RESTORING THE GLUCAGON SAFETY NET: IMPROVING THE EXPERIENCE OF HYPOGLYCAEMIA IN TYPE 1 DIABETES

Hypoglycaemia is a major clinical and day-to-day challenge in type 1 diabetes and has been identified as a research priority by people living with diabetes through the James Lind Alliance Type 1 Diabetes Priority Setting Partnership. Despite advances in insulin delivery and glucose monitoring, hypoglycaemia remains common, carrying immediate clinical risks and lasting effects on cognition, confidence, self-management and quality of life. Improving outcomes requires not only reducing hypoglycaemia but improving how it is experienced and managed in everyday life.

This Highlight Notice aims to support research that addresses both the immediate and underlying causes of hypoglycaemia, by utilising and improving our understanding of glucagon to reduce risk, improve recovery, and restore confidence and safety for people living with type 1 diabetes.

The Lived Experience of Hypos

This section has been informed by people living with type 1 diabetes and reflects shared experiences identified through engagement with DRSG2 Experts by Experience.

"Hypoglycaemia is more than a drop in blood glucose. It is unpredictable, varies between people and episodes, and can affect every aspect of daily life. Some hypos develop gradually, while others occur with little warning, making activities such as work, exercise, driving and sleep difficult to manage.

The effects often last beyond glucose recovery, affecting cognition, mood, confidence and decision-making before, during and after episodes. Often, we adapt our behaviour to reduce risk, but these adjustments can affect quality of life and independence.

A major challenge is the loss of a reliable physiological 'backup' when glucose falls. In people without diabetes, glucagon helps restore glucose levels, but in type 1 diabetes this response is impaired. Without this safety net, managing hypoglycaemia requires constant attention and creates a lasting burden. The effects can also extend beyond the individual, affecting family members, carers and others.

Improving hypoglycaemia means not only reducing its frequency, but making it more predictable, easier to manage and quicker to recover from. We need both practical solutions that improve life today and advances that restore physiological responses in the future. Research must be informed by people living with type 1 diabetes to ensure it addresses what matters most in everyday life."

Scientific Background and Rationale

Despite advances in diabetes care, hypoglycaemia remains a persistent challenge. Current clinical practice focuses largely on glycaemic metrics and insulin management. However, impaired glucagon responses alongside other biological, behavioural, environmental, and technological factors also drive defective counterregulation and glucose variability. Because hypoglycaemia experiences vary significantly between and within individuals, this

heterogeneity requires deeper study. Improving outcomes necessitates addressing both day-to-day management and the underlying physiological defences to improve how people with type 1 diabetes experience hypoglycaemia.

Near-Term Translational Opportunities: Improving the Experience of Hypos

Existing and emerging interventions, including mini-dose glucagon and novel delivery systems i.e. pumps, could prevent or mitigate hypoglycaemia during real-world scenarios. While these strategies can reduce severe episodes and support flexible self-management, their impact on lived experience is poorly understood. Research must evaluate recovery, cognitive and emotional outcomes, usability, and integration into routine care.

Longer-Term Ambition: Restoring Physiological Glucagon Function

In type 1 diabetes, the physiological "glucagon safety net" is impaired by alpha cell dysfunction, disrupted intra-islet signalling, and altered neural glucose sensing. Mechanistic studies should investigate how these systems dysregulate over time or with recurrent hypoglycaemia, and how they can be therapeutically targeted. While restoring glucagon responses will not solve every aspect of hypoglycaemia, it is a vital component of a broader solution with a clear pathway toward future translation.

Research Scope and Priorities

We welcome a broad range of research approaches spanning basic, clinical, translational, behavioural, implementation and health services research. Applicants are not expected to address every aspect of hypoglycaemia within a single proposal, but applications may focus on some of the following areas:

1. **Interventions and technologies to improve the lived experience of hypoglycaemia in real-world settings**

   We encourage studies evaluating new or existing interventions that improve how hypoglycaemia is prevented, experienced, managed or recovered from in everyday life.

   This may include:

   - Glucagon-based approaches (e.g. mini-dose strategies or novel delivery methods)
   - Digital or algorithm-driven tools
   - Behavioural or decision-support interventions
   - Particular interest lies in high-risk settings such as:
   - Exercise
   - During sleep
   - Illness or variable insulin requirements

2. **Mechanisms underlying impaired counterregulation and variability in hypoglycaemia experience**

We encourage studies investigating the biological and behavioural mechanisms that contribute to impaired counterregulation and variability in hypoglycaemia, using human, animal, in vitro, computational or other appropriate approaches.

Areas of interest include:

- Alpha cell dysfunction and intra-islet signalling
- Neural and central regulation of hypoglycaemia responses
- Adaptation to recurrent hypoglycaemia
- Factors underlying variability in hypoglycaemia experience between individuals and across contexts

Methodological Approaches and Considerations

For Clinical, Translational and Applied Research

- Experience-led outcomes are strongly encouraged.
- Studies should assess impacts on recovery, cognition, emotional wellbeing, confidence, functioning and overall lived experience, not solely glycaemic control.
- Qualitative, quantitative and mixed-methods approaches are welcomed.
- Real-world relevance should be demonstrated through evaluation in everyday contexts such as exercise, sleep, illness or changing insulin requirements.
- Meaningful involvement of people living with type 1 diabetes should be incorporated wherever appropriate.

For Mechanistic and Basic Science Studies

- Studies may focus on specific biological, physiological or behavioural mechanisms relevant to hypoglycaemia and impaired counterregulation.
- Human, animal, in vitro and computational approaches are all within scope.
- Proposals should articulate how findings could inform future intervention development, targeting, stratification or implementation.
- Where appropriate, researchers should consider how mechanistic insights may help explain variability in hypoglycaemia risk and experience.

Outcomes and Measurement

- Proposals should move beyond HbA1c and time-in-range as primary indicators of success. Applicants should justify the selection of outcome measures and use existing validated tools where appropriate.
- Development of new patient-reported outcome measures should only be undertaken where a clear unmet need exists.
- Researchers are encouraged to work with people living with type 1 diabetes to identify outcomes that are meaningful and relevant.
- Qualitative and mixed-methods approaches may provide important insights into unpredictability, recovery, behavioural adaptation and quality of life.

- Consideration should be given to broader functional, societal and health-economic impacts where relevant.

Funding

Diabetes UK invites research proposals that address these knowledge gaps in line with our project grant scheme. Funding of up to £500,000 is available over a period of up to five years, where the scale and duration of the proposed work are clearly justified.

£500,000 represents the maximum available award rather than the expected size of a grant. We anticipate that most applications will request less than this amount and/or a shorter duration. Applicants should cost their study realistically, ensuring that budgets are proportionate to the research questions, methods and delivery plan, and that costs are profiled appropriately across the lifetime of the award.

Applicants are encouraged to show evidence of substantial patient and public involvement in all stages of the development and delivery of their project.

Deadline

The deadline for applications is 1 December 2026 17:00 hrs (funding decisions will be made in May/June 2027)

How to apply

Apply for a **Diabetes UK Grants Portal** by selecting **2026 Dec Project Grant.**

For further details please contact the Diabetes UK Research team at research@diabetes.org.uk

Application assessment process

All applications received under this highlight notice will be assessed through the Diabetes UK standard assessment procedure for project grants and will be considered in competition with all applications submitted.

Applications will be assessed by the **Scientific Panel** on the following criteria:

- Potential difference the research will make to the lives of people living with and at risk of diabetes.
- Scientific excellence and potential impact.
- Track record of the applicants.
- Value for money.

Applications will be assessed by the **Grants Advisory Panel** on the following criteria:

- Relevance to people with diabetes and its potential impact.
- The timescale on which the project could make a difference to people living with and at risk of diabetes.
- The extent of involvement of people with diabetes in the development and the management of the study.