Breakthrough T1D™
Formerly JDRF

Breakthrough T1D Request for Applications: Studies assessing the clinical meaningfulness of insulin dose in type 1 diabetes

September 2025

Purpose

People with type 1 diabetes (T1D) take lifelong insulin therapy to compensate for a partial or complete lack of endogenous insulin production. Intensive insulin therapy is absolutely required for glucose control, avoidance of DKA, and reduction of the risk for long-term complications. It is generally thought that therapeutic approaches allowing for insulin dose to be reduced without compromising glucose and ketone control will be beneficial for people with T1D. This RFA is intended to solicit proposals investigating the effects of insulin dose and insulin dose reduction on acute and long-term T1D outcomes.

Background

Insulin is a life-saving therapy for people with T1D, and the advent of intensive insulin therapy as standard of care has led to dramatically improved T1D outcomes, especially reduction in the rate of long-term complications. Yet, like all therapies, insulin therapy has certain drawbacks; for example, insulin promotes weight gain, and intensive insulin therapy has been associated with risk of hypoglycemia. Additionally, high levels of insulin are hypothesized to contribute to insulin resistance and risk of cardiovascular disease (CVD). Overall, the relationships between insulin dose and both acute and long-term complications of T1D remain poorly defined.

A better understanding of the clinical meaningfulness of insulin dose reduction is important for the development of adjunctive (i.e., non-insulin) T1D therapies. One reason adjunctive therapies are essential for T1D is that most people with T1D do not achieve recommended glucose targets with insulin alone. While several adjunctive therapies that promote reductions in blood glucose (e.g. SGLT inhibitors, GLP1 receptor agonists, and others) have been tested in people with T1D, they often show less HbA1c-lowering benefit in T1D trials than in type 2 diabetes. One reason is that glucose-lowering therapies' effects on HbA1c in T1D trials may be diminished by participants' concomitant reductions in insulin dose to avoid hypoglycemia. A more rigorous understanding of the acute and long-term meaningfulness of such insulin dose reductions will help people with T1D, clinicians, drug developers, and regulators assess the benefits of emerging adjunctive therapies that reduce users' insulin needs.

Research into the clinical meaningfulness of insulin dose will also have value beyond adjunctive therapy development. First, it will inform the development of other kinds of T1D therapies, including novel insulin formulations that require lower doses than those currently available because, for example, they achieve a more physiological action profile or biodistribution, or are co-formulated with amylin-based therapies that reduce insulin needs. Second, like completed and ongoing studies

on continuous glucose monitor (CGM)-derived metrics (time-in-range, level 1 and level 2 hypoglycemia, etc.), research on the significance of insulin dose can inform risk models and clinical guidance for people with T1D.

Significant gaps exist in our knowledge of how insulin needs and dose influence outcomes in people with T1D. Breakthrough T1D is soliciting grant proposals that can fill this gap through either analysis of sufficiently large data sets that include both reliable insulin dose information and relevant clinical outcomes, or mechanistic clinical trials.

Objectives

Letters of intent (LOIs) are sought for studies that define the relationship between insulin dose (and insulin dose reductions) and T1D outcomes.

Examples of research topics appropriate for this RFA include, but are not limited to:

- Analysis of data from sources (e.g. registries, completed clinical trials, electronic health records, medical claims, other) that allow for assessment of the relationship between insulin dose and relevant clinical outcomes
- Retrospective cross-sectional, retrospective longitudinal, and prospective observational studies
- Clinical trials to assess mechanistic hypotheses about the effects of insulin dose on relevant outcomes

Examples of research not covered by this RFA include:

- Studies in preclinical models
- Discovery of novel biomarkers associated with T1D complications
- Research on pathophysiological pathways unrelated to insulin
- Studies investigating T1D disease modifying therapies or beta cell replacement therapies
- Development of novel insulins or insulin delivery systems
- Health economics and outcomes research

Applicants are encouraged to consult with the Breakthrough T1D Scientific Staff below to discuss the alignment of their proposal to this RFA and to develop the proposed study concept.

Critical Considerations

- Clinically relevant outcomes may include hypoglycemia, long-term complications (e.g. CVD, diabetic kidney disease, diabetic retinopathy, other), and others.
- As secondary objectives in proposals analyzing large data sets, applicants may investigate associations of variables beyond insulin dose, such as CGM-derived metrics and estimates of insulin resistance (e.g. estimated glucose disposal rate), to clinical outcomes.

- We encourage proposals that seek to leverage ongoing or planned studies.
- We encourage applicants to form collaborations that allow for analysis of multiple cohorts for greater analytical power.
- Assessment of the direct impact of insulin dose on T1D outcomes is complicated by the causative relationships between insulin and HbA1c lowering, and HbA1c lowering and reductions in long-term complications. Letters of intent should explain how HbA1c and other confounders will be handled.
- This RFA is not a recommendation for people with T1D to reduce their insulin dose or otherwise modify their diabetes management.

Deliverables

Examples of deliverables from completed grants include, but are not limited to:

- Assessment of the association between T1D outcomes and insulin dose, including with adjustment for HbA1c and other confounders.
- Identification of factors that mediate any effects of insulin dose on T1D outcomes.
- Determination of whether insulin dose improves prediction of T1D outcomes beyond established risk factors.
- Novel risk models for long-term complications that incorporate insulin dose.
- Mechanistic insights into whether and how insulin dose and changes in insulin dose affect T1D outcomes.
- Evidence that informs how insulin dose as a trial endpoint should be considered by clinicians, therapy developers, and regulators.

Clinical Studies

Breakthrough T1D follows the U.S. Department of Health and Human Services (HHS) regulations for the protection of human subjects in research (45 CFR 46).

Budget

SRA and IDDP applications may request up to a total of $750,000 over a maximum of two years.

Breakthrough T1D may consider applications with increased scope (time, budget) where there is a strong justification, and applicants interested in such should discuss with the Breakthrough T1D scientific contact below. Note that the above budget figure is a maximum, and Breakthrough T1D will also consider projects with substantially smaller budgets. In all cases, the level of requested funding should be commensurate with the studies proposed and non-Breakthrough T1D resources (funds, personnel, other) available to successfully complete the project. Appropriateness of budget in relation to scope will be considered as part of the review criteria.

Mechanisms

In response to this announcement, Letters of Intent (LOI) can be submitted under the following mechanism(s):

Strategic Research Agreement (SRA)

Strategic Research Agreements are intended for support of research activities at non-for-profit entities such as academic institutions. For more information on the SRA grant mechanism please refer to the Grant Handbook. SRA applications may include up to 10% indirect costs as part of the total request.

Industry Discovery and Development Partnerships (IDDPs)

For-profit entities may apply under Breakthrough T1D's Industry Discovery & Development Partnership (IDDP) funding mechanism, which entails additional requirements including company matching funds. If you would like to submit an Industry Discovery and Development Partnership (IDDP) project LOI to this RFA, please review the IDDP guidelines available in the Grant Handbook. Indirect costs are not permitted on IDDP applications. IDDP applications that are invited to a full proposal will receive their own timeline for completion of due diligence and finalization of an agreement.

Eligibility

Applications may be submitted by domestic and foreign non-profit organizations, public and private, such as universities, colleges, hospitals, laboratories, units of state and local governments, and eligible agencies of the federal government. Applicants must hold an M.D., D.O., D.M.D., D.V.M., Ph.D., or equivalent and have a faculty position or equivalent at a college, university, medical school, or other research facility. Please note that applications from for-profit entities or industry collaborations with academia may be submitted to this RFA; however, additional information will be requested from for-profit entities if a full application is invited.

There are no citizenship requirements for this program. To assure continued excellence and diversity among applicants and awardees, Breakthrough T1D welcomes applications from all qualified individuals and encourages applications from persons with disabilities, women, and members of minority groups underrepresented in the sciences.

Letter of Intent (LOI)

Prospective applicants should submit a letter of intent (LOI) using the template provided online via RMS360. The LOI should be 2 pages and submitted online to be considered for a full proposal invitation. Applicants will be notified according to the timeline below if they have been approved to submit a full application.

Proposal

An approved LOI is required prior to the submission of a full proposal. Upon notification of a request for a full proposal, the application must be completed using the templates provided in RMS360. Complete information should be included to permit a review of each application without reference to previous applications.

Note that all applications involving human subject research must include supplemental information to address subject safety, study design and investigational product information. More details can be found in the Human Subject Research Guidelines in the Grant Handbook, page 82.

Review Criteria

Applications will be evaluated based on Breakthrough T1D's standard confidential award policy and according to the following criteria:

- Significance
- Approach
- Innovation
- Investigator Experience
- Environment

Projected Timeline

Milestone	Date
LOI deadline	November 5, 2025
Notification of LOI outcome	December 1, 2025
Full proposal deadline	January 20, 2026
Award notification	May 2026
Earliest anticipated start	July 2026

Program Contacts

Scientific

Jonathan Rosen, Ph.D.
Director, Research
jrosen@breakthroughT1D.org

Administrative Inquiries

Sanjukta Mukerjee
Program Administrator, Research
smukerjee@breakthrought1d.org

If you have any system questions as you work within RMS360, please contact the administrative contact listed above.