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Clinical evidence for high-risk medical devices used to manage diabetes: protocol for a systematic review and meta-analysis

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ABSTRACT

Introduction Medical devices, including high-risk medical devices, have greatly contributed to recent improvements in the management of diabetes. However, the clinical evidence that is submitted for regulatory approval is not transparent, and thus a comprehensive summary of the evidence for high-risk devices approved for managing diabetes in Europe is lacking. In the framework of the Coordinating Research and Evidence for Medical Devices group, we will, therefore, perform a systematic review and meta-analysis, which will evaluate the efficacy, safety and usability of high-risk medical devices for the management of diabetes.

Method and analysis This study has been reported according to the guidelines of the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols. We will search Embase (Elsevier), Medline All (Ovid), Cochrane Library (Wiley), Science Citation Index Expanded and Emerging Sources Citation Index (Web of Science) to identify interventional and observational studies that evaluate the efficacy and/or safety and/or usability of high-risk medical devices for the management of diabetes. No language or publication dates' limits will be applied. Animal studies will be excluded. In accordance with the Medical Device Regulation in European Union, high-risk medical devices are those in classes IIb and III. The following medical devices for diabetes management are considered as having a high risk: implantable continuous glucose monitoring systems, implantable pumps and automated insulin delivery devices. Selection of studies, data extraction and quality of evidence assessment will be performed independently by two researchers. Sensitivity analysis will be performed to identify and explain potential heterogeneity.

Ethics and dissemination No ethical approval is needed for this systematic review, as it is based in already published data. Our findings will be published in a peer-reviewed journal.

PROSPERO registration number CRD42022366871.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This study will systematically review and meta-analyse the evidence on the efficacy, safety and usability of high-risk medical devices which received CE marking for the management of diabetes.
⇒ Observational and interventional studies will be included and analysed separately.
⇒ The protocol follows the guidelines of the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols.
⇒ We will evaluate the quality of evidence in accordance with study designs.
⇒ Our results can be limited by the quantity and quality of eligible studies.

INTRODUCTION

The classification of medical devices in the European Union applies a risk-based system that takes account of the vulnerability of the human body and the potential risks associated with the devices. High-risk medical devices in class IIb or III according to the new Medical Device Regulation (MDR[1]; EU 2017/745) include devices and software that support or sustain human life or prevent impairment of human health but, when used, pose high risks to patients (serious deterioration of health, irreversible deterioration of health or death).[1] During recent decades, the management of diabetes has changed profoundly and the ability to control glucose levels has improved significantly.[2] The development of several medical devices has greatly contributed to this progress.[3–5] Some of the devices belong to the high-risk category as they either involve automated drug delivery or implanted components.

To date, the clinical evidence that is submitted for regulatory approval is not transparent, and thus a comprehensive summary of the evidence on the efficacy, safety and usability of high-risk devices approved for managing diabetes in Europe is lacking. In the framework of the Coordinating Research and Evidence for Medical Devices group, we will review the literature on high-risk medical devices for diabetes monitoring and treatment before and after the CE mark approval.[6]

Toward this end, we will conduct a systematic review and meta-analysis to assess whether high-risk medical devices for diabetes

management are useful, safe and effective. We will review study designs, statistical methods, reported outcomes and overall quality of evidence. If possible, we will consider additionally stratifying by sex, age and other patient characteristics. Generated insights shall contribute to greater transparency in the field of high-risk medical devices for diabetes monitoring and treatment, by presenting available treatment modalities and exchanging information pertaining to their efficacy, safety and usability profiles to support decisions and recommendations.[7]

High-risk medical devices for diabetes management

The MDR specifies a number of criteria to define high-risk medical devices (classes IIb and III). Among others, all implantable devices and long-term surgically invasive devices are in class III if they are intended: (a) to have a biological effect; (b) to be wholly or mainly absorbed; (c) to undergo chemical change in the body (except if the devices are placed in the teeth) or (d) to administer medicines (Rule 8, medical device regulations).[1] All devices incorporating, as an integral part, a substance which, if used separately, can be considered to be a medicinal product, and which is liable to act on the human body with action ancillary to that of the devices, are in class III (Rule 13, medical device regulations).[1] Software intended to provide information which is used to take decisions with diagnosis or therapeutic purposes is classified as class III medical device if such decisions have an impact that may cause death or an irreversible deterioration of a person's state of health and is classified as class IIb if such decisions have an impact that may cause serious deterioration of a person's state of health (Rule 11, medical device regulations).[1] Active therapeutic devices with an integrated or incorporated diagnostic function which significantly determines the patient management by the device, such as closed loop systems, are classified as class III (Rule 22, medical device regulations).[1]

Applying these criteria to the field of diabetes, we consider the following medical devices as having a high risk:

- Implantable continuous glucose monitoring systems.
- Implantable pumps (regardless of mode of insulin delivery).
- Automated insulin delivery devices (software as a medical device): herein, we will exclude sensor-augmented insulin pumps with low glucose threshold suspend and predictive low glucose suspend features.

These devices represent a special case for high-risk devices because they incorporate components for monitoring glucose levels, which if standalone would qualify as in vitro diagnostic devices, combined with external and internally implanted hardware, and drug delivery systems driven by control algorithms.

Given the current lack of a complete and fully functional database with registered CE-marked devices, we will attempt to identify information on manufacturers, authorised representatives, notified bodies, date of certification and vigilance data for each device through: (a) press releases available online or scientific publications mentioning the date of CE marking; (b) contacting the device manufacturers and (c) national databases of European Regulatory Authorities or other stakeholders. We will also consult European Database on Medical Devices database with the knowledge that registration of medical devices is not mandatory yet.[8] A draft list of eligible medical devices in the field of diabetes is provided in table 1.

Table 1 Draft list of eligible medical devices in the field of diabetes

Class of device	Device	Manufacturer	CE mark approval date
Implantable CGM devices	Implantable Eversense CGM sensor	Senseonics Inc.	2016
Implantable insulin pumps	MiniMed MIP2007C	Medtronic	2013
	DiaPort	Roche	2012
Automated insulin delivery devices			
Hybrid closed-loop systems	MiniMed 670G	Medtronic	2018
	MiniMed 780 G	Medtronic	2020
	Control-IQ	Tandem Diabetes Care	2020
	DBLG1	Diabeloop	2018
	Inreda AP	Inreda Diabetic	2016
	Tidepool Loop	Tidepool	Pending
	Omnipod 5 system	Insulet	2022
	iLet Bionic Pancreas System	Medtech Beta Bionics	Pending
	CamAPS FX	CamDiab	2020
Fully closed-loop systems	CamAPS HX	CamDiab	2020*

*CE mark approval but not commercially available
CGM, continuous glucose monitoring.

METHODS AND ANALYSIS

Study protocol

The current protocol has been registered in PROSPERO (CRD42022366871) and has been reported using the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols Guidelines (online supplemental material 1).[9] We will consult the Cochrane Collaboration Handbook to perform our systematic review.[10] The systematic review will be reported in accordance with the PRISMA 2020 guidelines for transparent reporting.[11]

Searches

An expert medical librarian carried out the literature searches. A variety of databases including Embase (Elsevier), Medline All (Ovid), Cochrane Library (Wiley), Science Citation Index Expanded and Emerging Sources Citation Index (Web of Science) were searched from inception to 2022 (online supplemental material 2). The search strategy consists of controlled vocabulary terms (eg, MeSH and EMTREE) and free text terms for the following main elements: (a) diabetes and hyperglycaemia, (b) device-sensitive search algorithms and (c) study design. Study design search filters were adapted and applied to the search strategies. Animal studies were excluded. No language or publication dates limits were applied. Search strategies were translated accordingly for each information source. Grey literature sources were not searched. Prior to the formal abstract screening, a pilot phase between the reviewers was carried out to ensure adequate comprehension and high inter-rater reliability. The final search strategy is presented in online supplemental material 2.

Eligibility criteria

Inclusion criteria

We will include published clinical investigations:

- That evaluate the efficacy and/or safety and/or usability of high-risk medical devices applied for the management of diabetes.
- Of observational and experimental designs, including randomised controlled trials, non-randomised trials, cohort studies, case–control studies, cross-sectional studies and case series.
- Performed in humans.
- No restrictions will be imposed on language or time.

Exclusion criteria

We will exclude:

- Studies in animals, letters to the editor, proceedings, reviews, systematic reviews, meta-analyses, conference abstracts, case studies or expert opinion documents.
- Clinical investigations on medical devices that are not CE marked or not on a CE roadmap at the time of the search.

PICO components

Population/study, intervention, comparator and outcome (PICO) components are specified as follows:

- Participants/population: subjects with hyperglycaemia or diabetes.

We will include both paediatric and adult populations.

- Intervention/exposure: high-risk medical devices for diabetes management.
- Comparator(s)/control: any or no comparator.

Eligible studies should evaluate at least one of the devices of interest in comparison to any control group (active intervention, sham-procedure, placebo or no intervention).

- Outcomes: outcomes related to the efficacy, safety, and usability of medical devices.

Outcomes include:

Efficacy

Metrics of glucose control which include glycated haemoglobin (reflecting average blood glucose concentrations for the past 2–3 months) as well as metrics calculated from blood glucose or interstitial glucose concentrations (eg, proportion of values within, above and below range), according to a recently published international consensus statement[12]; acute and chronic glucose-related complications.

Safety

- Severe hypoglycaemia and diabetic ketoacidosis.
- Device-related serious adverse events.
- Device deficiencies (eg, malfunction, misuse and inadequate labelling).
- Field safety notices.

Usability

- Objective usability (technical performance, eg, % time device was operational).
- Perceived usability (eg, technology acceptance, ease of use and perceived usefulness).
- Patient-reported outcome measures for devices used for disease self-management (eg, INSPIRE measures and measures of quality of life, fear of hypoglycaemia and diabetes distress).[13]

Study selection and data extraction

Search results from database searches will be exported to EndNote (V.20) citation management tool. Search results will be de-duplicated in EndNote (V.20), and imported to the Rayyan screening software for title/abstract and full text screening.[14] Two independent reviewers will screen the titles and abstracts of the studies retrieved during the searches, and the full text articles of identified articles will be obtained and fully evaluated. Any disagreements regarding inclusion will be resolved through consensus. In case of disagreement, a third independent reviewer will be consulted. The full texts and reference lists of the selected articles will also be hand searched in order to identify additional studies for inclusion. Abstracts and articles written in a language not spoken by the authors will be translated with the help of an online translator tool (eg, DeepL). Data extraction will be performed for each study using a predesigned data collection form.

In particular, the following PICO components will be extracted from each study.

Population/study

- Journal, first author name, year of publication and funding sources (industry-related/non-industry-related/both/none declared).
- Study design, including observational or experimental; prospective or retrospective and outpatient or inpatient or supervised environments (clinical research facilities, hotels and diabetes camps).
- Recruitment period and follow-up duration.
- Sample size of the study and demographics of study participants.

Intervention

- Product name.
- Manufacturer.
- Date of CE mark approval if available.
- CE mark number and name of the notified body if available.

Comparator

- Medical therapy/standard care.
- Devices, drug-delivery devices, non-drug treatments.
- Sham procedure.
- No intervention.

Outcome

In each study, we will specify the outcome of interest, the outcome measure and the time-point of the assessment during follow-up. We will also record whether sex or age-specific subgroups analyses are performed.

Risk of bias assessment of included studies

The quality of the included studies will be assessed separately by two reviewers. We will use the Newcastle-Ottawa Scale (NOS) for observational studies. The NOS scale evaluates the study quality based on three domains, namely, the selection of participants, the comparability of study groups and the ascertainment of the outcomes of interest.[15] Each study can be awarded a maximum of nine stars. We will assess the quality of interventional studies using a revised tool for assessing the risk of bias in randomised trials (RoB 2) and a tool for assessing the risk of bias in non-randomised studies of interventions (ROBINS-I).[16 17] The strength of the overall quality of the evidence will be evaluated using the Grading of Recommendations Assessment, Development and Evaluation scale.[18]

Strategy for data synthesis

We will provide a narrative synthesis of the findings of the included studies. Effect estimates will be reported in a summary table. Using descriptive statistics, we will report study characteristics, type of interventions and results for each device. We will assess potential differences across different study designs (ie, observational studies vs randomised trials), across different classes of devices, and across different products in the same class of device. We will assess characteristics of the clinical studies that were available prior to the market release (CE marking) of the device and the evidence obtained post-market approval. If applicable, we will evaluate whether there are differences in the results when comparing men versus women, and younger versus older populations. The studies will be ordered by ascending year and we will evaluate whether the earliest published studies report sex or age differences more often than the subsequently published studies. For comparisons between categorical variables, we will use the χ^2 test, or Fisher's exact test, as appropriate. The data will be quantitatively synthesised if at least two studies report effect estimates on a particular medical device and a particular outcome that are sufficiently homogenous for meta-analysis. If a meta-analysis is possible, the effect estimates will be pooled using random effects models, and forest plots will be constructed. Heterogeneity will be assessed by using the I^2 statistic according to the most recent version of the Cochrane Handbook: 0%–40%: might not be important; 30%–60%: may represent moderate heterogeneity; 50%–90%: may represent substantial heterogeneity and 75%–100%: considerable heterogeneity.[19] We will also perform 'leave-one out analysis' in order to evaluate the impact of individual studies on the overall results. The possibility of publication bias will be examined using funnel plots and Egger's test.[20] The statistical analyses will be performed in Stata V.15.1 (StataCorp LLC, TX, USA).

Patient and public involvement

None.

Ethics and dissemination

No ethical approval is needed for this systematic review, as it is based on already published data. Our findings will be published in a peer-reviewed journal. The systematic review is now in progress; the data extraction is scheduled to have started in February 2023, and the expected end time is October 2023.

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Collaborators On behalf of Coordinating Research and Evidence for Medical Device investigators (see Appendix).

Contributors AB and LB designed the study and drafted the study protocol. AB, TR and LB contributed to the preparation of the search strategy. AB, ML, FW, JK, TR, AGF, CS, RH and LB revised the protocol critically for important intellectual content. All authors read and approved the final study protocol. AB, ML and LB will be the guarantors of the review.

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Competing interests RH reports having received speaker honoraria from Eli Lilly, Dexcom and Novo Nordisk, receiving license fees from BBraun, and being director at CamDiab. All other authors declare no competing interests.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

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Appendix. CORE-MD Investigators

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Supplemental Material 1. PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist.

Recommended items to address in a systematic review protocol*

Topic	Item No	Checklist item	Section
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	Title
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	NA
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	Methods, paragraph 1
Authors:			Authors
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	NA
Support:			Support
Sources	5a	Indicate sources of financial or other support for the review	
Sponsor	5b	Provide name for the review funder and/or sponsor	
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	Introduction, paragraphs 1,2
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	Introduction, paragraph 3
METHODS			

Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	Methods, paragraph 5
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	Methods, paragraph 2; Supplemental Material 2
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	Methods, paragraph 2; Supplemental Material 2
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	Methods, paragraph 6
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	Methods, paragraph 6
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	Methods, paragraph 6
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	Methods, paragraph 6
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	Methods, paragraph 5
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	Methods, paragraph 7
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	Methods, paragraph 8
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	Methods, paragraph 8
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	Methods, paragraph 8
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	Methods, paragraph 8
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	Methods, paragraph 8

Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	Methods, paragraph 7

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

Abbreviation: NA, not applicable.

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.

Supplemental Material 2. Databases, coverage and search strategy

We searched the following information sources: Embase (Elsevier), Medline All (Ovid), Cochrane Library (Wiley), Science Citation Index Expanded and Emerging Sources Citation Index (Web of Science) from inception to 2022. Study design search filters were incorporated and adapted from the BMJ Best Practice: https://bestpractice.bmj.com/info/toolkit/learn-ebm/study-design-search-filters/ The Cochrane Handbook RCT search filter (sensitivity max. version 2008) was applied to the Medline All (Ovid) search: https://training.cochrane.org/handbook/current/chapter-04#section-4-4-7

Embase (Elsevier), Coverage 1947-Present

#13 #9 AND #12

#12 #10 OR #11

#11 'cohort analysis'/exp OR 'longitudinal study'/exp OR 'prospective study'/exp OR 'follow up'/exp OR 'retrospective study'/de OR 'cross-sectional study'/de OR 'observational study'/de OR 'population research'/de OR 'case control study'/exp OR 'major clinical study'/de OR cohort*:ab,ti OR (((prospectiv* OR populat* OR observ* OR retrospect* OR epidemiologic*) NEAR/3 (stud* OR trial*)):ab,ti) OR ((case* NEAR/3 control*):ab,ti) OR ((case* NEAR/3 series):ab,ti) OR ((cross NEAR/1 section*):ab,ti) OR 'case cohort*':ab,ti OR 'nested case control*':ab,ti OR prospectiv*:ab,ti OR retrospectiv*:ab,ti OR longitudinal*:ab,ti OR 'follow up':ab,ti OR followup:ab,ti OR population-based:ab,ti

#10 random*:ti,ab OR placebo*:ti,ab OR 'single blind*':ti,ab OR 'double blind*':ti,ab OR 'triple blind*':ti,ab OR ((clinical NEXT/1 trial*):ti,ab) OR 'randomized controlled trial'/exp

#9 #7 NOT #8

#8 [animals]/lim NOT [humans]/lim

#7 #5 AND #6

#6 #3 OR #4

#5 #1 OR #2

#4 'ambulatory insulin infusion pump*':ti,ab OR 'artificial pancreas':ti,ab OR 'artificial endocrine pancreas':ti,ab OR 'automated pancreas':ti,ab OR 'automated insulin delivery':ti,ab OR 'automated insulin therapy':ti,ab OR 'automated insulin dosing':ti,ab OR 'bionic pancreas':ti,ab OR 'closed-loop control':ti,ab OR 'closed-loop system':ti,ab OR 'continuous intraperitoneal insulin infusion*':ti,ab OR 'do-it-yourself automated pancreas':ti,ab OR 'hybrid closed-loop':ti,ab OR 'implantable glucose monitor*':ti,ab OR 'implantable continuous glucose monitor*':ti,ab OR 'implanted insulin pump*':ti,ab OR 'implantable insulin pump*':ti,ab OR 'implanted infusion pump*':ti,ab OR 'implantable infusion pump*':ti,ab OR 'implantable cgm*':ti,ab OR 'sensor-augmented pump*':ti,ab OR 'implantable glucose sensor*':ti,ab OR 'medtronic 670g':ti,ab,dn,df OR minimed*:ti,ab,dn,df OR diaport*:ti,ab,dn,df OR 'control iq*':ti,ab,dn,df OR diabeloop*:ti,ab,dn,df OR tidepool*:ti,ab,dn,df OR 'omnipod* 5':ti,ab,dn,df OR 'ilet bionic pancreas*':ti,ab,dn,df OR eversense*:ti,ab,dn,df OR 'camaps hx*':ti,ab,dn,df OR 'camaps fx*':ti,ab,dn,df OR

dblg1*:ti,ab,dn,df OR (((closed OR hybrid) NEAR/3 (insulin OR glucose) NEAR/3 (system* OR delivery OR device* OR therapy OR algorithm)):ti,ab)

#3 'artificial pancreas'/exp OR 'closed loop control'/de OR 'closed loop control system'/de OR 'closed loop insulin delivery'/de OR 'closed loop insulin delivery system'/de OR 'continuous glucose monitoring device'/de OR 'glucose monitoring/insulin pump system'/de OR 'hybrid closed loop system'/de OR 'implantable drug delivery system'/de OR 'implantable infusion pump'/de OR 'insulin delivery device'/de OR 'insulin implant'/exp OR 'insulin pump therapy'/de

#2 diabet*:ti,ab OR hypoglycemi*:ti,ab OR hypoglycaemi*:ti,ab OR hyperglycemi*:ti,ab OR hyperglycaemi*:ti,ab OR 'iddm':ti,ab OR 'niddm':ti,ab OR 't1dm':ti,ab OR 't2dm':ti,ab

#1 'diabetes mellitus'/de OR 'insulin dependent diabetes mellitus'/exp OR 'non insulin dependent diabetes mellitus'/de

Medline All (Ovid), Coverage 1946-Present

1 diabetes mellitus/ or diabetes mellitus, type 1/ or diabetes mellitus, type 2/

2 (diabet* or hypoglycemi* or hypoglycaemi* or hyperglycemi* or hyperglycaemi* or iddm or niddm or t1dm or t2dm).ti,ab.

3 infusion pumps, implantable/ or pancreas, artificial/

4 ("ambulatory insulin infusion pump*" or "artificial pancreas" or "artificial endocrine pancreas" or "automated pancreas" or "automated insulin delivery" or "automated insulin therapy" or "automated insulin dosing" or "bionic pancreas" or "closed-loop control" or "closed-loop system" or

"continuous intraperitoneal insulin infusion*" or "do-it-yourself automated pancreas" or "hybrid closed-loop" or "implantable glucose monitor*" or "implantable continuous glucose monitor*" or "implanted insulin pump*" or "implantable insulin pump*" or "implanted infusion pump*" or "implantable infusion pump*" or "implantable cgm*" or "sensor-augmented pump*" or "implantable glucose sensor*" or "medtronic 670g" or minimed* or diaport* or "control iq*" or diabeloop* or tidepool* or "omnipod* 5" or "ilet bionic pancreas*" or eversense* or "camaps hx*" or "camaps fx*" or dblg1* or ((closed or hybrid) adj3 (insulin or glucose) adj3 (system* or delivery or device* or therapy or algorithm))).ti,ab.

5 1 or 2

6 3 or 4

7 5 and 6

8 exp animals/ not humans/

9 7 not 8

10 exp cohort analysis/ or cross-sectional studies/ or observational study/ or case control studies/ or (cohort* or ((prospectiv* or populat* or observ* or retrospect* or epidemiologic*) adj3 (stud* or trial*)) or (case* adj3 control*) or (case* adj3 series) or (cross adj1 section*) or case cohort* or nested case-control* or prospectiv* or retrospectiv* or longitudinal* or follow-up or followup or population-based).ab,ti.

11 randomized controlled trial.pt.

12 controlled clinical trial.pt.

13 randomi?ed.ab.

14 placebo.ab.

15 drug therapy.fs.

16 randomly.ab.

17 trial.ab.

18 groups.ab.

19 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18

20 exp animals/ not humans.sh.

21 19 not 20

22 10 or 21

23 9 and 22

Cochrane Library (Wiley), Coverage 1996-Present

Advanced Search via Search Manager

#1 [mh ^"diabetes mellitus"] OR [mh ^"diabetes mellitus, type 2"] OR [mh ^"diabetes mellitus, type 1"] OR [mh "latent autoimmune diabetes in adults"]

#2 diabet*:ti,ab OR hypoglycemi*:ti,ab OR hypoglycaemi*:ti,ab OR hyperglycemi*:ti,ab OR hyperglycaemi*:ti,ab OR iddm:ti,ab OR niddm:ti,ab OR t1dm:ti,ab OR t2dm:ti,ab

#3 [mh "pancreas, artificial"] OR [mh "infusion pumps, implantable"]

#4 ((ambulatory NEXT insulin NEXT infusion NEXT pump*) OR "artificial pancreas" OR "artificial endocrine pancreas" OR "automated pancreas" OR "automated insulin delivery" OR "automated insulin therapy" OR "automated insulin dosing" OR "bionic pancreas" OR "closed-loop control" OR "closed-loop system" OR (continuous NEXT intraperitoneal NEXT insulin NEXT infusion*) OR "do-it-yourself automated pancreas" OR "hybrid closed-loop" OR (implantable NEXT glucose NEXT monitor*) OR (implantable NEXT continuous NEXT glucose NEXT monitor*) OR (implanted NEXT insulin NEXT pump*) OR (implantable NEXT insulin NEXT pump*) OR (implanted NEXT infusion NEXT pump*) OR (implantable NEXT infusion NEXT pump*) OR (implantable NEXT cgm*) OR (sensor NEXT augmented NEXT pump*) OR (implantable NEXT glucose NEXT sensor*) OR "medtronic 670g" OR minimed* OR diaport* OR (control NEXT iq*) OR diabeloop* OR tidepool* OR (omnipod* NEXT 5) OR (ilet NEXT bionic NEXT pancreas*) OR eversense* OR (camaps NEXT hx*) OR (camaps NEXT fx*) OR dblg1* OR ((closed OR hybrid) NEAR/3 (insulin OR glucose) NEAR/3 (system* OR delivery OR device* OR therapy OR algorithm))):ti,ab

#5 #1 OR #2

#6 #3 OR #4

#7 #5 AND #6

Science Citation Index Expanded and Emerging Sources Citation Index (Web of Science), Coverages, 1900-Present & 2017-Present

1 TS=(diabet* OR hypoglycemi* OR hypoglycaemi* OR hyperglycemi* OR hyperglycaemi* OR iddm OR niddm OR t1dm OR t2dm)

2 TS=("ambulatory insulin infusion pump*" OR "artificial pancreas" OR "artificial endocrine pancreas" OR "automated pancreas" OR "automated insulin delivery" OR "automated insulin therapy" OR "automated insulin dosing" OR "bionic pancreas" OR "closed-loop control" OR "closed-loop system" OR "continuous intraperitoneal insulin infusion*" OR "do-it-yourself automated pancreas" OR "hybrid closed-loop" OR "implantable glucose monitor*" OR "implantable continuous glucose monitor*" OR "implanted insulin pump*" OR "implantable insulin pump*" OR "implanted infusion pump*" OR "implantable infusion pump*" OR "implantable cgm*" OR "sensor-augmented pump*" OR "implantable glucose sensor*" OR "medtronic 670g" OR minimed* OR diaport* OR "control iq*" OR diabeloop* OR tidepool* OR "omnipod* 5" OR "ilet bionic pancreas*" OR eversense* OR "camaps hx*" OR "camaps fx*" OR dblg1* OR ((closed OR hybrid) NEAR/3 (insulin OR glucose) NEAR/3 (system* OR delivery OR device* OR therapy OR algorithm)))

3 TS=((cohort* OR ((prospectiv* OR populat* OR observ* OR retrospect* OR epidemiologic*) NEAR/3 (stud* OR trial*)) OR (case* NEAR/3 control*) OR (case* NEAR/3 series) OR (Cross NEAR/2 section*) OR case-cohort* OR nested-case-control* OR prospectiv* OR retrospectiv* OR longitudinal* OR follow-up OR followup OR population-based))

4 TS=(random* OR placebo* OR "single blind*" OR "double blind*" OR "triple blind*" OR (clinical NEAR/0 trial*) OR "randomized controlled trial" OR RCT)

5 #3 OR #4

6 #1 AND #2 AND #5