

Designing the Next Generation of Type 1 Diabetes Trials: From Insulin to Disease Modification

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Type 1 diabetes (T1D) affects ~9.5 million people globally, with more than 513,000 new cases diagnosed in 2025 alone (Ogle et al., 2025).¹ For decades, disease management relied on lifelong exogenous insulin delivered through multiple daily injections or pump therapy, coupled with continuous glucose monitoring and the ongoing challenge of avoiding hypo- or hyperglycemic events. Today, however, the field is entering a new era. Scientific advances have shifted the focus beyond glycemic control towards disease-modifying therapies, beta cell replacement strategies, immune interventions, and cure-directed approaches.

As science has evolved, so have the demands for clinical development. Endpoints, target patient populations, safety considerations, and regulatory expectations now vary significantly depending on the therapeutic modality being studied. Increasingly, the greatest challenges are no longer scientific feasibility but operational execution. Recruiting the right patients at the right stage of disease, managing complex biomarker and immunologic assessments, addressing long-term safety requirements, and maintaining participant engagement over extended follow-up periods can determine whether a promising therapy reaches its development milestones.

For biotechnology and emerging biopharmaceutical companies advancing novel T1D therapies, the path from early clinical development to regulatory approval requires more than scientific innovation. Success depends on an operational strategy that is aligned with the unique demands of modern T1D drug development and capable of translating breakthrough science into meaningful clinical outcomes.

How Has the Treatment Paradigm Shifted?

For most of T1D's history, clinical development focused on improving insulin delivery, glucose monitoring, and overall glycemic control. That changed in 2022, when the U.S. Food and Drug Administration (FDA) approved teplizumab (TZIELD), the first disease-modifying therapy for T1D and the first treatment shown to delay the onset of any autoimmune disease (Keam 2023; Goldman & Choi, 2023).^{2,3} Approved for adults and pediatric patients aged eight years and older with Stage 2 T1D, teplizumab, demonstrated that the disease could potentially be intercepted before clinical onset rather than simply managed after diagnosis. (National Library of Medicine TZIELD-teplizumab-mzwv, 2022).⁴ This approval fundamentally changed how researchers, regulators, clinicians, and patients think about the T1D treatment continuum.

Since then, the development landscape has expanded rapidly. Today's pipeline includes immune-modulating therapies designed to preserve beta-cell function, antigen-specific approaches intended to induce immune tolerance, and cell-based therapies aimed at restoring endogenous insulin production. In June 2023, the FDA approved Lantidra (donislecel), the first allogeneic pancreatic islet cellular therapy for adults with T1D who experience recurrent severe hypoglycemia despite intensive management.

This approval marked another important milestone, bringing cell therapy into the treatment armamentarium, although the procedure requires extended or lifelong immunosuppression (LANTIDRA-donislecel solution, 2026; NIH NIDDK pancreatic islet transplantation, 2018).^{5,6} Meanwhile, engineered regulatory T cell (Treg) therapies, including autologous CAR Treg approaches, have entered early phase clinical testing, offering a

potential strategy to address the autoimmune process underlying the disease.[\(ClinicalTrials.gov, 2026; Toumela & Levings, 2024\)](#).^{7,8}

The implications extend well beyond the science. Emerging therapies are reshaping clinical trial design, shifting endpoints from traditional glycemic measures toward beta-cell preservation, C-peptide outcomes, and continuous glucose monitoring (CGM)-based metrics. Advanced modalities also introduce new operational complexities, including surgical procedures, immunosuppressive regimens, and long-term autoimmune risk management. As a result, the patient participation equation has changed. Therapies with the potential for meaningful disease modification generate real patient interest, yet they often require highly specialized academic sites, more intensive safety oversight, longer startup timelines, and increasingly sophisticated operational strategies. Success in modern T1D development therefore depends not only on scientific innovation, but also on the ability to execute complex studies across prevention, disease-modification, and cell therapy paradigms.

How Does the Modality Change the Trial?

In T1D development, modality and trial design are inseparable. The scientific mechanism of a therapy determines not only the endpoint strategy, but also the operational model, site requirements, safety oversight, and patient experience. As development moves beyond insulin replacement and glucose management toward disease modification and cellular therapies, development programs have become substantially more complex.

Each modality brings a distinct development model. Allogeneic islet transplantation studies operate more like procedural interventions, requiring portal vein infusion, specialized transplant expertise, and long-term immunosuppression management. [\(LANTIDRA-donislecel solution, 2026\)](#).⁵ Gene-edited cell therapies introduce additional regulatory and operational requirements, including characterization of genetic modifications, manufacturing controls, and extended long-term follow-up. Autologous cell therapies such as CAR Treg programs add apheresis, manufacturing, slot coordination, chain-of-identity, and chain-of-custody considerations that make logistics a core component of trial execution rather than a supporting function.

Endpoints evolve alongside the science. Disease-modification programs increasingly focus on preservation of endogenous beta-cell function, with stimulated C-peptide response during mixed-meal tolerance testing (MMTT) serving as a key measure of therapeutic effect rather than HbA1c alone [\(Evans-Molina et al., 2026\)](#).⁹ CGM-derived metrics, including time in range (TIR), time in tight range (TITR), and time below range (TBR), have become essential outcome measures because they provide a more sensitive assessment of glycemic control than HbA1c alone. International consensus recommendations now support TIR targets greater than 70% and TBR below 4% for most individuals living with T1D [\(Battelino et al., 2019; NIH NIDDK Clinical Targets for CGM Monitoring Data, 2020\)](#).^{10,11}

Importantly, the benefit risk equation in T1D differs fundamentally from oncology and other life-threatening disease. Individuals living with T1D already have access to effective insulin therapy, advanced automated insulin delivery systems, and CGM technologies. Consequently, acceptance of procedural interventions, cellular therapies, or chronic immunosuppression requires a significantly higher threshold of perceived benefit. Study designs must therefore incorporate robust patient education, informed consent processes, retention strategies, and ongoing engagement plans to successfully recruit and maintain participation throughout the study [\(NIH NIDDK pancreatic islet transplantation, 2018\)](#).⁶

The shift toward earlier intervention is adding further complexity. Many disease-modification programs are increasingly enrolling pediatric and adolescent populations, requiring development strategies that address not only clinical and regulatory considerations, but also family engagement, caregiver burden, school schedules, and long-term follow-up expectations. These patient populations often require operational models that balance scientific rigor with the practical realities of daily disease management.

Geography also plays a strategic role. Many early cell and gene therapy programs begin in Australia because the Clinical Trial Notification (CTN) pathway can accelerate first-in-human studies. [\(Australian Therapeutic Goods Administration Clinical Trial Notification \(CTN\) scheme; Jetro Guidebook for Clin Trials in Australia, 2024\)](#).^{12,13} However, rapid startup alone does not guarantee development success. Sponsors

must evaluate whether an early-phase strategy can also support efficient global expansion and later-stage development without requiring significant operational redesign. The most successful programs align modality, geography, manufacturing strategy, and long-term development objectives from the outset, creating a scalable pathway from first patient dosed through registration.

How Should Sponsors Read Glycemia?

CGM is not a device decision. It is a clinical development strategy decision.

The first question is how CGM data will be used in the program: as an efficacy endpoint, a safety tool, or both. That decision influences endpoint strategy, blinding requirements, data review processes, and operational workflows, and ultimately how the trial is conducted. When CGM data contributes to study endpoint, visibility becomes a protocol-defined choice. Whether data are blinded or unblinded has direct implications for device configuration, patient experience, site management, and the integrity of study conduct.

For regulatory-grade endpoint collection, patient-owned devices are rarely sufficient. Provisioned, protocol-specified CGM devices are the preferred route for endpoint collection, because sensor selection, wear duration, warm-up requirements, hypoglycemia performance, and data accessibility all affect endpoint integrity ([Danne et al., 2017](#)).¹⁴ A device designed primarily for day-to-day diabetes management may not meet the performance requirements expected for a regulatory endpoint.

Just as important as sensor selection is the data pathway. CGM data must be extracted, transferred, validated, and integrated into the study's electronic data capture ecosystem. Today, there is no universally available plug-and-play solution for CGM-to-EDC integration. The process remains largely bespoke, requiring early planning, vendor alignment, early defined transfer specifications, validation activities and dedicated budget. Programs that acknowledge this reality and design the required infrastructure into the protocol from the outset avoid downstream operational risk and establish greater credibility with regulators, investigators, and sponsors alike.

How Is Beta-Cell Function Measured?

The mixed-meal tolerance test (MMTT) remains the gold-standard functional assessment of endogenous insulin secretion and the cornerstone endpoint for many T1D disease-modification programs. By measuring C-peptide response to a standardized meal challenge over two to four hours, the MMTT provides a direct assessment of residual beta-cell function and treatment effect ([Greenbaum et al., 2008](#)).¹⁵

What gives the endpoint credibility, however, is not the assay itself. It is the precision of execution. MMTT data are exceptionally sensitive to timing. Meal administration, blood collection schedules, and sample processing must occur within tightly controlled windows, because even small deviations can affect the resulting C-peptide curve and compromise endpoint interpretability. As a result, feasibility planning must evaluate more than patient access. Sponsors should assess site workflow, staffing availability, collection logistics, and the physical layout between meal administration and phlebotomy locations to ensure protocol-defined timing can be achieved consistently across visits.

Operational consistency becomes even more important in multicenter studies. Meal standardization, four-hour collection schedules, sample handling procedures, and laboratory coordination all introduce opportunities for variability that protocol design must proactively control. While the MMTT has demonstrated high reproducibility and tolerability across age groups, that reliability depends on rigorous and uniform site execution ([Greenbaum et al., 2008](#)).¹⁵

The most successful programs treat MMTT execution as a feasibility consideration rather than a site-training exercise. Evaluating infrastructure, workflows, staffing models, and timed-collection capabilities early allows sponsors to identify sites capable of generating high-quality, protocol-compliant beta-cell function data and avoid operational variability that can weaken a program's regulatory position.

What Should Sponsors Ask a Development Partner?

For emerging biotech companies bringing a T1D asset into clinical development, the right development partner can be identified by the specificity of the answers to five questions:

- 1. How do you design CGM into the protocol?**
Not which sensor to use, but whether CGM serves as an endpoint, a safety tool, or both, and how data will be blinded, collected, transferred, and integrated.
- 2. How do you de-risk MMTT at feasibility?**
Timing precision, site workflows, staffing, and sample collection logistics should be evaluated during feasibility, not after deviations occur.
- 3. How do you approach consent and retention for cell therapy studies?**
In a disease where insulin and CGM are effective, enrollment and long-term retention require a clear understanding of the unique risk-benefit discussion facing participants.
- 4. How do you plan for global expansion?**
Early phase speed and global scalability are different challenges. Sponsors should understand how operational models evolve from first-in-human studies to multinational development.
- 5. Can you distinguish cell from gene therapy operationally?**
Islet replacement, gene-edited therapies, and autologous cell therapies each have distinct manufacturing, logistics, and execution requirements. A development partner should be able to articulate those differences before protocol finalization.

Worldwide's Commitment to T1D Development

T1D clinical development has entered its most scientifically promising and operationally complex era. Disease-modifying therapies, cell and gene therapies, beta-cell replacement approaches, and increasing sophisticated CGM- and MMTT-based endpoint strategies are reshaping the development landscape. As science advances, the operational demands of delivering these studies successfully continue to grow.

Success in modern T1D development depends on more than scientific innovation. It requires operational expertise that anticipates complexity before it becomes risk. Decisions involving CGM implementation, MMTT standardization, endpoint strategy, specimen handling, site selection, patient burden, and long-term participant retention must be addressed early and integrated into study design from the outset.

Worldwide Clinical Trials brings practical experience across these evolving development models. Having supported programs utilizing CGM, MMTT, advanced metabolic endpoints, and innovative therapeutic approaches, our teams understand the operational decisions that determine whether a study remains on track long after the protocol is finalized. Combined with deep expertise in cell and gene therapy development, decentralized and hybrid trial approaches, and complex biomarker-driven studies, Worldwide provides sponsors with the specialized capabilities required to translate scientific promise into clinical execution.

As T1D development continues to evolve toward disease modification and functional cure strategies, sponsors need a partner that understands both the science and the operational realities. Worldwide helps ensure that groundbreaking therapeutic innovation is matched by the disciplined execution required to bring meaningful advances to patients living with type 1 diabetes.

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