21st Century Trials in New-Onset Type 1 Diabetes

Workshop Summary

A public workshop convened by the Critical Path Institute (C-Path) Type 1 Diabetes Consortium, in collaboration with the U.S. Food and Drug Administration

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Prepared by C-Path's Type 1 Diabetes Consortium staff, drawing on workshop session transcripts and related source materials, with AI-assisted drafting support.

About This Summary

This document summarizes the discussion at C-Path's June 17-18, 2025 public workshop, *21st Century Trials in New-Onset Type 1 Diabetes*, which was attended by more than 400 stakeholders from academia, industry, patient advocacy organizations, and regulatory agencies to examine the scientific and regulatory considerations surrounding C-peptide and preserved beta-cell function as measures of disease modification in type 1 diabetes (T1D). Participants included representatives from the FDA, academic medical centers, patient advocacy organizations including Breakthrough T1D, and industry sponsors including Sanofi, Novo Nordisk, and Diamyd Medical.

This summary reflects a synthesis of themes and points raised across the workshop's sessions and panel discussions. Consistent with standard practice for meetings of this kind, comments made by individual participants — including representatives of the FDA — reflect the perspective of the speaker at the time and should not be construed as final agency policy or position.

The Burden of Type 1 Diabetes Today

The workshop opened by grounding the discussion in the current, persistent burden of T1D. A clinical perspective traced the evolution of T1D management over the past century — from a uniformly fatal disease prior to insulin therapy to a chronic condition managed with modern insulin analogs, continuous glucose monitoring (CGM), and hybrid closed-loop delivery systems. It was noted that most new diagnoses now occur in adulthood (mean age of diagnosis in the low thirties).

Despite technological advances in treatment (e.g. insulin pumps and CGM), presenters emphasized that current tools remain compensatory rather than disease-modifying. Diabetic ketoacidosis (DKA) at diagnosis remains common across age groups and is associated with worse long-term glycemic outcomes; life expectancy remains reduced for those diagnosed early in life; and the day-to-day burden of glycemic management — hypoglycemia, hyperglycemia, and constant decision-making — persists even with modern devices.

A patient perspective reinforced this point directly, describing the lived experience of managing T1D from adolescent diagnosis through adulthood: the transition from a "honeymoon" period of preserved insulin production to a more difficult phase as endogenous insulin secretion waned, the psychological

toll of glycemic swings, and the view that insulin-based management — however improved by technology — remains fundamentally a "band aid" rather than a treatment for the underlying disease.

Key Discussion Points

- Despite significant technological progress in insulin delivery and glucose monitoring, meaningful proportions of people with T1D do not meet glycemic targets, and disease burden remains high.
- Life expectancy and long-term complication risk remain measurably worse for those diagnosed at a young age.
- The patient experience of glycemic variability — not captured by HbA1c alone — was repeatedly emphasized as central to understanding disease burden.

The Scientific and Analytic Basis for C-Peptide as an Endpoint

A series of presentations laid out the biological and statistical rationale for using C-peptide, a marker of residual endogenous insulin secretion, as an outcome measure in T1D trials. Presenters described consistent observational evidence that preserved C-peptide (stimulated C-peptide measured over a 2-4 hour period) is associated with better glycemic control, reduced hypoglycemia and DKA risk, and improved long-term microvascular outcomes, drawing on long-running cohorts (including DCCT/EDIC-related work) and large national data sets.

A separate technical presentation addressed the analytic challenge of C-peptide measurement itself: while C-peptide assays are widely used and treated as a practical standard in mixed-meal tolerance testing, meaningful inter-assay variability persists across commercial platforms, particularly at the low concentrations relevant to T1D. The presenter distinguished this variability problem — an assay standardization and calibration issue, addressed through a proposed reference-method and calibration framework — from the separate, larger effort to pool and harmonize clinical trial data (discussed below); the two are related but distinct undertakings, and the pooled clinical trial dataset has not itself resolved the assay-level measurement issue.

Discussion also addressed the heterogeneity of the rate and degree of C-peptide decline across individuals, which is substantially explained by age and baseline C-peptide level, and methods (including a "quantitative response" metric) developed to account for this heterogeneity in trial design and analysis.

Key Discussion Points

- Observational evidence linking preserved C-peptide to reduced long-term complications was described as extensive and consistent.
- Assay-level standardization of C-peptide measurement remains an open technical issue, separate from — and not resolved by — pooled clinical trial data curation efforts.
- Heterogeneity in C-peptide decline (driven largely by age and baseline level) was identified as a key design consideration for future trials.

Regulatory Perspectives on C-peptide as an Endpoint

A dedicated panel brought together regulatory, academic, and industry perspectives — including representatives from sponsor organizations active in T1D drug development — to discuss how C-peptide fits into current regulatory frameworks.

From the regulatory perspective, the unmet need in T1D was explicitly and repeatedly acknowledged: a meaningful share of both children and adults fail to meet glycemic targets even with modern technology, and reduced life expectancy for those diagnosed young was cited directly. It was stated clearly that patients, clinicians, and advocates have communicated a willingness to accept some risk and uncertainty in exchange for meaningful benefit, and that this tolerance is not diminished by the availability of improved glucose technology.

At the same time, regulatory participants were direct about the central open questions: whether C-peptide preservation can be *directly* linked to clinical benefit (how a patient feels, functions, or survives) and whether the *magnitude* of C-peptide preservation achievable with current therapies is large enough to translate into benefit that patients would recognize — improved glycemic control, reduced hypoglycemia, or reduced treatment burden. It was emphasized that this benefit-risk assessment is necessarily drug-specific rather than class-wide: even where pooled data shows a general association between C-peptide preservation and outcomes, a specific product's magnitude of effect must be evaluated on its own terms.

Industry and academic participants offered a complementary framing: that C-peptide reflects disease biology more directly than glycemic measures, which are heavily influenced by insulin dosing, device use, and patient behavior, and that C-peptide may therefore be a "cleaner" signal of disease modification — particularly relevant as background standard of care (CGM, automated insulin delivery) increasingly narrows the room to detect treatment differences on HbA1c alone. Several participants also discussed the potential for defining patient subgroups — by baseline C-peptide, HLA type, or immunophenotype — to reduce heterogeneity and improve the odds of detecting a clear treatment effect in a feasible trial size, while acknowledging the tension this creates with broader access.

Regulatory participants reiterated that C-peptide is not currently considered a validated surrogate endpoint sufficient to support traditional approval on its own but is regarded as meeting the threshold of a "reasonably likely" surrogate endpoint that can support accelerated approval, subject to a post-marketing requirement to confirm clinical benefit. This was presented not as a fallback position but as an appropriate, purpose-built pathway for exactly this kind of scientific uncertainty — intended to give patients earlier access to promising therapies while that confirmatory evidence is generated.

Key Discussion Points

- Unmet need in T1D, and patient/advocate willingness to accept some risk for meaningful benefit, was explicitly and directly acknowledged.
- The central regulatory question is the lack of direct evidence linking C-peptide to clinical benefit and the magnitude of any clinical benefit that could be achieved with C-peptide preservation — assessed drug by drug (benefit:risk), not as a general class question.
- C-peptide was described as meeting the standard for a reasonably likely surrogate endpoint supportive of accelerated approval, with confirmatory post-marketing evidence required; it was not described as sufficient, on its own, for traditional approval.
- Enrichment strategies (baseline C-peptide, HLA type, immunophenotype) were discussed as a way to clarify detectable treatment effects, alongside acknowledgment of the access trade-offs this creates.

Statistical and Evidentiary Considerations

A further panel focused on the evidentiary and statistical questions underlying the C-peptide and HbA1c relationship. Discussion centered on TOMI-T1D, a large, curated, pooled dataset of new-onset T1D trials assembled by the consortium, which enables analyses — including those leveraging randomization within pooled trials — that individual studies cannot support alone. Regulatory participants credited this curation effort as an important advancement, while noting that the central open question remains the magnitude and consistency of the relationship between C-peptide preservation and HbA1c across trials, which current analyses characterize as a real but "shallow" and heterogeneous association once causal (randomized) evidence is isolated from purely observational patterns.

There was substantial discussion of confounding and sources of potential bias: participants agreed that accounting for variables such as insulin dose is essential to interpreting the C-peptide and HbA1c relationship, and that multivariate approaches — supported by the availability of patient-level data across multiple pooled trials — represent a valuable, appropriate next step, while randomized evidence remains the most persuasive basis for causal inference.

Regulatory participants clarified that long-term outcome data are not viewed as a near-term regulatory bottleneck; the current regulatory focus is on intermediate-term outcomes, even as long-term data continues to be encouraged and valued. On endpoints, it was stated plainly that glycemic control is not considered the only relevant benefit for people with new-onset T1D, and that current draft guidance already supports CGM-based metrics as key secondary endpoints. Regulatory participants expressed openness to discussing CGM-based measures and objective treatment-burden endpoints (such as reduced insulin dosing frequency) directly with sponsors, while noting that responsibility for proposing, justifying, and validating such measures rests with the field. Composite endpoints were seen as more often necessary when trials are underpowered, which was not viewed as the constraint here — in favor of hierarchical testing strategies that preserve statistical rigor while allowing multiple endpoints to be evaluated.

Discussion of patient-reported outcomes (PROs) acknowledged both their importance and their practical limitations: PRO development and validation is time-consuming, and existing tools are not yet validated for regulatory decision-making in new-onset T1D. Regulatory participants expressed openness to face-valid, objective measures of patient burden — for example, daily insulin injection counts or correction-dose frequency — while emphasizing that identification of which measures matter most should be led by patients, advocates, and clinicians and supported by data.

Key Discussion Points

- The pooled TOMI-T1D trial dataset was credited as an important, albeit limited, field-wide advancement, enabling randomization-based analyses not previously possible. Additional analyses along with an expanded dataset to address confounders and potential biases were encouraged as an informative next step.
- The relationship between C-peptide preservation and HbA1c was characterized as encouraging with a likely mechanistic link but modest and heterogeneous across trials; observational associations alone were viewed as insufficient for regulatory purposes without interventional data.
- Long-term outcome data were explicitly described as not a near-term regulatory requirement; the focus is on intermediate-term outcomes.
- CGM-based metrics were repeatedly and explicitly identified as endpoints the FDA is open to discussing as supportive or secondary measures — a notable and consistently reinforced signal across sessions.

- Objective, face-valid measures of treatment burden were favored over composite endpoints or immature PRO tools, with an emphasis on early co-development with patients and clinicians.

Concluding Panel: Synthesis and Path Forward

The workshop's closing panel brought regulatory, industry, academic, and patient-advocacy perspectives together to synthesize the two days of discussion.

Regulatory participants opened by reaffirming that C-peptide is biologically meaningful: observational data consistently link preserved C-peptide to better glycemic control, less hypoglycemia, and improved long-term outcomes, independent of age or disease duration, however direct causal data linking C-peptide to these effects is lacking. The unresolved question was framed clearly as one of *translation* — clinical trials employing different mechanisms have demonstrated that therapies can preserve C-peptide and reduce insulin requirements, but it remains uncertain why these effects do not consistently show up on trial-measured clinical outcomes like reductions in HbA1c or hypoglycemia. Possible explanations discussed included insufficient trial power, modest effect sizes relative to increasingly effective background therapy, and intervention occurring later in disease progression than may be optimal. Disentangling these explanations — and clarifying the conditions under which preserved C-peptide translates into measurable clinical benefit — was identified as a central priority for the field's continued analytic work.

A cross-disease analogy was raised to illustrate the point: in cardiovascular disease, lipoprotein(a) reliably predicts cardiovascular risk, yet earlier therapies that modestly lowered it failed to demonstrate clinical benefit, while newer therapies producing much larger reductions are still being evaluated to see whether benefit emerges. The parallel drawn was that a strong association between a marker and outcomes does not guarantee that a modest, drug-induced change in that marker will produce meaningful clinical benefit — larger, clearer biomarker shifts (as seen, for example, in islet transplantation, where large increases in C-peptide are clearly linked to hypoglycemia protection) make benefit easier to establish than the smaller changes typically achievable with current pharmacologic approaches in T1D. Panelists also discussed data suggesting that some positive trials show an initial rise in C-peptide followed by a decline with a slope similar to untreated patients — raising the question of whether a therapy needs to durably alter the *trajectory* of C-peptide decline, not just produce a transient shift, to represent true disease modification.

On existing pooled analyses, regulatory participants offered constructive input: current published analyses (including widely cited pooled and meta-regression work) were recognized as valuable contributions that have moved the field forward, with a shared sense that there is a clear opportunity to build on them. Incorporating a broader range of available trials and arms in a meta-analysis approach, and continuing to make analytic approaches as transparent and reproducible as possible, were highlighted as promising next steps that could further strengthen the evidentiary picture and support increasingly confident regulatory assessment over time.

On endpoints beyond HbA1c, the panel's discussion reinforced a theme heard throughout the workshop: advanced diabetes technology increasingly narrows the ability of trials to detect incremental benefit on traditional glycemic measures, making it more important — not less — to consider face-valid endpoints reflecting treatment burden and CGM-derived measures. A perspective offered during the discussion suggested CGM metrics could ultimately prove more sensitive than HbA1c for detecting incremental benefit in modern trial populations. Data clearly linking these measures to measures of clinical benefit (how a patient feels, functions, or survives) are lacking to date. Regulatory participants,

while supportive of CGM-based metrics as a valuable and explicitly encouraged direction, emphasized that any such measure still needs to be shown, through randomized data, to reliably distinguish drug effect from placebo before its value relative to HbA1c can be established.

Participants also discussed responder heterogeneity, cautioning that apparent C-peptide "super-responders" appear in both active and placebo arms and could be due to natural variability, and that regulatory conclusions must rest on population-level, pre-specified analyses rather than individual extremes.

The panel closed by returning to accelerated approval as the pathway best suited to the field's current evidentiary state: C-peptide was again described as meeting the bar for a reasonably likely surrogate endpoint, with the clear expectation that post-approval confirmatory evidence will still be required. Participants were consistent that this is a matter of evidentiary clarity — the task ahead is to bring more rigorous, more comprehensive, and more clearly interventional (rather than purely observational) data connecting specific magnitudes of C-peptide change to specific, patient-relevant clinical benefit.

Key Discussion Points

- FDA participants' central position — that C-peptide is biologically meaningful but not yet demonstrated to reliably predict clinical benefit at achievable magnitudes — was stated consistently across the workshop's sessions.
- The gap was repeatedly framed as one of evidentiary clarity and magnitude, not regulatory disagreement with the underlying biology.
- Existing pooled analyses were viewed as a valuable but incomplete foundation; more comprehensive and transparent meta-analytic work was encouraged.
- Accelerated approval, supported by C-peptide as a reasonably likely surrogate endpoint and followed by confirmatory evidence, was stated as an appropriate and available pathway for the field — not a fallback, but a Fit-For-Purpose route given where the evidence currently stands.

Summary and Next Steps

The workshop reflected broad, cross-sector agreement that C-peptide is biologically meaningful and prognostically important in type 1 diabetes, alongside a shared understanding of the specific evidentiary work still needed to establish it — or complementary endpoints — as a reliable basis for demonstrating clinical benefit. Participants across regulatory, academic, industry, and patient-advocacy communities converged on several themes:

1. The need for more comprehensive and transparent pooled analyses of clinical trial data (ideally RCTs);
2. The value of CGM-based and objective treatment-burden endpoints alongside C-peptide;
3. The importance of early, iterative engagement between sponsors and regulators; and
4. The recognition that modern standards of care require evidentiary strategies calibrated to detect increasingly subtle treatment effects.

Since the workshop, the field has continued to advance. In late June 2026, the FDA granted accelerated approval to the first disease-modifying therapy (Sanofi's Tzield) for stage 3 type 1 diabetes — a milestone that reflects, in part, the kind of regulatory pathway discussed throughout this workshop, and that underscores the continued importance of the shared evidentiary and regulatory-science work

described above. To address the above identified themes, C-Path's Type 1 Diabetes Consortium continues to expand its pooled dataset and to support the field's ongoing engagement with FDA on these questions, with the goal of building the shared frameworks needed to bring future disease-modifying therapies to people with T1D across all stages of disease.