Comment on: Atkinson. It's Time to Consider Changing the Rules: The Rationale for Rethinking Control Groups in Clinical Trials Aimed at Reversing Type 1 Diabetes. Diabetes 2011;60:361–363

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Although in his recent editorial Atkinson (1) made a persuasive argument to consider alternative trial designs for type 1 diabetes, we are in disagreement with the suggestion that placebo-controlled trials are no longer needed in studies evaluating therapies to alter the natural history of type 1 diabetes in recently diagnosed subjects.

Many of the frustrations about the pace of discovery felt by patients, families, and researchers confuse the actual facts about clinical trials. Although it is true that enrollment in clinical trials overall is difficult and hampers the national imperative to translate basic science to clinical care, clinical trials in new-onset type 1 diabetes have not had problems with enrollment. For example, a current placebo-controlled TrialNet study will be fully enrolled in less than four months.

It is important for individuals who enroll in clinical trials to understand that a clinical trial is an experiment—we do not know whether or not the therapy will be helpful, ineffective, or even harmful. The addition of a placebo arm is the best way to ensure that this central hypothesis of a clinical trial is rigorously tested. Non–placebo-controlled trials may lead to therapeutic misconceptions; we do patients and families no favors by implying clinical benefit even inadvertently.

Atkinson asserts that we have sufficient information about the natural history of insulin secretion after diagnosis to use this information as a standard historical "control" group. Unfortunately, this is not entirely true. There is significant variation in the rate of fall of C-peptide over time, and only a fraction of this variation is impacted by known variables. The studies cited by Atkinson contain approximately 100 placebo-treated patients, and those used for proposed power calculations contain fewer than 30 placebo-treated patients. Short of a miracle therapy in which all treated individuals had no fall in C-peptide over time, comparing the decline in C-peptide from uncontrolled trials with these published patients will not enable us to reliably choose how to move forward with further development of either single or combination therapy.

Most importantly, at this relative early stage of clinical trials in type 1 diabetes, we must not allow our emotions to get ahead of the science. Although recent results have been extremely encouraging, only limited information about true clinical benefit and harms can be obtained from the relatively small clinical trials reported to date (~60–200 patients). Performing such trials without a control group provides even less information for regulatory agencies and clinicians alike and may hinder the development of new "standards of care."

Novel approaches such as adaptive trial design could be particularly useful in the coming era of combination therapies for type 1 diabetes, but abandoning placebo-controlled studies moves us backward and not toward the future of successful modulation of the autoimmune process in type 1 diabetes.

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REFERENCES

1. Atkinson MA. It's time to consider changing the rules: the rationale for rethinking control groups in clinical trials aimed at reversing type 1 diabetes. Diabetes 2011;60:361–363

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