



# Type 1 Diabetes TrialNet: working together to prevent, delay or slow the progression of type 1 diabetes

Over the last 30 years, we have learnt a great deal about the processes that culminate in the clinical onset of type 1 diabetes (T1DM). We know that beta cells in the islets are targets of selective autoimmunity, and that autoimmunity – in the form of circulating islet autoantibodies – can be detected many years before clinical onset of diabetes and generally starts in infancy.<sup>1</sup> We are now able accurately to identify individuals at increased risk of T1DM, both among relatives of people with diabetes and children in the general population who are at high genetic risk.<sup>2</sup> We also know that the beta cells are destroyed by cell-mediated immunity. With these insights comes the possibility that we might be able to intervene to alter these processes – to slow or perhaps ultimately prevent the clinical onset of disease.

Early studies, such as the Canadian-European Cyclosporin Trial, provided proof of principle that modulating the autoimmune process could lead to clinically detectable effects and prolong the ‘honeymoon phase’ after diagnosis of T1DM. In the 1990s two major international studies, the European Nicotinamide Diabetes Intervention Trial (ENDIT) and the Diabetes Prevention Trial – Type 1 (DPT-1), took the first steps towards trying to delay or prevent the clinical onset of diabetes in high risk, islet antibody positive relatives of children with T1DM.<sup>3,4</sup> Unfortunately, neither of the agents tested achieved this, but very important lessons were learnt, not least the scale of such endeavours. ENDIT had to screen more than 30 000 relatives in 20 countries to recruit the 552 participants needed, and DPT-1 screened more than 100 000 individuals throughout North America to identify enough high risk relatives to complete trials of parenteral and oral insulin. Another key lesson was the obvious willingness of researchers, clinicians and families to collaborate in addressing this aim.

## What is TrialNet?

Type 1 diabetes TrialNet builds on this experience. It is an international network of clinicians and scientists working together to prevent or delay T1DM through understanding the natural history of the disease, identification of people at risk and clinical evaluation of potential therapies. It consists of 14 clinical centres in North America and – with the support of the Juvenile Diabetes Research Foundation – additional centres in the UK, Australia/New Zealand, Italy, Germany and Finland. Each centre has, in turn, its own network of affiliates and satellites, and the whole is supported by 20 central laboratories and support units. This critical mass not only facilitates rapid recruitment to studies but also ensures that standardised protocols are developed with input from the leading scientists and clinicians in the field, and allows outcome measures and surrogate markers to be fully evaluated. The structure also incorporates mechanistic studies that further increase our understanding of the disease process and prepare the way for further clinical trials.<sup>5</sup>

## The overall approach

Although the ultimate goal of TrialNet is prevention of T1DM, potential therapies are generally initially tested in patients soon after diagnosis, when approximately 10% of beta cell function remains. At this stage, preservation of residual C-peptide secretion provides clinical benefit to participants as it is associated with reduction in long-term complications and severe hypoglycaemia, but the potential consequences of accelerating further beta cell destruction by immunomodulation are less severe than in someone who does not yet have diabetes. A further operational advantage of this approach is that people with new onset T1DM are highly visible, very motivated to help with research and therefore easier to recruit to these sometimes demanding studies.

The safety and efficacy data obtained in new onset patients are then used to inform decisions on follow-on trials in individuals who are at earlier stages of the disease process. Several studies have demonstrated that the efficacy of interventions given after diagnosis is greatest in patients with short disease duration, and it is likely that they will be even more effective in individuals with more beta cell mass. If an intervention has relatively high potential toxicity it may be appropriate that the next trial is in people at extremely high risk of imminent progression to diabetes, such as those who already have impaired glucose tolerance. For an agent with less potential toxicity, the participants in follow-on trials could be at lower risk, with multiple islet autoantibodies but normal glucose tolerance. Trials of, for example, dietary interventions may be appropriately undertaken in individuals at even lower risk, such as that conferred by genetic susceptibility alone.

## Studies in established diabetes

The range of completed and ongoing studies in TrialNet is shown in Table 1. In the two completed studies of interventions at the time of diagnosis, mycophenolate mofetil and daclizumab combined therapy showed no treatment effect, but in the anti-CD20 (rituximab) trial, the first year data showed better preservation of beta cell function at one year in the rituximab-treated group compared with the placebo arm. The two-year follow-up data are awaited. A trial of CTLA4-Ig (abatacept) has completed enrolment and is in the advanced stages of follow up, two studies are currently recruiting and further protocols have been approved. With experience and growing recognition among clinicians and patients, the time from approval of the concept to completing enrolment has progressively fallen in each successive TrialNet study. Because recruitment to new onset trials has proved relatively easy and securing regulatory approval in different countries is time-consuming and expensive, these TrialNet studies have been largely restricted to North American centres.

## Diabetes prevention

The primary goal of TrialNet is, however, disease prevention and this is an area in which the international centres can make a major contribution. One of the consortium's earliest achievements was to establish a large international network to screen relatives of people with T1DM for the markers that indicate increased risk of diabetes. This Natural History Study (NHS) provides the mechanism for identifying potential participants for prevention trials, and also allows us to refine risk assessment strategies and undertake studies into the underlying disease mechanisms.<sup>6</sup> By February 2010, more than 72 000 relatives had been recruited.

The Oral Insulin Prevention Trial is TrialNet's first study prior to disease onset. It builds on the observation in DPT-1 that, although oral insulin did not result in any overall delay of clinical onset of diabetes, a post hoc analysis suggested that a subgroup of participants may benefit from the treatment. Among relatives with high levels of insulin autoantibodies (IAA), daily oral insulin was associated with a 44% reduction in progression to diabetes during follow up (95% CI 11–64%), estimated as equivalent to a delay in diabetes onset of around 4.5 years.<sup>4</sup> This was the first example of a potential effect in delaying diabetes other than in small pilot studies, and TrialNet, in conjunction with an external advisory committee convened by the National Institutes of Health, felt this warranted further investigation – particularly since the previous large trial had already demonstrated that the oral insulin was safe, even in small children, and did not cause hypoglycaemia. When taken by mouth, insulin is broken down in the stomach, thus losing its metabolic effects. It, however, retains the immune effects that are thought to be the basis for modulating islet autoimmunity and beta cell destruction.

The TrialNet Oral Insulin Prevention Trial is a randomised, double-blind, placebo-controlled study and has been designed to focus on the group in whom the potential benefit was seen in DPT-1. Participants must have a first or second degree relative with T1DM, normal glucose tolerance and at least two islet autoantibodies including IAA. This combination confers around 35% risk of progression to diabetes within five years. The study has been approved in the UK and other international TrialNet centres, and is now actively recruiting.

A second prevention study using the antigen-specific approach is also under development. This trial will evaluate another islet autoantigen, glutamate decarboxylase (GAD), using GAD-alum vaccine in a similar, moderate risk population with evidence of autoimmunity to GAD.

Anti-CD3 monoclonal antibodies have been shown to preserve residual beta cell function in patients with newly diagnosed T1DM. The third TrialNet prevention study, currently under consideration, will determine whether anti-CD3 delays progression to diabetes in antibody positive relatives in whom the oral glucose tolerance test is already abnormal (impaired glucose tolerance, impaired fasting glucose or high glucose values at interim time points).

**Table 1.** TrialNet activities

### Ongoing studies

- Natural History Study
- Prevention of diabetes
  - Oral insulin
- Progression of type 1 diabetes after onset
  - Abatacept (CTLA4-Ig)
  - GAD-alum vaccination
  - Meticulous metabolic control

### Completed studies

- Methodological/pilot and feasibility
  - Comparison of the mixed meal tolerance and glucagon simulation tests
  - Validation of T-cell assays
  - Nutritional intervention in infants
- Progression of type 1 diabetes after onset
  - Mycophenolate mofetil and anti-IL2 receptor monoclonal antibody (daclizumab)
  - Anti-CD20 monoclonal antibody (rituximab)

## What is TrialNet UK?

In the UK, TrialNet activities are coordinated from the University of Bristol. There are currently affiliate sites in Belfast, Birmingham, Norwich and Newcastle but we are hoping to expand this as prevention studies get underway. Approval is also in place allowing us to obtain consent for screening by telephone/post with blood samples being taken by local clinicians. If eligible individuals opt to take part in intervention trials, they would however need to be prepared to travel to one of the affiliate sites for baseline and follow-up visits.

## How to find out more

Further information on TrialNet activities is available on [www.diabetestrialnet.org/](http://www.diabetestrialnet.org/) which also lists contact details for international centres. TrialNet activities in the UK are provided on [www.bristol.ac.uk/trialnet-uk/](http://www.bristol.ac.uk/trialnet-uk/).

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## Conflict of interest statement

There are no conflicts of interest.

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References are available online at [www.practicaldiabetesinternational.com](http://www.practicaldiabetesinternational.com).



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