ISRCTN74214605 https://doi.org/10.1186/ISRCTN74214605

Hypoglycemia in type 1 diabetes

Submission date 11/03/2024	**Recruitment status** Recruiting	[X] Prospectively registered [X] Protocol [_] Statistical analysis plan [_] Results [_] Individual participant data [X] Record updated in last year
Registration date 26/03/2024	**Overall study status** Ongoing	
Last Edited 01/10/2026	**Condition category** Nutritional, Metabolic, Endocrine	

Plain English summary of protocol

Background and study aims
People with type 1 diabetes (T1D) are at risk of complications that can be minimized by maintaining normal blood glucose levels. Of particular concern to people with T1D is hypoglycemia, in which blood glucose levels drop below normal and can lead to sweating, confusion, excessive hunger and in some cases, coma. On average, a person with T1D has two episodes of hypoglycemia per week and one or more episodes per year of severe hypoglycemia, defined as requiring third-party assistance. In addition, a person who has experienced repeated hypoglycemic events over the years is at risk of becoming less aware of the oncoming symptoms, which places the person at greater risk. This phenomenon is called impaired awareness of hypoglycemia (IAH) and affects 20-25% of individuals with T1D. Therefore, this study aims to compare hybrid closed loop (HCL) devices with psycho-educational programs to determine which can reduce the occurrence of IAH events. An HCL system, also known as an artificial pancreas, consists of a continuous glucose monitor (CGM), an insulin pump, and an algorithm that automatically manages insulin delivery.

Who can participate?
Patients aged 18-75 years who have been clinically diagnosed with T1D for at least 10 years and have experienced impaired awareness of hypoglycemic events

What does the study involve?
A participant will be assigned to an intervention that consists of an HCL device and/or a psycho-educational program. After 12 months on the intervention, the investigators will determine whether the intervention has been effective in reducing the occurrence of IAH events. If yes, then the participant will continue with that intervention for months 13-24. If no, then the participant will be assigned an alternative intervention for months 13-24. Thus, a participant will be asked to continue in the study for 24 months, during which time there will be nine in-person clinic visits and 11 telephone/videoconference contacts.

What are the possible benefits and risks of participating?
The potential benefits of the CLEAR trial are that participants can learn the approach that works best for them in identifying and responding to hypoglycemic events. The risks from study participation include potential skin reactions where the continuous glucose monitor needle is inserted, potential bruising from blood draws (venipuncture), and the potential for hypoglycemic and hyperglycemic events.

Where is the study run from?
The Coordinating Center for the CLEAR trial is located at the Penn State College of Medicine (USA), and the eight recruitment sites are located at:
1. Advent Health (USA)
2. University of California, San Diego (USA)
3. University of Kentucky (USA)
4. University of Minnesota (USA)
5. University of Pennsylvania (USA)
6. University of Leicester (UK)
7. University of Sheffield (UK)
8. University of Melbourne (Australia)

When is the study starting and how long is it expected to run for?
September 2022 to December 2027

Who is funding the study?
National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) (USA)

Who is the main contact?
1. Vernon M. Chinchilli, vchinchi@psu.edu
2. Abid Kazi, akazi@pennstatehealth.psu.edu
3. Venus Grella, vgrella@pennstatehealth.psu.edu

Contact information

Type(s)
Principal investigator

Contact name
Dr Elizabeth Seaquist

Contact details
University of Minnesota
Medical School
MMC 194 Mayo
420 Delaware St. SE
Minneapolis, MN
United States of America
55455
+1 (0)612 625 3654
seaqu001@umn.edu

Type(s)
Principal investigator

Contact name
Dr Simon Heller

Contact details

School of Medicine and Biosciences
University of Sheffield
Beech Hill Road
Room FU24
Sheffield
United Kingdom
S10 2RX
+44 (0)114 215 9009
s.heller@sheffield.ac.uk

Type(s)
Principal investigator

Contact name
Dr Vernon Chinchilli

ORCID ID
https://orcid.org/0000-0001-6488-7809

Contact details
Department of Public Health Sciences
Penn State College of Medicine
90 Hope Drive, Suite 2200
Hershey, PA
United States of America
17033
+1 (0)717 531 7178
vchinchi@psu.edu

Type(s)
Scientific

Contact name
Ms Venus Grella

Contact details
Department of Public Health Sciences
Penn State College of Medicine
90 Hope Drive, Suite 2200
Hershey, PA
United States of America
17033
+1 (0)717 531 0003, Ext 343413
vgrella@pennstatehealth.psu.edu

Type(s)
Public

Contact name
Dr Abid Kazi

Contact details
Department of Public Health Sciences
Penn State College of Medicine
90 Hope Drive, Suite 2200
Hershey, PA
United States of America
17033
+1 (0)717 531 0003, Ext 320036
akazi@pennstatehealth.psu.edu

Additional identifiers

ClinicalTrials.gov (NCT)
NCT06325202

Protocol serial number
STUDY00020946

Study information

Scientific Title
Closed loop and education for hypoglycemia awareness restoration (CLEAR)

Acronym
CLEAR

Study objectives
Hypothesis 1: At 12 months, those allocated to Usual Care plus My HypoCOMPaSS will be more likely to have improved counter-regulatory responses (CRR) and total symptomatic responses than those allocated to hybrid closed loop (HCL).
Hypothesis 2: At 12 months, those allocated to HCL plus My HypoCOMPaSS will be more likely to have improved hypoglycemic awareness and improved CRR than those using HCL alone.
Hypothesis 3: At 24 months, CRR will improve further among those who had restored CRR at 12 months.
Hypothesis 4: At 24 months, those allocated to HARPdoc for months 12-24 will be more likely to have improved hypoglycemic awareness and CRR than those who continue with the therapy allocated at baseline.

Ethics approval required
Ethics approval required

Ethics approval(s)
1. Approved 31/10/2024, Penn State Human Research Protection Program (101 Technology Center, University Park, PA, 16802, United States of America; +1 (0)814 865 1775; irb-orp@psu.edu), ref: STUDY00020946

2. Approved 28/08/2024, East Midlands - Leicester Central Research Ethics Committee (2 Redman Place, Stratford, London, E20 1JQ, United Kingdom; +44 207 104 8284; leicestercentral.rec@hra.nhs.uk), ref: 24/EM/0156

Primary study design
Interventional

Study design
Multicenter unblinded sequential multiple assignment randomized trial (SMART) design over 24 months with possible re-randomization at 12 months

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Type 1 diabetes with impaired awareness of hypoglycemia

Interventions
The CLEAR trial involves three interventions in various combinations:
1. Hybrid closed loop (HCL) systems consist of a continuous glucose monitor (CGM), an insulin pump, and an algorithm that automatically modulates insulin delivery based on CGM sensor interstitial glucose values. HCL systems thus increase insulin delivery when the sensor glucose is predicted to be high and decrease insulin delivery when the sensor glucose is predicted to be low, and so are designed to help maintain time in range.
2. My HypoCOMPaSS (MyHC) is a brief, standardized psycho-educational program delivered in small groups. Facilitated discussions focus on advocating rigorous avoidance of hypoglycemia while maintaining time in target glycemic range. The four compass points (NESW) are used to illustrate the imperatives: 'Now; No delay' (never delay hypoglycemia treatment); 'Establish your Extra risks' (and times when risk is highest); 'Scan for Subtle Symptoms' (of hypoglycemia); be Wary even While asleep (through watchful detection and active prevention of hypoglycemia while asleep).
3. The HARPdoc intervention is a psychological intervention, delivered to small groups of adults with type 1 diabetes (n = approx. 6) by two diabetes educators trained and supported by a clinical psychologist, which uniquely addresses the unhelpful health beliefs of people with treatment-resistant impaired awareness of hypoglycemia and severe hypoglycemia. The educators use motivational interviewing and cognitive behavioral theory to address the main cognitive barriers to hypoglycemia avoidance addressed above.

CLEAR invokes a sequential multiple assignment randomized trial (SMART) design, which is an adaptive design. Participants not responding well to their initially randomized treatment are assigned/randomized to alternative treatments. There are two strata of study participants in the CLEAR trial, those naïve to an HCL device and those not naïve to an HCL device.

HCL naïve stratum:
1. Participants randomized to the HCL device who show improvement of the counterregulatory epinephrine and autonomic symptom responses, as determined by the measurements at 12 months, will continue with the HCL device for months 12-24
2. Participants randomized to the HCL device who do not show improved epinephrine and autonomic symptom responses, as determined by the measurements at 12 months, will be re-randomized to continued HCL (to determine if more time is needed for the intervention to be effective) or HCL + HARPdoc for months 12-24
3. Participants randomized to usual care (UC) + MyHC who show improved epinephrine and autonomic symptom responses as determined by the measurements at 12 months, will continue with UC + MyHC for months 12-24 to determine the durability of improved epinephrine and autonomic symptom responses

4. Participants randomized to UC + MyHC who do not show restoration of the counterregulatory epinephrine and autonomic symptom responses as determined by the measurements at 12 months, will be assigned to HCL for months 12-24

HCL non-naïve stratum:
1. Participants randomized to the HCL device who show improvement of the counterregulatory epinephrine and autonomic symptom responses, as determined by the measurements at 12 months, will continue with the HCL device for months 12-24
2. Participants randomized to the HCL device who do not show improvement of the counterregulatory epinephrine and autonomic symptom responses, as determined by the measurements at 12 months, will be re-randomized to HCL alone (to determine if more time is needed for the intervention to be effective) or to HCL + HARPdoc, an IAH psychoeducational program, for months 12-24
3. Participants randomized to HCL + MyHC who show improvement of the counterregulatory epinephrine and autonomic symptom responses, as determined by the measurements at 12 months, will continue with HCL + MyHC for months 12-24
4. Participants randomized to HCL + MyHC who do not show improvement of the counterregulatory epinephrine and autonomic symptom responses, as determined by the measurements at 12 months, will be re-randomized to continued HCL + MyHC (to determine if more time is needed for the intervention to be effective) or HCL + HARPdoc for months 12-24

The Coordinating Center will randomly assign participants to their interventions via its web-based data management system (DMS). Randomization will be stratified according to clinical center and duration of type 1 diabetes (< 25 years and ≥ 25 years). After a research coordinator confirms that a participant at day 0 is eligible for enrollment, the participant completes the baseline hyperinsulinemic-hypoglycemic clamp. Next, the research coordinator will enter the private and secure DMS via the internet and enter the appropriate information. The research coordinator will then receive the intervention assignment that the participant will follow for the first 12 months. After the 12-month visit with the second clamp, and after the lab analysis of epinephrine is determined, the research coordinator again will enter the DMS and enter the appropriate information and receive instructions as to whether the participant will maintain the current intervention or be re-randomized to a new intervention. Study interventions will not be blinded.

Intervention Type
Mixed

Primary outcome(s)
1. Epinephrine (pg/ml) measured using a plasma sample - a change in epinephrine (pg/ml) that exceeds 125 pg/ml between (1) 12 months and baseline, and (2) 24 months and baseline, measured during the clamp studies at 0 (baseline), 12, and 24 months
2. Hypoglycemia symptoms measured using the Towler questionnaire - the Towler questionnaire consists of 12 questions each on a 0-6 Likert scale; a change in the questionnaire that exceeds 20% between (1) 12 months and baseline, and (2) 24 months and baseline, measured during the clamp studies at 0 (baseline), 12, and 24 months

Key secondary outcome(s)
1. Glucagon measured from a plasma sample during the clamp studies at 0 (baseline), 12, and 24 months
2. Pancreatic polypeptide measured from a plasma sample during the clamp studies at 0 (baseline), 12, and 24 months

3. Free fatty acids measured from a plasma sample during the clamp studies at 0 (baseline), 12, and 24 months
4. Glucose infusion rate, measured as the rate at which dextrose is administered, during the clamp studies at 0 (baseline), 12, and 24 months
5. HbA1c measured from a plasma sample during the clamp studies at 0 (baseline), 12, and 24 months
6. % of time with hypoglycemia <70 mg/dL determined from the continuous glucose monitor (CGM) sensor, measured during the 4 weeks prior to each clamp study at 0 (baseline), 12, and 24 months
7. % of time with hypoglycemia <54 mg/dL determined from the continuous glucose monitor (CGM) sensor, measured during the 4 weeks prior to each clamp study at 0 (baseline), 12, and 24 months
8. Number of hypoglycemic events determined from the continuous glucose monitor (CGM) sensor, measured during the four weeks prior to each clamp study at 0 (baseline), 12, and 24 months
9. % time with glucose in range determined from the continuous glucose monitor (CGM) sensor, measured during the 4 weeks prior to each clamp study at 0 (baseline), 12, and 24 months
10. Sensor glucose coefficient of variation determined from the continuous glucose monitor (CGM) sensor, measured during the 4 weeks prior to each clamp study at 0 (baseline), 12, and 24 months
11. Sensor use as the average number of days per week determined from the continuous glucose monitor (CGM) sensor, measured during the 4 weeks prior to each clamp study at 0 (baseline), 12, and 24 months
12. Glycemia risk index determined from the continuous glucose monitor (CGM) sensor, measured during the 4 weeks prior to each clamp study at 0 (baseline), 12, and 24 months
13. Trail Making Test Part B – the amount of time required to complete the test during the clamp studies at 0 (baseline), 12, and 24 months
14. Four Choice Reaction Time, which measures reaction time and coordination, during the clamp studies at 0 (baseline), 12, and 24 months
15. Sleep duration determined from an activity monitor smartwatch, measured during the 2 weeks prior to each clamp study at 0 (baseline), 12, and 24 months
16. Sleep quality determined from an activity monitor smartwatch, measured during the 2 weeks prior to each clamp study at 0 (baseline), 12, and 24 months
17. 24-hour step count determined from an activity monitor smartwatch, measured during the 2 weeks prior to each clamp study at 0 (baseline), 12, and 24 months
18. Exercise bouts determined from an activity monitor smartwatch, measured during the 2 weeks prior to each clamp study at 0 (baseline), 12, and 24 months
19. Resting heart rate determined from an activity monitor smartwatch, measured during the 2 weeks prior to each clamp study at 0 (baseline), 12, and 24 months
10. Heart rate during exercise determined from an activity monitor smartwatch, measured during the 2 weeks prior to each clamp study at 0 (baseline), 12, and 24 months
11. Heart rate variability determined from an activity monitor smartwatch, measured during the 2 weeks prior to each clamp study at 0 (baseline), 12, and 24 months
12. Sleep quality, hypoglycemia fear, hypoglycemia burden, and other symptoms measured using the Hypo-METRICS questionnaire, a Person-Reported Outcome Measure (PROM) specific to hypoglycemia, measured 2 weeks prior to each clamp study at 0 (baseline), 12, and 24 months
13. Confidence in staying safe from severe hypoglycemic events measured using the Hypoglycemic Confidence Scale questionnaire, a Person-Reported Outcome Measure (PROM) specific to hypoglycemia, measured 2 weeks prior to each clamp study at 0 (baseline), 12, and 24 months
14. Activities to avoid hypoglycemia and fears about hypoglycemia measured using the Hypoglycemia Fear Survey-II, a Person-Reported Outcome Measure (PROM) specific to

hypoglycemia, measured 2 weeks prior to each clamp study at 0 (baseline), 12, and 24 months
15. Attitudes to, and activities to avoid, hypoglycemic events measured using the Attitudes to Awareness of Hypoglycaemia, a Person-Reported Outcome Measure (PROM) specific to hypoglycemia, measured 2 weeks prior to each clamp study at 0 (baseline), 12, and 24 months
16. Distress encountered in daily living due to type 1 diabetes measured using the Type 1 Diabetes Distress Scale, a Person-Reported Outcome Measure (PROM) specific to hypoglycemia, measured 2 weeks prior to each clamp study at 0 (baseline), 12, and 24 months
17. Activities pursued for managing one's diabetes measured using the Diabetes Self-Management Questionnaire, a Person-Reported Outcome Measure (PROM) specific to hypoglycemia, measured 2 weeks prior to each clamp study at 0 (baseline), 12, and 24 months
18. Activities pursued to manage one's diabetes measured using the Diabetes Management Experiences Questionnaire, a Person-Reported Outcome Measure (PROM) specific to hypoglycemia, measured 2 weeks prior to each clamp study at 0 (baseline), 12, and 24 months
19. Sleep quality and sleep disturbance measured using the PROMIS Sleep Disturbance – Short Form 8a, measured 2 weeks prior to each clamp study at 0 (baseline), 12, and 24 months
20. Anxiety and depression measured using the Hospital Anxiety and Depression Scale, measured 2 weeks prior to each clamp study at 0 (baseline), 12, and 24 months
21. Experiences and worries about hypoglycemic events measured using the 12-Item Hypoglycemia Impact Profile, measured 2 weeks prior to each clamp study at 0 (baseline), 12, and 24 months
22. Quality of life measured using EQ-5D-5L 2 weeks prior to each clamp study at 0 (baseline), 12, and 24 months
23. Device-related adverse events recorded using a self-reported data collection form throughout the duration of the 24 months of follow-up
24. Severe hypoglycemic events recorded using a self-reported data collection form throughout the duration of the 24 months of follow-up
25. Diabetic ketoacidosis (DKA) events recorded using a data collection form completed by a research coordinator throughout the duration of the 24 months of follow-up
26. Hospitalizations recorded using a data collection form completed by a research coordinator throughout the duration of the 24 months of follow-up
27. Emergency room (ER) visits recorded using a data collection form completed by a research coordinator throughout the duration of the 24 months of follow-up
28. Major adverse cardiovascular events (MACE) recorded using a data collection form completed by a research coordinator throughout the duration of the 24 months of follow-up
29. All-cause mortality recorded using a data collection form completed by a research coordinator throughout the duration of the 24 months of follow-up

Completion date
31/12/2027

Eligibility

Key inclusion criteria
1. Age 18-75 years
2. Clinical diagnosis of type 1 diabetes
3. Gold Score or Clarke Score ≥4 (highly associated with IAH)
4. Random non-fasting C-peptide <200 pmol/L
5. Diabetes duration ≥10 years
6. HbA1c <10.5%

7. Total Daily Insulin Dose of <1 unit/kg
8. Ability to read and speak English (because validated non-English versions of the cognitive tests and the educational interventions are not available)

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Mixed

Lower age limit
18 Years

Upper age limit
75 Years

Sex
All

Total final enrolment
0

Key exclusion criteria
1. Medical conditions that limit participation in study activities, as determined by the PI (including but not limited to cognitive dysfunction, reduced hearing, reduced vision, cancer under active treatment, untreated angina, and organ failure)
2. Active alcohol or drug abuse, as defined by DSM criteria of either
2.1. Recurrent use of alcohol/drugs resulting in a failure to fulfil major role obligations at work, school, or home
2.2. Recurrent alcohol/drug use in situations in which it is physically hazardous, or
2.3. Recurrent alcohol or drug-related legal problems
4. Social determinants of health that limit participation in study activities, as determined by the PI (including but not limited to homelessness, food insecurity, and inadequate social support)
5. Seizure disorder unrelated to hypoglycemia-associated seizures, unless documented seizure-free for >12 months and on a stable regimen of anticonvulsant therapy
6. Skin conditions that would preclude the use of a CGM
7. Super-physiologic exposure to steroids within one month of enrollment
8. eGFR <45 ml/min/1.73 m2
9. History of bariatric surgery that irreversibly alters gut innervation and structure
10. Hyper- or hypokalemia (serum potassium >5.5 or <3.5 mmol/L)*
11. Hemoglobin <10 g/dL*
12. Medical condition that requires intermittent or continuous use of glucocorticoids at greater than physiological replacement doses
13. Pregnancy, plan for pregnancy, or breastfeeding
14. Abnormal thyroid function tests of clinical significance, as determined by PI*
15. Liver transaminases >3 times the upper limit of normal*
16. Hospitalization for mental illness in the last year
17. History of adrenalectomy

* At the discretion of the PI, laboratory tests may be repeated once. If the participant is not eligible after the second attempt, then the participant may be screened again.

Date of first enrolment
17/09/2025

Date of final enrolment
30/06/2027

Locations

Countries of recruitment
United Kingdom

England

Australia

United States of America

Study participating centre
University of Leicester
Diabetes Research Centre
Leicester General Hospital
Gwendolen Rd.
Leicester
England
LE5 4PW

Study participating centre
University of Sheffield
School of Medicine and Biosciences
Beech Hill Road
Room FU24
Sheffield
England
S10 2RX

Study participating centre
University of California, San Diego
Altman Clinical and Translational Research Institute (ACTRI)
9452 Medical Center Dr. L1W-515
La Jolla, CA
United States of America
92037

Study participating centre
AdventHealth
Research Institute
301 East Princeton St.
Orlando, Florida
United States of America
32804

Study participating centre
University of Kentucky
Healthy Kentucky Research Building, Room 233
760 Press Ave.
Lexington, Kentucky
United States of America
40508

Study participating centre
University of Minnesota
Medical School
MMC 194 Mayo
420 Delaware St. SE
Minneapolis, MN
United States of America
55455

Study participating centre
University of Pennslyvania
Perelman School of Medicine
12-134 Smilow Center for Translational Research
3400 Civic Center Blvd.
Philadelphia
United States of America
19104

Study participating centre
University of Melbourne
St Vincent’s Hospital
35 Victoria Pde.

Fitzroy, Victoria
Australia
3065

Study participating centre
The Kids Research Institute Australia
Perth Children's Hospital
15 Hospital Avenue
Nedlands
Australia
WA 6009

Sponsor information

Organisation
National Institute of Diabetes and Digestive and Kidney Diseases

ROR
https://ror.org/00adh9b73

Funder(s)

Funder type
Government

Funder Name
National Institute of Diabetes and Digestive and Kidney Diseases

Alternative Name(s)
NIH National Institute of Diabetes and Digestive and Kidney Diseases, NIH/National Institute of Diabetes, Digestive & Kidney Diseases, Experimental Biology and Medicine Institute, National Institute of Arthritis and Metabolic Diseases; National Institute of Arthritis, Metabolism, and Digestive Diseases, National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases, NIDDK, NIAMDD

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location

United States of America

Results and Publications

Individual participant data (IPD) sharing plan

The datasets generated during and/or analyzed during the CLEAR trial will be stored in a publicly available repository: NIDDK Central Repository (https://repository.niddk.nih.gov/home/). It is anticipated that the datasets will be available at the NIDDK Central Repository during the latter part of 2028. The NIDDK Central Repository typically requires that the datasets be in SAS format and that the submission also should include a data dictionary, the data collection forms, the protocol, and the informed consent. Finally, the NIDDK Central Repository requires that the data be de-identified.

IPD sharing plan summary

Available on request, Stored in publicly available repository

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol file		06/03/2024	22/03/2024	No	No