Review protocol for managing type 1 diabetes using hybrid closed loop systems in people who are planning to become pregnant, pregnant or in the postpartum period

ID	Field	Content
0.	PROSPERO registration number	Not applicable.
1.	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.
2.	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 fetal/neonatal outcomes, compared to standard insulin therapy?
3.	Objective	To determine the clinical and cost effectiveness of hybrid closed loop systems in improving maternal and fetal/neonatal outcomes in people with type 1 diabetes in the pre-conception, antenatal or postpartum period.
4.	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) Searches will be restricted by: Date limitation - from 2019 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.
5.	Condition or domain being studied	Managing type 1 diabetes (T1D) using hybrid closed loop systems.
6.	Population	People with type 1 diabetes who are: • planning to become pregnant • pregnant • in the postpartum period (up to 6 months post childbirth)
7.	Intervention	• 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: o a licence for use in pregnancy o a glucose target of ≤ 5mmol/L o 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.
8.	Comparator/Reference standard/Confounding factors	• 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) o 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.
9.	Types of study to be included	Include published full-text papers: • Systematic reviews of RCTs • RCTs
10.	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: o data has not been reported for the subgroup of type 1 diabetes patients OR, o 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
11.	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.
12.	Primary outcomes	**Maternal outcomes** 1. % time spent in the pregnancy-specific/postpartum* target glucose range: o Time spent within target glucose range o Time spent above target glucose range o Time spent below target glucose range o 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: o Hypoglycaemia (dichotomous or continuous outcome, depending how it is reported): ▪ severe hypoglycaemia (defined as requiring third party assistance) ▪ nocturnal hypoglycaemia o Diabetic ketoacidosis (DKA) 3. Quality of Life outcomes - measured using validated tools. For example:

		○ Diabetes Distress Scale ○ Hypoglycaemia Fear Survey Questionnaire **Fetal and 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)
13.	Secondary outcomes	• HCL device-related adverse events, including malfunctioning of device and user error.
14.	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.
15.	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.
16.	Strategy for data synthesis	**Intervention review:** 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 I^2 statistic. Alongside visual inspection of the point estimates and confidence intervals, the following criteria will be used to assess heterogeneity: no serious I^2 = <40%; serious I^2 = 40-60%; very serious I^2 = >60%. Where I^2 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). To assess imprecision, where available, published MIDs will be used, such as: • Time in range (%): MID = 5% change in time in range (Battelino T et al. Diabetes Care 2019;42:1593-1603) • Diabetes distress scale: MID = 0.25 units (Banks J et al. Ascertainment of Minimal Clinically Important Differences in the Diabetes Distress Scale-17: A Secondary Analysis of a Randomized Clinical Trial. JAMA Netw Open. 2023 Nov 1;6(11):e2342950. doi: 10.1001/jamanetworkopen.2023.42950. PMID: 37966840; PMCID: PMC10652154.) Where there are no published MIDs available, the MID will be set as the line of no effect for all outcomes (1.0 for dichotomous outcomes and 0 for continuous outcomes).

17.	Analysis of sub-groups	Evidence will be subgrouped by: • Type of hybrid closed loop system: o Standard o Pregnancy-specific • Breastfeeding status: Any breastfeeding versus none. Where evidence is subgrouped 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.
18.	Type and method of review	☒ Intervention ☐ Diagnostic ☐ Prognostic ☐ Qualitative ☐ Epidemiologic
		☐ Service Delivery ☐ Other (please specify)
19.	Language	English
20.	Country	England

21.	Anticipated or actual start date	2nd January 2026		
22.	Anticipated completion date	26th August 2026		
23.	Stage of review at time of this submission	**Review stage**	**Started**	**Completed**
		Preliminary searches	☐	☐
		Piloting of the study selection process	☐	☐
		Formal screening of search results against eligibility criteria	☐	☐
		Data extraction	☐	☐

		Risk of bias (quality) assessment	☐	☐
		Data analysis	☐	☐
24.	Named contact	• **5a. Named contact** NICE • **5b Named contact e-mail** Diabetesinpregnancy@nice.org.uk • **5e Organisational affiliation of the review** National Institute for Health and Care Excellence (NICE)		
25.	Review team members	• Ms Clare Wohlgemuth, NICE • Tayyaba Mumtaz, NICE • Paul Jacklin, NICE • Lina Gulhane, NICE		
26.	Funding sources/sponsor	This systematic review is being completed by NICE which receives funding from the Department of Health and Social Care.		
27.	Conflicts of interest	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 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.
28.	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
29.	Other registration details	None

30.	Reference/URL for published protocol	None
31.	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.
32.	Keywords	Type 1 diabetes Preconception Pregnancy Postpartum Hybrid closed loop Automated insulin delivery Glycaemic control

33.	Details of existing review of same topic by same authors	None
34.	Current review status	☒ Ongoing ☐ Completed but not published ☐ Completed and published ☐ Completed, published and being updated ☐ Discontinued
35..	Additional information	[Provide any other information the review team feel is relevant to the registration of the review.]
36.	Details of final publication	www.nice.org.uk