Breakthrough T1D™
Formerly JDRF

Breakthrough T1D Request for Applications: Clinical trials to advance therapies for cardiovascular disease in type 1 diabetes

September 2025

Summary

- The goal of this funding opportunity is to advance therapies to improve cardiovascular outcomes in people with established type 1 diabetes (T1D).
- This funding opportunity will prioritize clinical trials evaluating promising therapies, whether repositioned, repurposed, in development, or already approved, for cardiovascular disease (CVD) in people with T1D.
- This initiative will award grants for clinical studies to academic investigators and industry partners of up to $3,000,000.00 over 3 years.

Funding Opportunity Description

Breakthrough T1D is committed to the development of therapies to improve clinical outcomes in people with type 1 diabetes (T1D). Cardiovascular disease (CVD) is the primary cause of morbidity and mortality in people with T1D. There is currently a lack of targeted therapies for CVD approved for use by people with T1D, in part because people with T1D are seldom included in drug trials for these diabetic complications. To fill this gap, Breakthrough T1D invites applications for clinical trials to advance therapies to improve CVD outcomes in T1D.

Background

CVD is the leading cause of morbidity and mortality in adults with T1D, representing a significant and common long-term complication. People with T1D face a disproportionately high burden of CVD, often with earlier onset and more severe outcomes than the general population. Alongside kidney disease, CVD is a major contributor to the reduced life expectancy observed in people living with T1D.

The pathogenesis of CVD in T1D is multifactorial. Chronic hyperglycemia and long disease duration continues to play a central role in driving endothelial dysfunction and accelerating atherosclerosis. However, even individuals who achieve glycemic targets are not exempt from heightened risk, as they face more than double the likelihood of cardiovascular events relative to their non-diabetic peers. Additional contributors such as insulin resistance, dyslipidemia, hypertension, chronic inflammation, and diabetic kidney disease compound vascular injury and accelerate disease progression.

Despite the high prevalence and clinical impact of CVD in T1D, there is a gap in effective, approved therapies specifically evaluated in this population. Most cardiovascular interventions currently available to people with T1D address modifiable risk factors such as hyperglycemia, blood pressure, and lipid levels resulting in an urgent unmet need for treatments that directly improve cardiovascular outcomes.

The therapeutic landscape for type 2 diabetes (T2D) has expanded to multiple drug classes, including sodium-glucose cotransporter (SGLT) inhibitors, glucagon-like peptide-1 (GLP-1) receptor agonists, and mineralocorticoid receptor antagonists (e.g., finerenone), which have demonstrated cardiovascular benefit and gained regulatory approvals. These agents are increasingly used not only in T2D but also in individuals without diabetes who have chronic kidney disease or heart failure. Although much of T1D-CVD management has been extrapolated from evidence in T2D, the lack of T1D specific data and the limited inclusion of T1D patients in pivotal cardiovascular outcome trials have prevented inclusion of these transformative therapies in clinical care guidelines and practice for this high-risk population.

Emerging classes of CVD therapies offer promising avenues for intervention for people with T1D. Key mechanistic contributors to CVD in T1D include chronic low-grade inflammation, dysregulated lipid metabolism, endothelial dysfunction, and impaired vascular remodeling. Autoimmunity and suboptimal glycemic control fuel chronic immune activation, leading to elevated levels of pro-inflammatory cytokines such as IL-1β, IL-6, and TNF-α. This sustained inflammatory state accelerates atherosclerotic progression and promotes the destabilization of vascular plaques. Dyslipidemia in T1D, often marked by elevated triglycerides, altered apolipoprotein profiles, and increased lipoprotein oxidation, also exacerbate vascular risk even in people with well-managed glycemic control. Hepatic insulinopenia coupled with peripheral hyperinsulinemia contributes to high-density lipoprotein (HDL) depletion, hypertriglyceridemia, and insulin resistance. Additionally, metabolic stress and mitochondrial dysfunction reduce metabolic flexibility and promote the accumulation of lipotoxic intermediates, further undermining vascular integrity.

Targeting these underlying mechanisms, along with adapting pharmacological strategies from T2D, may offer a more tailored approach to mitigating cardiovascular risk in T1D. Integrating interventions that address inflammation, lipid imbalances, oxidative stress, metabolic dysfunction, and endothelial dysfunction may yield synergistic benefits, paving the way for precision cardiometabolic care in this high-risk population.

This RFA aims to drive progress by soliciting proposals that advance promising cardiovascular therapies, whether repositioned, repurposed, in development, or already approved, for evaluation in people with T1D. Clinical trials to assess safety and efficacy of these agents in this understudied population are essential to close the gap in care and reduce the disproportionate burden of CVD in T1D.

Objectives

Letters of intent (LOIs) are sought from academic or industry applicants for clinical trials to evaluate therapies for CVD, including heart failure, in T1D. Except in rare situations, we anticipate trials built around mechanistic endpoints or surrogate endpoints for CVD. 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 projected study concept. Applicants should consult the Breakthrough T1D research abstracts database, NIH Reporter, and clinicaltrials.gov to assess the landscape of ongoing trials and prevent redundancy with ongoing funded trials.

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

- Proof of concept trials evaluating CVD outcomes of novel therapies in people with T1D
- Pilot T1D clinical trials evaluating therapies with demonstrated efficacy for CVD in non-T1D populations
- Trials evaluating therapies in stratified samples of people with T1D likely to have the most favorable benefit–risk profile given the therapy's mechanism of action
- Trials evaluating therapies targeted to T1D-specific aspects of CVD pathophysiology, e.g. autoimmunity and its cardiac sequelae
- Innovative trial designs to overcome the feasibility challenges (duration, number of participants, budget) of conducting traditional CVD trials
- Mechanistic clinical studies that will enable subsequent trials with validated surrogate endpoints
- Ancillary studies to existing or planned T1D-focused clinical trials to collect mechanistic, imaging, or biomarker data relevant to cardiovascular risk
- Inclusion of people with T1D in existing or planned clinical trials evaluating drugs for CVD in a non-T1D population
- Inclusion of people with T1D in company-sponsored trials
- Post-hoc analysis of people with T1D included in ongoing or completed trials, especially cardiovascular outcome trials
- Mechanistic interventional trials exploring the link between autoimmunity and cardiovascular disease in T1D, aimed at identifying and validating druggable pathways and informing whether a specific therapy ought to be pursued for T1D
- T1D-focused real world studies collecting efficacy and safety data on therapies with expected CVD benefits

Examples of research not covered by this RFA include:

- Trials that are not well-differentiated from ongoing studies
- Interventional clinical studies with a primary endpoint of weight loss
- Clinical trials that do not include people with T1D. (However, trials may include other populations in addition to people with T1D.)
- Clinical trials evaluating lifestyle interventions such as diet and exercise
- Non-clinical studies

Deliverables

- Trials should be designed to generate critical data regarding mechanism, efficacy, and safety in people with T1D. Trial results should allow for determination of whether selected therapies merit further development toward the ultimate goal of regulatory approvals and/or enhancement of clinical guidelines for people with T1D
- Projects should be designed to achieve key inflection points appropriate to project duration, budget, and initial stage of development
- Successful experimental medicine and mechanistic clinical studies will provide data that can be used to inform future therapy development efforts

Critical considerations

- Innovative trial designs, such as adaptive trials, are highly encouraged
- Choice of surrogate and mechanistic endpoints in the trial should be well justified
- Breakthrough T1D strongly encourages applications from and/or collaborations with industry
- It is the responsibility of the applicant to obtain drug for their study. Breakthrough T1D funding will be contingent on a written commitment from the drug manufacturer to provide study drug and placebo
- It is the responsibility of the applicant to identify study sites for their study and provide a feasibility plan for successful execution of study.
- Breakthrough T1D supports collaborative approaches, including between academic applicants and industry partners. Breakthrough T1D can assist industry applicants seeking an academic partner, or vice versa, **prior to submission of the LOI**
- We encourage investigators to collaborate with other sites to increase recruitment feasibility.
- We will consider support of trials at any stage of development (phase 1, 2 or 3; from early trials focused on safety, PD markers, or mechanistic endpoints to later trials with powered effectiveness endpoints)
- Breakthrough T1D encourages proposals that seek to leverage existing or planned clinical trials by adding people with T1D or ancillary studies
- The feasibility of future commercial and regulatory paths will be a key part of the proposal and carefully considered as part of Breakthrough T1D's funding decision
- Clinical studies should recruit a diverse population representative of the real world in terms of ethnicity, socioeconomic status, and other demographic features

- Proposals for trials evaluating therapies that are already available to people with T1D should clarify why the study is essential (e.g., a hypothesis that the therapy has additional benefit in T1D relative to the general population, or that despite clinical availability more research is necessary to promote therapy uptake)

- Breakthrough T1D follows U.S. National Institutes of Health (NIH) Public Health Service Policy guidelines for the humane care and use of animals in research and the U.S. Department of Health and Human Services (HHS) regulations for the protection of human subjects in research (45 CFR 46). Breakthrough T1D requires the Grantee Institution to comply with these guidelines.

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.

- 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.

Funding Mechanisms

In response to this announcement, applications may request up to a **total of $3,000,000 USD for up to three years**.

- The level of funding will vary depending on the scope and overall objectives of the proposal. 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.

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 IDDP project LOI to this RFA, please see our Grant Handbook for additional information and contact Dr. Courtney Ackeifi (cackeifi@breakthroughT1D.org) to discuss proposed scope and budget prior to submitting an application. 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.

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.

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.

Clinical studies

- Note that all applications involving human subject research must include supplemental information to address subject safety, study design, and investigational product information.
- Breakthrough T1D follows U.S. National Institutes of Health (NIH) Public Health Service Policy guidelines for the humane care and use of animals in research and the U.S. Department of Health and Human Services (HHS) regulations for the protection of human subjects in research (45 CFR 46). Breakthrough T1D requires the Grantee Institution to comply with these guidelines.
- More details can be found in the Human Subject Research Guidelines section of the Grant Handbook.

Review Criteria

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

- Significance
- Relevance
- Approach

- Innovation
- Environment
- Resource sharing plan
- Clinical translation roadmap

Clinical Trial Site Participation

Breakthrough T1D recognizes that some clinical sites may be interested in participating in trials led by others. We also understand that recruiting small, targeted subpopulations within the T1D community remains a consistent challenge across clinical research.

To proactively address this risk, we are identifying clinical sites with both interest and capacity to engage in studies funded through this RFA. Investigators interested in joining trials led by others are invited to submit a **Participating Clinical Site Form** to indicate their willingness to be considered for future participation. Investigators proposing studies to this RFA should not plan to rely solely on this initiative to identify sites for their trials.

The site forms should briefly describe:

- Institutional experience with and capacity for T1D clinical research
- Access to relevant patient populations, including high-risk or underrepresented groups
- Available infrastructure to support trial execution (e.g., CGM integration, investigational pharmacy, recruitment methodology)
- Prior involvement in multicenter trials or collaborative research consortia

Participating Site forms may be submitted at any time during the RFA cycle and should be sent to **Courtney Ackeifi [cackeifi@BT1D.org] and Gianna Strand [gstrand@BT1D.org].** This information will help inform site selection and trial feasibility planning as funded studies move toward trial execution. Responses may be shared with investigators during full proposal development based on need and fit.

Projected Timeline

Milestone	Date
LOI deadline	October 29, 2025
Notification of LOI outcome	November 19, 2025
Full proposal deadline	January 13, 2026
Award notification	May 2026
Earliest anticipated start	July 2026

Program Contacts

Strategic Fit and Scientific Inquires

Courtney Ackeifi, PhD
Senior Scientist
Breakthrough T1D
cackeifi@BT1D.org

Administrative Inquiries

Sanjukta Mukerjee, PhD
Program Administrator, Research
Breakthrough T1D
smukerjee@BT1D.org