Type 1 Diabetes TrialNet: A Multifaceted Approach to Bringing Disease-Modifying Therapy to Clinical Use in Type 1 Diabetes

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Diabetes Care 2018;41:653–661 | https://doi.org/10.2337/dc17-0806

What will it take to bring disease-modifying therapy to clinical use in type 1 diabetes? Coordinated efforts of investigators involved in discovery, translational, and clinical research operating in partnership with funders and industry and in sync with regulatory agencies are needed. This Perspective describes one such effort, Type 1 Diabetes TrialNet, a National Institutes of Health–funded and JDRF-supported international clinical trials network that emerged from the Diabetes Prevention Trial–Type 1 (DPT-1). Through longitudinal natural history studies, as well as trials before and after clinical onset of disease combined with mechanistic and ancillary investigations to enhance scientific understanding and translation to clinical use, TrialNet is working to bring disease-modifying therapies to individuals with type 1 diabetes. Moreover, TrialNet uses its expertise and experience in clinical studies to increase efficiencies in the conduct of trials and to reduce the burden of participation on individuals and families. Herein, we highlight key contributions made by TrialNet toward a revised understanding of the natural history of disease and approaches to alter disease course and outline the consortium's plans for the future.

Since it was established in 2001, building on the work of many researchers over the preceding 20–30 years (1–6), Type 1 Diabetes TrialNet has emerged as a global leader for multicenter longitudinal studies of type 1 diabetes natural history and mechanistic investigations, as well as clinical trials of disease-modifying therapy (Fig. 1). With 25 Clinical Centers and hundreds of affiliate sites in the U.S., Canada, U.K., Sweden, Finland, Germany, Italy, Australia, and New Zealand, TrialNet is an international collaborative effort between clinical investigators and their teams, immunologists, and islet cell biologists that aims to bring disease-modifying therapy to clinical use, complementing the work of the other groups across the world currently focusing on this objective (7–10).

INCREASING OUR UNDERSTANDING OF THE NATURAL HISTORY OF TYPE 1 DIABETES: TRIALNET PATHWAY TO PREVENTION AND LIFT STUDIES

TrialNet recruits around 15,000 research subjects per year and, since study inception, has tested more than 180,000 relatives of individuals with type 1 diabetes for the presence of islet autoantibodies. Approximately 5% have one or more autoantibodies against islet antigens (GAD65 [GADA], insulin [micro–insulin autoantibody (mIAA)], insulinoma-associated protein 2 [IA-2A], zinc transporter 8 [ZnT8A], and islet cell antibodies [ICA]) and are eligible for regular follow-up in the TrialNet Pathway to Prevention study. In the Diabetes Prevention Trial–Type 1 (DPT-1), about 35% of multiple autoantibody–positive relatives with normal glucose tolerance and 65% of those with

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Received 21 April 2017 and accepted 13 December 2017.

See accompanying article, p. 667.

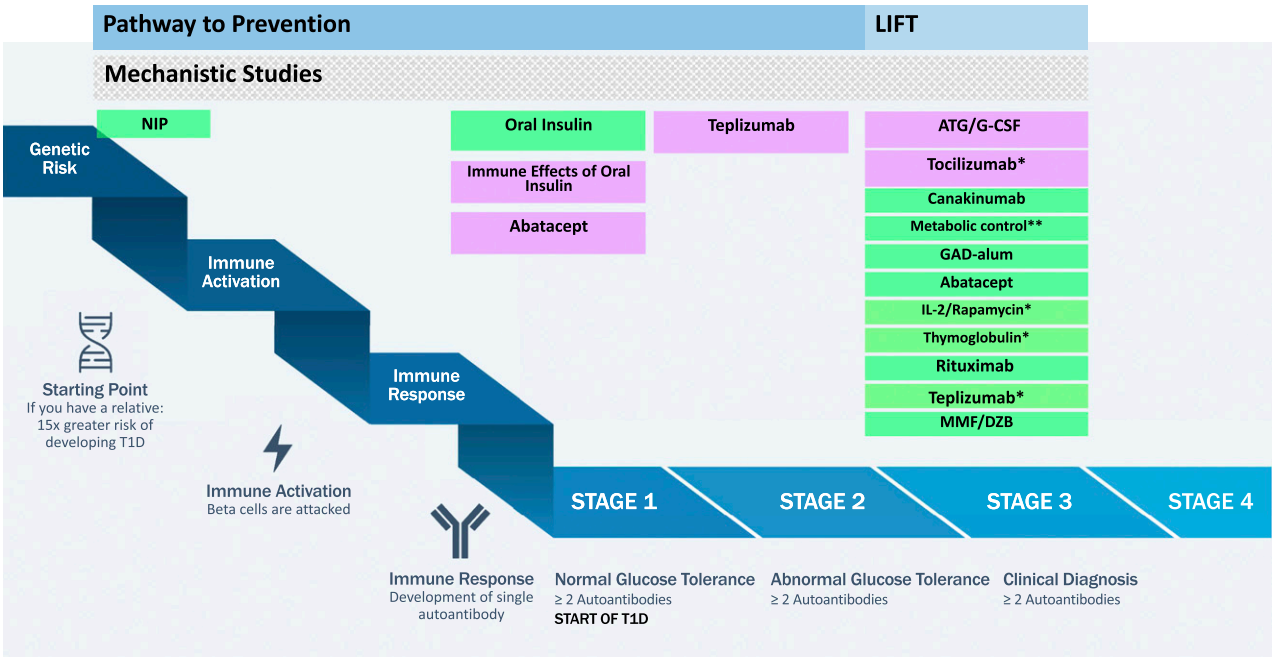

Figure 1—Stages of diabetes and corresponding TrialNet studies. Green are completed intervention trials, purple are ongoing studies, and blue are natural history studies. *Studies in conjunction with Immune Tolerance Network. **Studies in conjunction with Diabetes Research in Children Network (DirecNet) Study Group. DZB, daclizumab; IL-2, interleukin-2; MMF, mycophenolate mofetil; NIP, Nutritional Intervention Pilot; T1D, type 1 diabetes.

abnormal glucose tolerance developed clinical type 1 diabetes within 5 years (11,12). More recent data from ongoing follow-up of genetically at-risk infants (13,14) and relatives taking part in the TrialNet Pathway to Prevention study (15,16) suggest that the risk of disease progression does not level off over time. A joint analysis of previous studies of multiple autoantibody–positive infants followed from birth found the risks of clinical diabetes over 5, 10, and 15 years to be 44%, 70%, and 84%, respectively (14). TrialNet data confirm the extremely high risk of type 1 diabetes among relatives with multiple autoantibodies; overall, the rate of progression from multiple autoantibodies to clinical diabetes is 10–12% per year (15,17). Life tables from these studies illustrate the key concept that this rate of progression appears constant over time. Thus, essentially all individuals with confirmed multiple autoantibodies are destined to develop clinical type 1 diabetes.

These insights into the course of diabetes progression led to the development of a new staging system for type 1 diabetes that was proposed in 2015 (18). Stage 1 diabetes is defined as the presence of two or more autoantibodies with normoglycemia. The transition to stage 2 is marked by progression from normoglycemia to dysglycemia in the context of ongoing autoimmunity. Stage 3 denotes the clinical diagnosis of type 1 diabetes, which is often but not always accompanied by symptoms.

This staging system highlights the progressive nature of pre–type 1 diabetes and the fact that the disease is present long before clinical presentation. It emphasizes that the onset of disease can be defined by a "point of no return" in the pathway—the detection of two or more autoantibodies. Clinical trials in this population with multiple autoantibodies are therefore treating an established disease—the disease of islet autoimmunity. Treating islet autoimmunity does not therefore equate to the previous concept of intervening in healthy people to prevent a disease. This is analogous to hypertension, a disease that we treat to prevent stroke and coronary artery disease (CAD). Of those with hypertension, 2.4/100 will develop CAD and 1.9/100 will have a stroke within 5 years. Treating 100 individuals with hypertension prevents two people from developing CAD or stroke within 5 years (19). In the case of islet autoimmunity, at least 35/100 individuals with multiple autoantibodies and normal glucose tolerance and at least twice that number with abnormal glucose tolerance will develop clinical diabetes within 5 years. Current clinical trials in those with multiple autoantibodies and normal glucose tolerance have been designed to reduce the risk by 40%; if successful, treating 100 people would prevent 14 from progressing to clinical type 1 diabetes in that time. Hence, an understanding that treating islet autoimmunity is treating a disease offers a new perspective for both potential participants and regulatory agencies considering the risks and benefits of clinical trials (18).

TrialNet has also studied changes in insulin secretion over time. George Eisenbarth's model of the natural history of type 1 diabetes proposed a linear decrease in and eventual absence of insulin secretion (20). TrialNet, however, found that insulin secretion does not change appreciably until 6–12 months prior to clinical onset (21) and that after diagnosis, secretion falls most rapidly during the first year, decreasing much more slowly after that time (22). Together, these data suggest that β-cell function is relatively stable in autoantibody-positive relatives until they reach a cliff edge, heralding a steep drop prior to diagnosis, and continues to fall for about a year before leveling off again. Emerging data from the Long-Term Investigative Follow-up in TrialNet (LIFT) study testing individuals through the peridiagnostic period emphasize the arbitrary nature of the "diagnostic"

glucose threshold derived from an oral glucose tolerance test and suggest that attempts to preserve β-cell function should start before this steep fall in insulin production.

Results from TrialNet and other studies have also shown that age is the most important factor in progression at any stage of the disease process (Fig. 2). About one-fifth of single autoantibody–positive individuals progress to more than one autoantibody in 5 years (23,24). Even at this stage, age has a major influence on risk of progression, with young children much more likely to develop multiple autoantibodies than older relatives. A key point is that older children and adults with a single autoantibody are not, however, immune to progression, particularly those with high titers of GADA (23,24). Similarly, age influences response to therapy. For example, post hoc analysis of abatacept and rituximab trials at stage 3 of disease demonstrated that the effectiveness of therapy was most pronounced in children (15). The recognition that type 1 diabetes is different in children and adults has important ethical and regulatory implications for conducting clinical trials of disease-modifying therapy (15).

TrialNet studies have also begun to yield other insights into heterogeneity of the disease course. For example, a recent analysis emphasized that HLA type impacts the development of autoantibodies but does not markedly effect progression from that point (25). TrialNet reported differences in the age- and HLA-associated risk of developing additional autoantibodies in single autoantibody–positive relatives who are mIAA positive versus those who are GADA positive, suggesting potentially different disease pathways (23,24). In contrast, sex is not a significant factor in disease progression at any stage. Non-Hispanic white individuals are more likely to be autoantibody positive and more likely than other racial/ethnic groups to have two or more autoantibodies on initial screening (26,27), yet neither race nor ethnicity is associated with C-peptide decline after clinical diagnosis (22). With these robust observations, studies can now be conducted to increase our understanding of the heterogeneity of progression addressing the questions of why age is such an important influence and why ~80% of people with a single autoantibody do not progress within 5 years. More than 25,000 samples from TrialNet studies have already been used to gain additional descriptive and mechanistic insights regarding disease pathogenesis and heterogeneity (as reviewed in Battaglia et al. [28]). TrialNet has recently initiated multidimensional "omic" studies to address progression through the early stages of disease.

CLINICAL TRIALS OF DISEASE-MODIFYING THERAPY: WHAT IS TRIALNET AIMING FOR AND WHAT HAVE WE ACHIEVED?

Despite almost 100 years of insulin treatment for the symptoms of type 1 diabetes (i.e., hyperglycemia), no therapies exist to treat the underlying etiopathology. In contrast, the goal of treatment of rheumatic disease in both children and adults is no longer control of symptoms (e.g., pain control, better aids to address disability); rather, the objective is to change the underlying course of disease. Disease-modifying therapy has not cured their disease but has markedly changed the lives of those with arthritis. Immunotherapy, particularly if used early in disease, not only acutely reduces pain but also reduces disability (29).

This experience provides key lessons for disease-modifying therapy in type 1 diabetes. Better insulin delivery, glucose measurements, and tools to diminish the mental and psychological demands of living with type 1 diabetes are important developments, yet treating the underlying disease process, particularly early in the course of disease, even if not curative, holds the promise of significant clinically relevant benefits. Any delay in the transition from multiple autoantibody positivity (stage 1 or stage 2 diabetes) to hyperglycemia and insulin therapy would be of clear clinical benefit.

Disease-Modifying Therapy at Stage 3

For those with clinical disease, preservation of C-peptide is associated with better glycemic control and fewer complications. The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) study demonstrated that short-term aggressive glucose control results in long-term benefits (e.g., reduction of micro- and macrovascular complications) (30). Thus, even short-term preservation of C-peptide, as seen in clinical trials to date, holds the promise of both short-term and long-term benefits (31,32).

It has now been over 30 years since studies using cyclosporin A in recent-onset diabetes provided proof of principle that intervention could alter the course of the disease process and prolong endogenous insulin production, albeit temporarily (1,33). It seems timely to ask how much further have we come toward this goal. By the time that TrialNet was established, intervention trials using other agents at clinical diagnosis had built on and extended the success of this approach, although prolonged preservation of C-peptide secretion in this situation

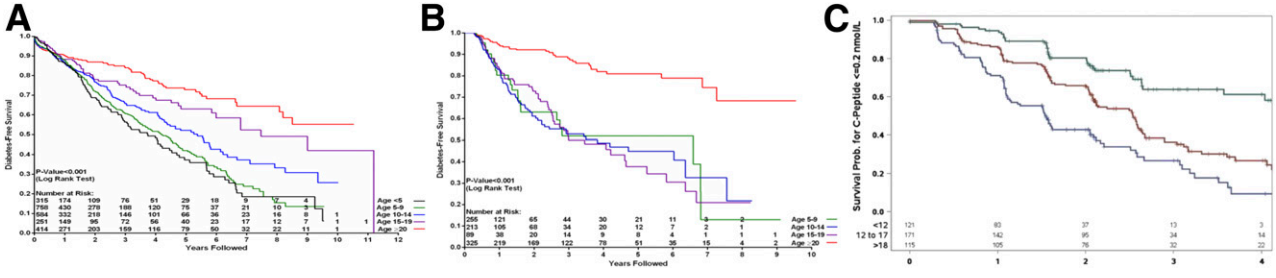

Figure 2—Effects of age on progression of type 1 diabetes. *A* and *B*: Impact of age on risk for disease progression in autoantibody-positive relatives participating in the TrialNet Pathway to Prevention study. *A*: Life table of progression to diabetes according to age in double autoantibody–positive relatives (15). *B*: Life table of progression to diabetes according to age in double autoantibody–positive subjects from time of abnormal glucose tolerance (15). *C*: Life table of progression from randomization in stage 3 clinical trial to mixed-meal tolerance test–stimulated peak C-peptide ≤0.2 nmol/L (55). Prob., probability.

remained elusive (4,34). The outcome of TrialNet trials of daclizumab with mycophenolate mofetil and canakinumab (anti–interleukin-1) were, however, negative in spite of promising preclinical studies and experience in other autoimmune disease (35,36). Particularly disappointing, in the light of its ease of administration and tolerability, was that antigen-specific therapy with GAD-alum also had no impact on C-peptide secretion (37).

Other approaches, however, have been more fruitful. Compared with placebo, the B lymphocyte–depleting agent rituximab (anti-CD20) slowed decline in stimulated C-peptide and was associated with lower insulin requirements and HbA_{1c} levels over 12 months in patients with recent-onset type 1 diabetes (38). It is important to note that rituximab was given only as a single course of drug in this study, in marked contrast to the way the drug is used in clinical practice for other autoimmune diseases. It is therefore not surprising that after the initial delay, the rate of fall in C-peptide secretion was similar in the two groups, such that there was no significant difference in C-peptide at 24 months (39). Abatacept (CTLA4-Ig) acts to block costimulatory pathways in the key interaction between antigen-presenting cell and T lymphocyte. It is in clinical use in rheumatoid arthritis (RA) and has been shown to have beneficial effects in other autoimmune diseases. The TrialNet abatacept intervention trial in stage 3 (recent-onset) diabetes showed that after 2 years of treatment, this agent was associated with 59% (95% CI 6.1–112) more C-peptide secretion compared with placebo and that C-peptide secretion remained higher in the treated group 1 year after cessation of treatment. Importantly, treatment was also well tolerated and had minimal adverse events (40).

It has been said that these results of clinical trials to date are disappointing because the effect of therapy is limited and transient, leading to the misconception that immunotherapy is not effective in type 1 diabetes. Yet, the results of these trials are remarkably similar to those observed in other diseases. For example, phase 2 trials that led to approval of abatacept in RA demonstrated a 20% improvement in the clinical score (41) compared with a 59% increase in C-peptide secretion in abatacept-treated versus placebo groups (40). Thus, immunotherapy "works" in type 1 diabetes just as effectively as it "works" in other autoimmune diseases. Extending the duration of effect is likely to require repeated, intermittent therapy, as is routine practice in children and adults with RA, inflammatory bowel disease, and other conditions. Clinical trials have not yet been conducted testing this premise in type 1 diabetes using modern immunotherapeutics; TrialNet is currently evaluating ideas for clinical trials using sequential administration of several therapies and/or repeated treatment courses.

Disease-Modifying Therapy at Stages 1 and 2

The most significant outcome of the successful clinical trials at stage 3 has been the ability to test two of these agents, teplizumab (anti-CD3) and abatacept (CTLA4-Ig), at earlier stages of disease and thus address a critical question in the field: when is the optimal time to intervene? As described below, TrialNet is conducting multiple trials at stages 1 and 2 of disease, most of which are fully powered, placebo-controlled, randomized studies. Having identified hundreds of autoantibody-positive individuals, TrialNet is also in a position to conduct proof-of-mechanism and early-phase studies—one of which was able to complete recruitment within 9 months.

Stage 1 Type 1 Diabetes (Multiple Islet Autoantibodies With Normal Glucose Tolerance)

Oral Insulin (NCT00419562). The first TrialNet prevention study in at-risk relatives arose as result of a post hoc analysis of the oral insulin arm of DPT-1. This showed that although the outcome of the study as a whole was negative, there appeared to be a treatment effect in the subgroup of participants with higher levels of mIAA equivalent to a median delay in progression to clinical onset of diabetes of 4.5 years (12). This was the first indication of possible benefit in any type 1 diabetes prevention study, and, if confirmed, a treatment effect of this magnitude would certainly be clinically important. The TrialNet oral insulin study used the same dose (7.5 mg daily) as employed in DPT-1. The primary cohort used similar inclusion criteria as DPT-1, but the TrialNet study also included additional cohorts with other autoantibody combinations and/or low insulin secretion (Table 1). Oral insulin did not prevent or delay type 1 diabetes in the primary cohort or the entire study population; there was, however, a significant delay in diabetes onset in a secondary cohort of individuals with low first-phase insulin release at randomization (17). The placebo group in this cohort had the most rapid rate of progression to clinical type 1 diabetes compared with the rest of study participants, and, interestingly, this was also true of the DPT-1 subgroup with high mIAA in which oral insulin appeared to delay diabetes. These results could be considered counterintuitive and question the notion that antigen therapy would be most beneficial earlier in disease. They suggest an alternative hypothesis that therapies

Table 1—Results of TrialNet's oral insulin prevention study according to stratum

	Primary stratum		Stratum 1		Stratum 2		Stratum 3	
N	389		55		114		2	
Autoantibodies	mIAA and ICA or both GAD65Ab and ICA512Ab		mIAA and ICA or both GAD65Ab and ICA512Ab		mIAA and either GAD65Ab or ICA512Ab		mIAA and either GAD65Ab or ICA512Ab	
First-phase insulin secretion*	Above threshold		Below threshold		Above threshold		Below threshold	
Outcome: progression to stage 3 (clinical type 1 diabetes)	No effect ($P = 0.21$)		31-month delay in progression ($P = 0.006$)		No effect ($P = 0.11$)			
Annual rate of progression to stage 3 (clinical type 1 diabetes)	Oral insulin 8.8%	Placebo 10.2%	Oral insulin 18.1%	Placebo 34.1%	Oral insulin 5.1%	Placebo 4.7%		

*Threshold as defined in DPT-1 (14).

may need to be administered during a time of active disease. Work is under way to explore these and other ideas in trying to understand the reasons underlying the beneficial outcome in the subgroup.

Immune Effects of Oral Insulin (NCT02580877). To complement the outcome from the randomized, placebo-controlled trial of 7.5 mg of oral insulin and building on results from the Pre-POINT study of oral insulin (42), TrialNet launched a randomized trial testing two other oral insulin dosing regimens: 67.5 mg daily or 500 mg every other week. No safety concerns were identified with either dose. Work is ongoing to evaluate immune responses before, during, and after 6 months of treatment. Together with improved understanding of the mechanistic differences in the randomized trial using the much lower dose of drug, these data will provide insight into future studies of oral insulin at the early stages of diabetes.

Abatacept (NCT01773707). The effect of this drug given at stage 3 (recent-onset) diabetes (40), combined with its favorable side-effect profile, make it appropriate for testing at an earlier stage in the disease process. In 2018, TrialNet expects to complete recruitment of relatives aged 6 years and above for the TrialNet abatacept prevention trial testing whether therapy can delay progression from stage 1 to stage 2 diabetes.

Other Approaches. A trial of hydroxychloroquine in stage 1 is currently in the planning phase. This antimalarial agent is widely and safely used in the treatment of rheumatic diseases in both children and adults. It reduces innate and adaptive immune activation and has been shown to slow progression of autoimmunity in the early stages of RA and systemic lupus erythematosus (43). TrialNet will launch a trial of the antihypertensive agent methyldopa in autoantibody-positive relatives in 2018. This agent inhibits antigen presentation to $CD8^+$ lymphocytes by HLA-DQ8 in vitro, in animal models, and in patients with recent-onset (stage 3) type 1 diabetes, potentially leading to inhibition of effector lymphocytes (44,45).

Stage 2 Type 1 Diabetes (Multiple Islet Autoantibodies With Abnormal Glucose Tolerance)

Teplizumab (NCT01030861). Teplizumab, a humanized monoclonal antibody that binds CD3 on the T-cell receptor, has been shown to delay decline in endogenous insulin production after clinical diagnosis. This effect was most marked in individuals who used less insulin and had lower HbA_{1c} levels at baseline (46), thus providing the rationale for testing the agent in autoantibody-positive relatives with abnormal glucose tolerance (stage 2). Recruitment is now complete for the study, and results are anticipated in the next 18 months.

Other Approaches. TrialNet is actively exploring the notion of early-phase trials to test sequential therapy of rituximab followed by abatacept. In addition, the consortium is looking at emerging data from ongoing stage 3 trials to determine which interventions to bring to stage 2 testing. These include results from a JDRF-sponsored trial of imatinib (NCT01781975) and from TrialNet's study of antithymocyte globulin (ATG) ± granulocyte-colony stimulating factor (G-CSF) (NCT02215200). The ATG/G-CSF study builds on promising results from a pilot study that found that the combination preserved endogenous C-peptide production for a full year in patients with established type 1 diabetes (47).

Investigators are increasingly considering therapies that may work directly on β-cells to reduce stress or apoptosis. Pilot studies testing difluoromethylornithine (DFMO) and tauroursodeoxycholic acid (TUDCA) as well as a fully powered trial with liraglutide combined with immune therapy are under way (NCT02384889, NCT02218619, and NCT02443155, respectively). If these or other agents are shown to have effects on β-cells in humans, TrialNet would be eager to use these in combination with therapies designed to keep the immune response at bay.

While TrialNet currently identifies autoantibody-positive individuals by screening relatives, other studies have identified those at the early stages of disease by screening the general population (48–50). Importantly, such studies suggest that the rate of progression in multiple autoantibody–positive children is the same whether they are identified from the general population or are relatives (13,18,51); thus, future TrialNet studies will include individuals identified using either approach. While outside TrialNet's current scope, efforts at primary prevention (preventing the appearance of autoantibodies) continue, and it remains an important goal for the field (42).

IMPROVING CLINICAL TRIALS: STANDARDIZATION, ENGAGEMENT OF PARTICIPANTS, INCREASING EFFICIENCIES AND EFFECTIVENESS

TrialNet decided early on to use standard entry and outcome criteria in trials at stage 3 of disease (recent-onset) to facilitate comparisons between trials. Studies comparing two outcome measures of β-cell function—responses to glucagon stimulation and to a mixed meal—demonstrated that both tests were highly reproducible but not the same and established the mixed-meal tolerance test as the preferred measure (52). Similar studies were performed comparing multiple measures of T-cell activity in type 1 diabetes; while some assays achieved high sensitivity and specificity, these efforts illustrated the challenges in reproducibly detecting low-frequency cells with the tools available in 2009 (53).

Combining data from TrialNet stage 3 studies has yielded important information for designing future trials for both academia and industry (22,54,55). The impact of therapies on vaccination and infection has also been formally studied in all trials to inform eventual clinical application (56–58).

Recently, using pooled data from placebo-treated participants in multiple trials to understand the variance in C-peptide over time, TrialNet employed adaptive design to determine the sample size for our ATG and G-CSF study. This approach enabled investigators to limit the sample size and thus the time needed to enroll this trial. TrialNet also took advantage of new knowledge to shorten the time to study end point in our trial testing abatacept in those at stage 1 of disease. Here, the intermediate end point of progression to stage 2 (multiple autoantibodies and abnormal glucose tolerance) has been used as the primary efficacy measure. A TrialNet ancillary study is evaluating the use of continuous glucose monitoring in early stages of disease to determine whether this could contribute to entry criteria or end points in clinical trials.

Using the combined data from TrialNet stage 3 (recent-onset) diabetes trials, we have also developed a model for predicting decline in β-cell function after clinical diagnosis: given a recently diagnosed

individual's age and baseline C-peptide value, we can now accurately assign a "predicted" C-peptide 1 or 2 years later (59). It also presents a novel way to consider "responders" and "nonresponders" to therapy. Experience in other autoimmune diseases highlights the reality that some individuals do not respond to a particular therapy; such clinical responders and nonresponders are also evident in type 1 diabetes clinical trials (46,60,61). Understanding the demographic, genetic, and immunologic baseline and longitudinal characteristics of responders and nonresponders can aid in understanding underlying mechanisms and help to target therapies to individuals most likely to benefit. With our ability to predict an individual's C-peptide, as described above, we can now consider responders and nonresponders according to how their observed response differs from their predicted response. The key point is that this predictive model can be used across all trials. In this way, mechanistic comparisons can be made between responders in different studies.

Improving the Participant Experience

> Often, clinical trials are aptly named: they are trials—difficult and exhausting, at a time when a patient's physical and emotional capacities are already stretched thin.
>
> — Margaret Anderson (62)

In addition to improving clinical trial design and interpretation with robust and standardized measures, TrialNet places a high priority on developing processes and procedures that can help individuals understand the studies, reduce the participant burden, and gain efficiencies in the conduct of trials. For example, all TrialNet studies have "Research Volunteer Handbooks" that supplement written consent forms with clear descriptions of study visits and procedures. Potential TrialNet study participants answer multiple-choice questions about the study to assess their understanding. Misconceptions about a study, if any, are thereby readily identified and reviewed prior to documenting informed consent. These efforts have paid off. For example, in the TrialNet study testing GAD-alum therapy at stage 3 of disease, TrialNet fully enrolled 145 individuals aged 3–45 years within 12 months, with end point compliance in this study exceeding 97% (37). Studies at stages 1 and 2 of disease require long-term participation; while loss to follow-up was only 3.3% per year, some individuals were part of the oral insulin study for 10 years (17).

Prior to widespread use of the Internet, TrialNet's outreach and recruitment efforts were focused on direct interaction with health care providers treating patients with diabetes, research update programs for individuals with diabetes, and presentations at scientific meetings. While these efforts continue, TrialNet is increasingly embracing social media in our recruitment and engagement strategies. Since 68% of all U.S. adults use Facebook regularly, TrialNet actively manages its Facebook presence through frequently updated content, connections with other type 1 diabetes groups, and systematic evaluation of each approach. These targeted efforts have led to dramatic increases in engagement; interest in our Facebook page increased more than sixfold to almost 40,000 "likes." TrialNet also maintains a Twitter feed, engages with bloggers, and actively monitors social media for comments and discussions about TrialNet. TrialNet recently launched a completely revamped website aiming to engage participants in entirely new ways. The website uses a mobile-first design, incorporates simplified graphics (image and video), and embraces the peer-to-peer voice. Indeed, TrialNet aims to make the entire process from learning about trial participation to study enrollment as quick and painless as possible.

Finally, TrialNet continues to identify and mitigate barriers to participation. As mentioned previously, of the 15,000 new individuals per year that TrialNet current screens for autoantibodies, only 5% will be autoantibody positive. Thus, for the vast majority of individuals, the initial screening step will be the only procedure necessary. Currently, that step requires venipuncture. While simple from the study team's perspective, it can represent a significant hurdle for families. TrialNet has therefore explored alternative means of screening. In the first effort, study staff obtained a finger-stick capillary sample from participants and placed the blood on filter paper to test for GADA, IA-2A, and ZnT8A and compared the results with those from simultaneous venipuncture. Though not sensitive enough to identify all individuals with a single autoantibody, this method identified 95.5% of multiple autoantibody–positive individuals and 98.6% of autoantibody-negative individuals. An important insight was gained from asking participants about their experience. Investigators were surprised to learn that although 60% of participants perceived the finger-stick as more painful than the venous blood draw, they preferred this method to the inconvenience of going to a TrialNet site (63). In a follow-up study, participants or their parents collected capillary samples into tubes themselves, and families again reported strong preferences for home collection of capillary blood sampling over venipuncture at a clinical site, particularly for children less than 8 years of age (64). While venipuncture is still the gold standard, TrialNet now offers capillary test kits for home blood collection as an alternative option to further facilitate enrollment and screening. Importantly, TrialNet is prospectively collecting metrics to evaluate the effectiveness of these changes.

USING A CENTRAL INSTITUTIONAL REVIEW BOARD: RESPONDING TO NIH REQUIREMENTS AND PIONEERING UNCHARTED TERRITORY IN THE U.S.

As of January 2018, all newly National Institutes of Health (NIH)-funded multisite clinical trials will be required to use a central institutional review board (CIRB) (65). The aim of this mandate is to enhance efficiencies in the approval process by eliminating the requirement for IRB approval at each study site. With the establishment of a CIRB, trials will essentially be "turned on" at multiple sites after review by a single IRB. The expectation is that the CIRB will benefit funders, investigators, and participants by expediting enrollment, lessening workload, reducing the cost of clinical trials, and assuring more consistency in multicenter studies. These premises, however, remain to be tested.

As a first step, TrialNet developed criteria to select our CIRB of record and then initiated a pilot project to develop procedures for establishing agreements between the relying institution and the CIRB as well as to collect data for objective information about the impact of implementing a CIRB. With the completion of the pilot phase, the remaining Clinical Centers are now under the CIRB and TrialNet is rapidly transitioning as many as

several hundred additional sites under the CIRB. As an international clinical trials network, there is hope that demonstrating the effectiveness of a CIRB for multicenter U.S. clinical trials will enable other countries where centralized systems are not already in place to consider this approach. Thus, TrialNet will be a pioneer in uncharted territory in the realm of ethics research review and looks forward to reporting on its progress with this most important endeavor.

CHALLENGES

Given the challenges in identifying autoantibody-positive individuals, the long duration from detection of autoantibodies to changes in glucose metabolism, the need to study children, the requirement to address the issues of industry and regulatory and granting agencies, and the challenges of choosing which therapeutic interventions are most promising, making progress in disease-modifying therapy is a long and complex process. TrialNet has faced these issues, recognizing that they have slowed our progress at times, and is working to address these challenges by improving internal processes and meeting with industry and regulators. The international nature of the consortium presents additional challenges due to different legal and regulatory environments among the participating sites, but the non-U.S. sites represent a major strength of TrialNet. International investigators, who receive funding from JDRF in addition to the NIH, are making increasingly important contributions to study recruitment, data analysis, and new trial ideas. The international investigators can also help assure fruitful discussion and collaboration with other initiatives.

SUMMARY

TrialNet aims to bring disease-modifying therapy (Table 2) to clinical use in type 1 diabetes and is the leading international network conducting trials to delay disease progression in those with early disease stages defined by multiple autoantibodies (stages 1 and 2) through clinical diagnosis (stage 3). Alone and/or in collaboration with others, TrialNet has conducted multiple randomized controlled trials of disease-modifying therapies in those at stage 3 as well as other studies evaluating clinical trial and mechanistic end points. While the overall results from the oral insulin study at stage 1 were negative, the provocative findings demonstrating a delay in disease progression in the subgroup of 55 individuals emphasize the unmet need to identify approaches targeting the "right" person at the "right time." TrialNet has proved to be an important resource to the broader scientific community. In addition to the biological samples dispersed to academic and industry scientists, TrialNet data are used by industry and academic investigators alike to gain insights into the pathogenesis of disease. As clinical trial experts, TrialNet investigators design and conduct high-quality studies while aiming to ease the demands that clinical trial participation puts on individuals and families. TrialNet employs innovative trial

Table 2—Key observations and future opportunities

	Key observation/implication	TrialNet current activities and future opportunities
Natural history of type 1 diabetes		
Stages of type 1 diabetes	• Intervention in those with two or more autoantibodies represents treatment of islet autoimmunity • Progression between stages can be used to define intermediate end points for clinical trials	• The objective of the abatacept prevention trial is to delay progression from stage 1 to stage 2 • Studies into mechanisms underlying progression between stages 1, 2, and 3 and key transition from single to multiple autoantibodies
Rapid decline in β-cell function occurs 6–12 months prior to clinical diagnosis	• This "cliff edge" for loss of β-cell function suggests this is a key time for intervention • The cause of this rapid change in β-cell function needs to be understood	• Future studies may use β-cell function as entry/end point for trials at stage 1 and/or stage 2 • Studies into immune mechanisms associated with onset of rapid decline
Age is a major determinant of the clinical course of type 1 diabetes at all stages of disease	• Mechanisms underlying the effect of age are unknown • Age of participants must be considered in clinical trial design	• Studies into immune and genetic mechanisms underlying age effect • Inclusion criteria and analytic plan for the teplizumab prevention trial vary by age
Disease-modifying therapies	• Immunotherapy "works" in type 1 diabetes, though the effect wanes • Changes in C-peptide after clinical diagnosis are predictable • C-peptide secretion falls most rapidly over the first 6 months after diagnosis • Heterogeneity of the disease process, both within and between stages, is likely to demand appropriately tailored therapeutic approaches	• Future studies with sequential therapy and/or repeat dosing • Standard definitions of responder/nonresponder to disease-modifying therapy • Characterizing immune changes in the "therapeutic window" 0–6 months post-diagnosis • Investigating how "early" disease differs from "late" disease, including drug responsiveness and determinants of persistent C-peptide secretion after diagnosis
Efficiencies in clinical trials	• Social media and peer-to-peer outreach • Processes and procedures to ease burdens for participants • Use of CIRB in U.S.	• Metrics to determine best practices • Home capillary testing • Online consenting • Evaluate impact of transition on sites and network

designs, system-wide initiatives, and research volunteer–focused resources and procedures to increase the effectiveness and efficiencies of clinical trials. Ideas for trials, analytic approaches, or mechanistic studies are welcome and encouraged. Clinicians and investigators can learn more at DiabetesTrialNet.org.

Funding. The Type 1 Diabetes TrialNet Study Group is a clinical trials network funded by the NIH and JDRF.

The contents of this article are solely the responsibility of the authors and do not necessarily represent the official views of the NIH or JDRF.

Duality of Interest. M.A.A. holds a patent on ATG plus G-CSF for treatment of type 1 diabetes. No other potential conflicts of interest relevant to this article were reported.

Prior Presentation. TrialNet oral insulin trial results were presented at the 77th Scientific Sessions of the American Diabetes Association, San Diego, CA, 9–13 June 2017.

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