in pregnancy.*
Beunen, Kaat, Van Wilder, Nancy, Ballaux, Dominique et al. (2023) Closed-loop insulin delivery in pregnant women with type 1 diabetes (CRISTAL): a multicentre randomized controlled trial - study protocol. BMC pregnancy and childbirth 23(1): 180	- Not a relevant study design *Study protocol.*
Bozkurt, L. and Stulnig, T. (2024) Advances in the use of technology for the management of diabetes in pregnancy: a comprehensive review. Diabetes, Stoffwechsel und Herz 33(6): 344-349	- Not a relevant study design *Narrative review of the evidence on the use of continuous glucose monitors or hybrid closed-loop insulin pump therapy in pregnant women with type 1 or type 2 diabetes or gestational diabetes.*
Buschur, EO, Reedy, J, Berget, C et al. (2025) Mixed Methods RCT comparing quality of life for pregnant women with type 1 diabetes using Hybrid Closed-Loop (HCL) to Sensor-Augmented Pump Therapy (SAPT). Endocrine practice	- Study does not contain a relevant intervention *Only includes a standard hybrid closed loop that does not have a license for use in pregnancy (Medtronic 670G)*
Burk, J., Colagiuri, S., Ross, G. et al. (2024) CONTINUOUS GLUCOSE MONITORING IMPROVES PERINATAL OUTCOMES ACROSS WOMEN WITH DIABETES IN PREGNANCY: A SYSTEMATIC REVIEW. Diabetes Technol. Ther. 26: A335-None	- Full text paper not available
Burk, Jessica, Ross, Glynis P, Hernandez, Teri L et al. (2025) Evidence for improved glucose metrics and perinatal outcomes with continuous glucose monitoring compared to self-monitoring in diabetes during pregnancy. American journal of obstetrics and gynecology 233(3): 162-175	- Others *None of the included RCTs uses HCL as an intervention*
Buschur, Elizabeth O, Reedy, Julia, Berget, Cari et al. (2025) Mixed Methods Randomized Controlled Trial Comparing Quality of Life for Pregnant Women With Type 1 Diabetes Using Hybrid Closed-Loop to Sensor-Augmented Pump Therapy. Endocrine practice : official journal of the American College of Endocrinology and the American Association of Clinical Endocrinologists 31(4): 494-502	- Duplicate reference
Cindy, G., Guerci, B., Morel, O. et al. (2024) Pregnancy in patients with type 1 diabetes: Metabolic and obstetrical results before the use of the hybrid closed loop. Medecine des Maladies Metaboliques 18(2): 120-129	- Study not reported in English *French study*

Study	Code [Reason]
Dickens, Laura T and Gonzalez, Maritza G (2025) Approach to the Patient Using Diabetes Technology in Pregnancy. The Journal of clinical endocrinology and metabolism 110(7): e2317-e2326	- Not a relevant study design *Narrative review of the current evidence on the use of continuous glucose monitors and hybrid closed-loop insulin pumps.*
Diez Alvarez, Sergio, Fellas, Antoni, Wynne, Katie et al. (2024) The Role of Smartwatch Technology in the Provision of Care for Type 1 or 2 Diabetes Mellitus or Gestational Diabetes: Systematic Review. JMIR mHealth and uHealth 12: e54826	- Study does not contain a relevant intervention *Only includes studies using smartwatch technology as an intervention*
DiStefano, Michael J, McQueen, R Brett, Gao, Valerie et al. (2025) The Cost of Continuous Glucose Monitoring Versus Self-Monitoring of Blood Glucose in Type 1 Diabetes Pregnancies in the United States: A Cost-Consequences Analysis Using Real-World Evidence. Diabetes technology & therapeutics 27(4): 329-333	- Not a relevant study design
Donovan, Lois E, Feig, Denice S, Lemieux, Patricia et al. (2023) A Randomized Trial of Closed-Loop Insulin Delivery Postpartum in Type 1 Diabetes. Diabetes care 46(12): 2258-2266	- Study does not contain a relevant intervention *Only includes a standard hybrid closed loop that does not have a license for use in pregnancy*
Donovan, Lois E, Bell, Rhonda C, Feig, Denice S et al. (2024) Glycaemic patterns during breastfeeding with postpartum use of closed-loop insulin delivery in women with type 1 diabetes. Diabetologia 67(10): 2154-2159	- Comparator in study does not match that specified in protocol *Comparator is open-loop insulin therapy.*
Donovan, Lois E, Lemieux, Patricia, Dunlop, Amy D et al. (2025) Closed-Loop Insulin Delivery in Type 1 Diabetes in Pregnancy: The CIRCUIT Randomized Clinical Trial. JAMA	- Study does not contain a relevant intervention *Only includes a standard hybrid closed loop that does not have a license for use in pregnancy*
Feig, DS, Asztalos, E, Corcoy, R et al. (2016) Erratum to: CONCEPTT: Continuous Glucose Monitoring in Women with Type 1 Diabetes in Pregnancy Trial: A multi-center, multi-national, randomized controlled trial - Study protocol. BMC pregnancy and childbirth 16(1): 249	- Others *Correction for incorrect affiliation - no additional data*
Fisher, S.A., Xu, N.Y., Huang, J. et al. (2023) Continuous subcutaneous infusion versus multiple daily injections of insulin for type 1 diabetes in pregnancy. American Journal of Obstetrics and Gynecology 228(1): S743-S744	- Conference abstract

Study	Code [Reason]
Geerts, Ina, Beunen, Kaat, Peeters, Mart et al. (2025) Who Benefits Most from Advanced Hybrid Closed Loop Therapy in Pregnancy Across Different Subgroups: A Secondary Analysis of the Randomized Controlled CRISTAL Trial. Diabetes technology & therapeutics	- Others *No additional outcomes reported from the original CRISTAL trial*
Jones, Leanne V, Ray, Amita, Moy, Foong Ming et al. (2019) Techniques of monitoring blood glucose during pregnancy for women with pre-existing diabetes. The Cochrane database of systematic reviews 5: cd009613	- Others *All of the included RCTs were published before 2018*
King, J, Buschur, E, Snell-Bergeon, J et al. (2024) Glycemic Variability in Pregnant Individuals Using Assisted Hybrid Closed-Loop Therapy Versus Sensor-Augmented Pump Therapy. Journal of diabetes science and technology 18(5): 1260-1262	- Data not reported in an extractable format *No protocol relevant outcomes. Study reports glucose variability outcomes: Low Blood Glucose Index High Blood Glucose Index Mean Amplitude of Glycaemic Excursions Continuous Overlapping Net Glycaemic Action J - index*
King, Jocelynn, Buschur, Elizabeth, Garcetti, Rachel et al. (2025) Changes to insulin pump settings throughout pregnancy for individuals using assisted hybrid closed-loop therapy versus sensor-augmented pump therapy. Journal of diabetes and its complications 39(4): 109000	- Study does not contain relevant outcomes *Outcomes reported are insulin dose, number of changes to pump settings, active insulin time and carbohydrate-to-insulin ratios and not outcomes specified in the protocol.*
Lee, Tara T M, Collett, Corinne, Man, Mei-See et al. (2022) AiDAPT: automated insulin delivery amongst pregnant women with type 1 diabetes: a multicentre randomized controlled trial - study protocol. BMC pregnancy and childbirth 22(1): 282	- Not a relevant study design *Study protocol for AiDAPT trial*
Lee, Tara TM, Collett, Corinne, Bergford, Simon et al. (2024) Automated closed-loop insulin delivery for the management of type 1 diabetes during pregnancy: the AiDAPT RCT.	- Secondary publication of an included study that does not provide any additional relevant information
Mantaj, Urszula, Gutaj, Pawel, Ozegowska, Katarzyna et al. (2019) Continuous subcutaneous insulin infusion reduces neonatal risk in pregnant women with type 1 diabetes mellitus. Ginekologia polska 90(3): 154-160	- Not a relevant study design *It's a retrospective cohort study*
Ozaslan, Basak, Deshpande, Sunil, Doyle, Francis J 3rd et al. (2021) Zone-MPC Automated Insulin Delivery Algorithm Tuned for Pregnancy Complicated by Type 1 Diabetes. Frontiers in endocrinology 12: 768639	- Not a relevant study design

Study	Code [Reason]
Ozaslan, Basak, Levy, Carol J, Kudva, Yogish C et al. (2022) Feasibility of Closed-Loop Insulin Delivery with a Pregnancy-Specific Zone Model Predictive Control Algorithm. Diabetes technology & therapeutics 24(7): 471-480	- Not a relevant study design *This study was not a randomised controlled trial, but instead it compared a one week unsupervised run-in phase with a 48hour supervised session.-week unsupervised run-in phase with a 48-hour supervised session.*
Pham, David Q, Thorsell, Ashley, Castorino, Kristin et al. (2024) A review of CONCEPTT study findings including subanalyses in pregnant women using continuous glucose monitoring with type 1 diabetes and their offspring. Endocrine connections 13(2)	- Not a relevant study design
Pickup, JC; Freeman, SC; Sutton, AJ (2011) Glycaemic control in type 1 diabetes during real time continuous glucose monitoring compared with self monitoring of blood glucose: meta-analysis of randomised controlled trials using individual patient data. BMJ (Clinical research ed.) 343(7815): d3805	- Does not contain protocol specific population *Only includes studies with non-pregnant population* - Study does not contain a relevant intervention *Compares CGM with SMBG. Doesn't give much study level detail to check if CGM device was a HCL or not*
Polsky, Sarit, Buschur, Elizabeth, Dungan, Kathleen et al. (2024) Randomized Trial of Assisted Hybrid Closed-Loop Therapy Versus Sensor-Augmented Pump Therapy in Pregnancy. Diabetes technology & therapeutics 26(8): 547-555	- Study does not contain a relevant intervention *Hybrid closed loop used does not have a license to use in pregnancy or a pregnancy-specific HCL.*
Rademaker, Doortje, van der Wel, Anne W T, van Eekelen, Rik et al. (2023) Continuous glucose monitoring metrics and pregnancy outcomes in insulin-treated diabetes: A post-hoc analysis of the GlucoMOMS trial. Diabetes, obesity & metabolism 25(12): 3798-3806	- Does not contain protocol specific population *Have mixed type 1 and 2 diabetic population. Only 35% of included participants have type 1 diabetes.*
Ramirez, A.C.A., Ore, J.V.S., Murga, O. et al. (2025) Continuous Subcutaneous Insulin Infusion Versus Multiple Daily Injections For Glycemic Control In Pregnant Patients With Type 1 Diabetes: A Systematic Review And Meta-analysis. ENDO 2025 9: A604-None	- Conference abstract
Richmond, A.K.; Morrison, A.E.; Meek, C.L. (2025) Management of pre-existing diabetes in pregnancy. Obstetrics, Gynaecology and Reproductive Medicine	- Not a relevant study design *Narrative review of the management of pre-existing diabetes in pregnancy.*
Rizos, Evangelos C, Markozannes, Georgios, Charitakis, Nikolaos et al. (2025) Continuous Glucose Monitoring in Type 1	- Does not contain protocol specific population

Study	Code [Reason]
Diabetes, Type 2 Diabetes, and Diabetes During Pregnancy: A Systematic Review with Meta-Analysis of Randomized Controlled Trials. Diabetes technology & therapeutics 27(7): 537-552	*Includes studies with mixed T1 and T2 population. The inclusion was also not restricted to male/ female or people who are prgnant or planning to becaome pregnant. The includes of SR suggests that none of the studies had HCL as an intervention and protocol relevant population.*
Roberto, Dodesini Alessandro, Elena, Ciriello, Anna, Corsi et al. (2023) Sensor augmented pump therapy with predictive suspension function for low glucose levels reduces time in hypoglycaemia in pregnant women with type 1 diabetes. Acta diabetologica 60(9): 1283-1285	- Review article but not a systematic review
Rudland, V.L., Price, S.A.L., Hughes, R. et al. (2020) ADIPS 2020 guideline for pre-existing diabetes and pregnancy. Australian and New Zealand Journal of Obstetrics and Gynaecology 60(6): e18-e52	- Not a relevant study design *Australasian Diabetes in Pregnancy Society (ADIPS) 2020 guideline for pre-existing diabetes and pregnancy.*
Stamati, Athina and Christoforidis, Athanasios (2025) Automated insulin delivery in pregnant women with type 1 diabetes mellitus: a systematic review and meta-analysis. Acta diabetologica 62(4): 441-452	- Others *All relevant studies in this SR have already been included in the review*
Stewart, ZA, Wilinska, ME, Hartnell, S et al. (2018) Day-and-Night Closed-Loop Insulin Delivery in a Broad Population of Pregnant Women With Type 1 Diabetes: a Randomized Controlled Crossover Trial. Diabetes care 41(7): 1391-1399	- Data not reported in an extractable format
Stewart, ZA, Yamamoto, JM, Wilinska, ME et al. (2018) Adaptability of Closed Loop During Labor, Delivery, and Postpartum: a Secondary Analysis of Data from Two Randomized Crossover Trials in Type 1 Diabetes Pregnancy. Diabetes technology & therapeutics 20(7): 501-505	- Not a relevant study design
Tahir, Sohaira, Naeem, Shafia, Nayyab, Izzah et al. (2025) Hybrid closed loop insulin therapy versus standard therapy in pregnant women with type 1 diabetes: A systematic review and meta-analysis of randomized controlled trials. European journal of obstetrics, gynecology, and reproductive biology 310: 113969	- Others *All relevant studies in this SR have already been included in the review*
Talbo, Meryem K, Katz, Alexandra, Hill, Lee et al. (2023) Effect of diabetes technologies on the fear of hypoglycaemia among people living with type 1 diabetes: a systematic	- Does not contain protocol specific population *Only includes studies with non-pregnant adults (≥18 years)*

Study	Code [Reason]
review and meta-analysis. EClinicalMedicine 62: 102119	
Teixeira, Tamara, Godoi, Amanda, Romeiro, Pedro et al. (2024) Efficacy of automated insulin delivery in pregnant women with type 1 diabetes: a meta-analysis and trial sequential analysis of randomized controlled trials. Acta diabetologica 61(7): 831-840	- Others *SR's includes 5 RCTs. All relevant studies matching the review protocol have already been included in the review*
Teo, Evelyn, Hassan, Norasyikin, Tam, Wilson et al. (2022) Effectiveness of continuous glucose monitoring in maintaining glycaemic control among people with type 1 diabetes mellitus: a systematic review of randomised controlled trials and meta-analysis. Diabetologia 65(4): 604-619	- Does not contain protocol specific population *Only includes studies with non-pregnant population* - Study does not contain a relevant intervention *Compares CGM with SMBG. Looks like none of the included studies uses HCL system as an intervention*
Tundidor, Diana, Meek, Claire L, Yamamoto, Jennifer et al. (2021) Continuous Glucose Monitoring Time-in-Range and HbA1c Targets in Pregnant Women with Type 1 Diabetes. Diabetes technology & therapeutics 23(10): 710-714	- Study does not contain a relevant intervention *Sub analysis of CONCEPTT trial. Trial uses Guardian REAL-Time or MiniMed Minilink System, in the intervention group and masked iPro2 Professional CGM in the control group. None of these devices are HCL*
Waraphok, Sineenat; Gary, Faye; Griggs, Stephanie (2025) The impact of continuous glucose monitoring on glycated hemoglobin in pregnant women with type 1 diabetes: an integrative review. The journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstetricians 38(1): 2582947	- Not a relevant study design
Wilkie, Gianna L; Delpapa, Ellen; Leftwich, Heidi K (2023) Intrapartum continuous subcutaneous insulin infusion vs intravenous insulin infusion among pregnant individuals with type 1 diabetes mellitus: a randomized controlled trial. American journal of obstetrics and gynecology 229(6): 680e1-680e8	- Study does not contain a relevant intervention *Intervention of the study is continuous subcutaneous insulin infusion (CSII) but it is not specified (unclear from the data provided) if CSII is a part of a hybrid closed loop system.*
Wyckoff, Jennifer A, Lapolla, Annunziata, Asias-Dinh, Bernadette D et al. (2025) Preexisting Diabetes and Pregnancy: An Endocrine Society and European Society of Endocrinology Joint Clinical Practice	- Not a relevant study design *It is a guideline / consensus document*

Study	Code [Reason]
Guideline. The Journal of clinical endocrinology and metabolism 110(9): 2405-2452	
Yamamoto, J M, Corcoy, R, Donovan, L E et al. (2019) Maternal glycaemic control and risk of neonatal hypoglycaemia in Type 1 diabetes pregnancy: a secondary analysis of the CONCEPTT trial. Diabetic medicine : a journal of the British Diabetic Association 36(8): 1046-1053	- Study does not contain a relevant intervention *CONCEPTT trial compares CGM with SMBG. CGM was done using Medtronic iPro™2, which is a professional, non-real-time (masked) continuous glucose monitoring (CGM) system and not a HCL.*
Yamamoto, J.M. and Murphy, H.R. (2022) Technology and Pregnancy. Diabetes Technology and Therapeutics 24(s1): 96-s106	- Review article but not a systematic review *looks like a review/ journal article*
Yamamoto, J.M. and Murphy, H.R. (2019) Technology and Pregnancy. Diabetes Technology and Therapeutics 21(s1): 101-s111	- Not a relevant study design
Yamamoto, Jennifer M and Murphy, Helen R (2021) Benefits of Real-Time Continuous Glucose Monitoring in Pregnancy. Diabetes technology & therapeutics 23(s1): 8-s14	- Not a relevant study design

Abbreviations: AiDAPT: Automated Insulin Delivery Amongst Pregnant Women with Type 1 Diabetes; CGM: continuous glucose monitor; CONCEPTT: Continuous glucose monitoring in pregnant women with type 1 diabetes; CRISTAL: Closed-loop insulin delivery in pregnant women with type 1 diabetes: a randomized controlled trial; CSII: subcutaneous insulin infusion; HCL: hybrid closed loop system; IV: Intravenous therapy; RCT: Randomized Controlled Trial; SMBG: self-monitoring of blood glucose; SAP: sensor-augmented pump; SR: systematic review; T1: Type 1 diabetes; T2: Type 2 diabetes.

Economic

No economic study was reviewed at full text and excluded from this review.

Appendix J - Methods

Selecting studies for inclusion

All references identified by the literature searches were uploaded into EPPI reviewer software (version 5) and de–duplicated. References to studies included in the previous NICE guideline NG3 and TA943 were also considered for inclusion in the updated review. Titles and abstracts were assessed for possible inclusion using the criteria specified in the review protocol.

The full text of potentially eligible studies was retrieved and assessed according to the criteria specified in the review protocol. A standardised form was used to extract data from included studies and full evidence tables are presented in appendix D.

Methods of combining evidence

Two trials were included: one comparing pregnancy-specific HCL with standard care, and another comparing non-pregnancy-specific HCL with standard care. Because the technologies evaluated in these trials differed substantially, the evidence could not be pooled for any outcome. Forest plots were created in Cochrane Review Manager (RevMan Web) to provide a visual representation of the trial data.

Evidence was stratified by the following stages:

- Preconception
- During pregnancy
- Postnatal period

Based on the data available in the included trial, it was not possible, as originally intended, to further stratify the outcomes within these categories into the following time-points

- Pregnancy:

    - Pre 24 weeks' gestation
    - Post 24 weeks' gestation
- Postnatal:
    - Day of delivery to 3 months postpartum
    - 4 to 6 months postpartum

When studies reported outcomes at multiple time points (for example, by trimester), and no overall combined estimate was provided, the time-specific data were assessed for variability. If the results showed minimal differences between time points, the review team extracted either the dataset with the largest number of participants or the dataset judged to be the most representative. When a study provided both time-specific estimates and an overall pooled result, the overall estimate was extracted in accordance with NICE's preference for the least selective and most comprehensive summary.

It was not possible to conduct the pre–specified subgroup analyses, owing to the data reported in the trial.

Appraising the certainty of evidence

RCTs were quality assessed using the Cochrane Risk of Bias tool (version 2.0). Evidence for subjective outcomes and objective outcomes for each study, was classified into one of the following:

- Low risk of bias – The true effect size for the study is likely to be close to the estimated effect size.
- Moderate risk of bias – There is a possibility the true effect size for the study is substantially different to the estimated effect size.
- High risk of bias – It is likely the true effect size for the study is substantially different to the estimated effect size.

Each individual study was also classified into 1 of 3 groups for directness, based on if there were concerns about the population, intervention, comparator, outcomes, or both, in the study and how directly these variables could address the specified review question. Studies were rated as follows:

- Direct – No important deviations from the protocol in population, intervention, comparator and/or outcomes.
- Partially indirect – Important deviations from the protocol in one of the following areas: population, intervention, comparator and/or outcomes.
- Indirect – Important deviations from the protocol in at least two of the following areas: population, intervention, comparator and/or outcomes.

Minimally important differences (MIDs) and clinical decision thresholds

Clinical decision thresholds were used to assess imprecision using GRADE and aid interpretation of the size of effects for different outcomes.

The Core Outcome Measures in Effectiveness Trials (COMET) database was searched to identify published minimal clinically important difference thresholds; none were identified for our pre-specified outcomes of interest.

The following clinical decision thresholds were used in the analysis:

- For the percentage of time spent in the target glucose range (TIR), a MID of 5% change was applied. This threshold had previously been used in the development of NICE guideline NG3 and is based on the findings of Batelino et al 2019. Evidence of benefit occurs when the point estimate and entire CI lie on the beneficial side of the MID (5%), showing a statistically significant improvement. Evidence of disbenefit is when both the estimate and CI fall fully on the harmful side, indicating a statistically significant worsening. An uncertain effect is when the point estimate leans toward benefit or harm but the CI crosses the MID of 5% change, meaning the true effect could be beneficial, harmful, or null. Evidence of no effect applies when the point

estimate is equivalent to MID (5%) and the CI crosses it, indicating no detectable difference between intervention and comparator.

- For the quality-of-life outcome, the diabetes distress scale, a MID of 0.25 units was used , based on the findings of Banks et al (2023). Evidence of benefit occurs when the point estimate and entire CI lie on the beneficial side of the MID (0.25), showing a statistically significant improvement. Evidence of disbenefit is when both the estimate and CI fall fully on the harmful side, indicating a statistically significant worsening. An uncertain effect is when the point estimate leans toward benefit or harm but the CI crosses the MID of 0.25 units, meaning the true effect could be beneficial, harmful, or null. Evidence of no effect applies when the point estimate is equivalent to 0.25 units (MID) and the CI crosses it, indicating no detectable difference between intervention and comparator.

- For all dichotomous outcomes, the line of no effect as an MID and statistical significance was used to assess the effectiveness of intervention. The judgement relied on whether the 95% confidence interval (CI) crossed the value indicating no difference between the intervention and comparator. The line of no effect is 1 for relative measures such as risk ratio (RR), odds ratio (OR) and Peto OR and the line of no effect is 0 for absolute measures such as risk difference (RD). Evidence of benefit occurs when the point estimate and entire CI lie on the beneficial side of the line of no effect, showing a statistically significant improvement. Evidence of disbenefit is when both the estimate and CI fall fully on the harmful side, indicating a statistically significant worsening. An uncertain effect is when the point estimate leans toward benefit or harm but the CI crosses the line of no effect, meaning the true effect could be beneficial, harmful, or null. Evidence of no effect applies when the point estimate sits exactly on the line of no effect (RR = 1 or RD/MD = 0) and the CI crosses it, indicating no detectable difference between intervention and comparator.

GRADE for intervention studies analysed using pairwise analysis

GRADE was used to assess the quality of evidence for the outcomes specified in the review protocol. Data from randomised controlled trials (which were quality assessed using the Cochrane risk of bias tool) were initially rated as high quality. The quality of the evidence for each outcome was downgraded or not from this initial point, based on the criteria given Table 11.

Table 11: Rationale for downgrading quality of evidence for intervention studies

GRADE criteria	Reasons for downgrading
Risk of bias	Not serious: If less than (<) 50% of the overall weighting in a meta-analysis came from studies at moderate or high risk of bias, the overall outcome was not downgraded. Serious: If greater than (>) 50% overall weighting in a meta-analysis came from studies at moderate or high risk of bias, the outcome was downgraded 1 level. Very serious: If > 50% of the weighting in a meta-analysis came from studies at high risk of bias, the outcome was downgraded 2 levels.
Indirectness	The following definitions were used for downgrading: • Direct – No important deviations from the protocol in population, intervention, comparator and outcomes.

	• Partially indirect – Important deviations from the protocol in one of the following areas: population, intervention, comparator or outcomes. • Indirect – Important deviations from the protocol in at least two of the following areas: population, intervention, comparator or outcomes. Where meta–analysis is possible, the weighting of the studies in the meta–analysis and downgrading evidence based on percentage of overall weighting was applied: • Not serious: If <50% of overall weighting came from studies which are partially direct or indirect, the overall outcome was not downgraded. • Serious: If >50% of overall weighting came from studies which are partially direct or indirect, the overall outcome was downgraded 1 level. • Very serious (downgrade 2 levels): If >50% of overall weighting came from studies which are indirect, the overall outcome was downgraded 2 levels. No studies in this review were identified to be partially indirect or indirect.
Inconsistency	Concerns about inconsistency of effects across studies, occurring when there is unexplained

	variability in the treatment effect demonstrated across studies (heterogeneity). This was assessed using the I squared (I^2) statistic. Not serious: If the I^2 was < 50% the outcome was not downgraded. Serious: If the I^2 was between 50% and 79%, the outcome was downgraded 1 level. Studies from a single study were downgraded by 1 level. Very serious: If the I^2 was 80% or greater, the outcome was downgraded 2 levels.
Imprecision	Imprecision is judged in two ways depending on whether MID thresholds are available. When MID thresholds are available, imprecision is assessed by checking whether the confidence interval crosses these thresholds: if the CI stays within both MIDs, outcome is not downgraded; if it crosses either MID, outcome is downgraded once; and if it crosses both MIDs, outcome is downgraded twice. When MID thresholds are not available, or when the MID equals the line of no effect, imprecision is judged using the OIS (Optimal Information Size) approach. • For continuous outcomes, if the total sample size (N) is ≥ OIS or ≥ 800, outcome is not downgraded; if N is smaller than OIS, outcome is downgraded once, and if N is <30% of OIS, outcome is downgraded twice.

	• For dichotomous outcomes reported as RR or OR, if the ratio of the upper to lower CI boundary is very wide (≥2.5 for OR or ≥3 for RR), outcome is downgraded twice; otherwise, OIS is calculated and outcome is downgraded once if N < OIS, or not at all if N ≥ OIS. • For dichotomous outcomes reported as RD, Peto OR, if N ≥ OIS outcome is not downgraded, if N < OIS outcome is downgraded once, and if N <30% of OIS outcomes is downgraded twice.
Publication bias	Not applicable, less than 10 studies in the review.

Appendix K - Research recommendations

Research recommendation

Based on routinely collected real-world data, in women, trans men and non-binary people with type 1 diabetes, who are planning to become pregnant, are pregnant, or are in the postpartum period, what is the effectiveness and cost effectiveness of using hybrid closed loop systems to improve fetal and neonatal outcomes, compared to other forms of insulin delivery?

Why this is important

The Committee noted that there was a lack of clinical evidence showing the effectiveness of using hybrid closed loop systems, compared with other forms of insulin delivery, to improve fetal and neonatal outcomes. The Committee acknowledged that the association between glucose levels during pregnancy and pregnancy outcomes is well established. Therefore, they were confident the evidence from the AiDAPT and CRISTAL trials, for improved maternal glucose from early pregnancy onwards, will have clinically relevant health benefits both for pregnant women and pregnant people and for their babies. However, they considered that it would be valuable to do research using routinely collected real world data, including audits, to examine the effect of hybrid closed loop systems compared to other forms of insulin delivery on fetal and neonatal outcomes, including:

- preterm births
- large birthweight
- neonatal care admissions.

Rationale for research recommendation

Importance to the population

Use of routinely collected data would enable direct assessment of the population-level impact of recommended HCL, rather than relying on inference from 2 trials identified in this review that were underpowered to assess the effectiveness of HCL systems for fetal and neonatal outcomes during pregnancy and postnatal periods.

Relevance to NICE guidance

NICE is increasingly drawing on routinely collected real-world healthcare data to evaluate the effectiveness of interventions, close gaps in the evidence base, and facilitate patient access to innovation.

Relevance to the NHS

Understanding the effectiveness of HCL compared with other forms of insulin delivery in improving important neonatal and fetal outcomes may help in improved maternal glycaemic management and reduction in adverse neonatal and fetal outcomes. Therefore, improved outcomes such as preterm births and neonatal intensive care unit admissions, may help in reducing time and costs for the NHS in treating fetal and neonatal adverse events attributed to maternal blood glucose management.

National priorities

Improving neonatal and fetal outcomes in people affected by type 1 diabetes is a high national priority, as reflected in the Saving Babies' Lives Care Bundle version 3, which emphasises optimised diabetes management to reduce perinatal morbidity and mortality. In parallel, NHS England's Hybrid Closed-Loop 5-year implementation strategy supports phased national adoption of psHCL technologies in line with NICE technology appraisal guidance, highlighting the need for robust real-world evidence to inform future NICE recommendations and implementation decisions.

Current evidence base

There are currently 2 RCTs (AiDAPT and CRISTAL trials) included in this review that assess the effectiveness of HCL systems for people with type 1 diabetes during pregnancy, intrapartum period and postnatal period. These trials were underpowered to detect the effectiveness of HCL in improving adverse neonatal and fetal outcomes. NICE does not have current evidence base for HCL system using routine healthcare data.

Equality considerations

The research recommendation addresses equality by explicitly including women, trans men and non-binary people in the preconception, pregnancy and postpartum periods, reflecting the need to avoid gendered language that may create access barriers. It also focuses on HCL systems, where the EHIA highlights potential inequities related to disability, literacy, language and digital exclusion, and real-world data could help identify unequal uptake and outcomes

Table 7 Research recommendation protocol outline

Population	Women, trans men and non-binary people with type 1 diabetes, who are planning to become pregnant, are pregnant, or are in the postpartum period
Interventions	Pregnancy-specific hybrid closed loop systems
Comparator	• Other forms of insulin delivery • Non-pregnancy specific hybrid closed loop system

Outcomes	• Neonatal intensive care unit admissions longer than 24 hours
	• Adverse events:
	  ○ Mortality:
	  ▪ pregnancy loss (miscarriage, defined as <24weeks)
	  ▪ stillbirth, ≥24 weeks
	  ▪ neonatal loss, up to 28 days)
	  ○ Neonatal hypoglycaemia
	  ○ Preterm birth
	  ○ Large/ small for gestational age

Study type	Any non-randomised study adjusting for confounders and using routine healthcare data or data from registries or audits
Timeframe	Long term
Other information	Evidence should be stratified by type of hybrid closed loop system: • Standard • Pregnancy-specific Evidence should be stratified by feeding practices: • Exclusive breastfeeding • Exclusive formula feeding • Mixed feeding Evidence should be stratified by the following stages: • Preconception • During pregnancy • Postnatal period Appropriate methods should be utilised to adjust data for confounders, such as those related to disability, literacy, language etc.

Research recommendation

Based on routinely collected real-world data, in women, trans men and non-binary people with type 1 diabetes, who are planning to become pregnant, are pregnant, or are in the postpartum period, what is the effectiveness and cost effectiveness of using hybrid closed loop (HCL) systems to reduce the risk of adverse outcomes for the mother or parent, compared to other forms of insulin delivery?

Why this is important

The committee noted that there was not enough clinical evidence on the effectiveness of using HCL systems compared with other forms of insulin delivery, to reduce the risk of adverse outcomes for the mother or parent. The committee acknowledged that the association between glucose levels during pregnancy and pregnancy outcomes is well established. Therefore, they were confident that the improved maternal blood glucose levels from early pregnancy onwards, as shown in the AiDAPT and CRISTAL trials, will have clinically relevant health benefits both for pregnant women and pregnant

people using HCL systems and for their babies. However, they agreed that it would be valuable to do research using routinely collected real-world data, including audits, to examine the effect of HCL systems compared to other forms of insulin delivery on reducing the risk of adverse outcomes for the mother or parent, including:

- severe hypoglycaemia
- nocturnal hypoglycaemia and
- diabetic ketoacidosis.

Rationale for research recommendation

Importance to the population

Use of routinely collected data would enable direct assessment of the population-level impact of recommended HCL, rather than relying on inference from 2 trials identified in this review that were underpowered to assess the effectiveness of HCL systems in reducing adverse events for mother or parent.

Relevance to NICE guidance

NICE is increasingly drawing on routinely collected real-world healthcare data to evaluate the effectiveness of interventions, close gaps in the evidence base, and facilitate patient access to innovation.

Relevance to the NHS

Understanding the effectiveness of HCL systems compared with other forms of insulin delivery in reducing clinically significant maternal adverse outcomes could support improvements in glucose management throughout preconception, pregnancy and the postpartum period. Better glucose control may reduce the risk of serious maternal complications such as severe hypoglycaemia, nocturnal hypoglycaemia, and diabetic ketoacidosis. Consequently, improved maternal outcomes may reduce the need for acute

NHS interventions and hospital admissions, leading to potentially reducing pressure on NHS maternity and diabetes services, as well as lowering the time and costs associated with managing avoidable complications.

National priorities

Improving maternal adverse outcomes in people affected by type 1 diabetes is a high national priority, as reflected in the Saving Babies' Lives Care Bundle version 3, which emphasises optimised diabetes management to reduce perinatal morbidity and mortality. In parallel, NHS England's Hybrid Closed-Loop 5-year implementation strategy supports phased national adoption of psHCL technologies in line with NICE technology appraisal guidance, highlighting the need for robust real-world evidence to inform future NICE recommendations and implementation decisions.

Current evidence base

There are currently 2 RCTs (AiDAPT and CRISTAL trials) included in this review that assess the effectiveness of HCL systems for people with type 1 diabetes during pregnancy, intrapartum period and postnatal period. These trials were underpowered to detect the effectiveness of HCL in improving adverse maternal outcomes. NICE does not have current evidence base for HCL system using routine healthcare data.

Equality considerations

The research recommendation addresses equality by explicitly including women, trans men and non-binary people in the preconception, pregnancy and postpartum periods, reflecting the need to avoid gendered language that may create access barriers. It also focuses on HCL systems, where the EHIA highlights potential inequities related to disability, literacy, language and digital exclusion, and real-world data could help identify unequal uptake and outcomes.

Table 8 Research recommendation protocol outline

Population	Women, trans men and non-binary people with type 1 diabetes, who are planning to become pregnant, are pregnant, or are in the postpartum period
Interventions	Pregnancy-specific hybrid closed loop systems
Comparator	• Other forms of insulin delivery • Non-pregnancy specific hybrid closed loop system

Outcomes	• Adverse events:
	  ○ hypoglycaemia (dichotomous or continuous outcome, depending how it is reported)
	  ○ severe hypoglycaemia (defined as requiring third party assistance)
	  ○ nocturnal hypoglycaemia
	  ○ diabetic ketoacidosis (DKA)

Study type	Any non-randomised study adjusting for confounders and using routine healthcare data or data from registries or audits
Timeframe	Long term
Other information	Evidence should be stratified by type of hybrid closed loop system: • Standard • Pregnancy-specific Evidence should be stratified by feeding practices: • Exclusive breastfeeding • Exclusive formula feeding • Mixed feeding Evidence should be stratified by the following stages: • Preconception • During pregnancy • Postnatal period Appropriate methods should be utilised to adjust data for confounders, such as those related to disability, literacy, language etc