American Diabetes Association

SUMMARY of Request for Proposals for a Pragmatic Clinical Trial (a final, more detailed RFP will be provided to finalists)

2021

Overcoming Therapeutic Inertia in Type 2 Diabetes:
Using an Automated Opt-Out Referral to Drive Clinician Agnostic Diabetes Education or Medication Management

professional.diabetes.org/grants
I. Introduction

Despite more than 40 new diabetes treatment options being approved since 2005, and the ADA and other organizations developing clear guidelines and treatment algorithms, there has been no measurable improvement in glycemic control. In fact, between 1999 and 2014 the percentage of diabetes patients with an A1C > 9% actually increased. At the root of this problem is therapeutic inertia, “The failure and to initiate, intensify, or de-intensify therapy when therapeutic goals are not reached.”

To address this global problem, The ADA has developed a multi-year Overcoming Therapeutic Inertia (OTI) initiative to assist the greater community of diabetes stakeholders in developing practical, real-world solutions to this complex problem that is adversely affecting outcomes for people living with diabetes. Its overall goal is to promote the adoption of evidence-based practices, strategies, programs, and tools that address key determinants of therapeutic inertia in diabetes care, leading to more timely treatment modification and improved outcomes among adults with type 2 diabetes.

Through the OTI initiative, ADA is ushering in a paradigm shift in the care of type 2 diabetes, advancing the latest thought-leadership, resources, and tools in overcoming therapeutic inertia for primary care. We are working to help physicians, nurse practitioners, physician assistants, pharmacists, dietitians, and diabetes educators more effectively partner with their patients with diabetes to help them live longer, healthier lives.

Through this initiative, we are engaged in research, education, and collaborative barrier-busting activities aimed at understanding and addressing all the forces and factors that contribute to delay in implementing the most effective care for each person with diabetes. Below are the objectives of this campaign, each of which is to be addressed, to a greater or lesser degree, within the context of this pragmatic trail:

1. Improving understanding of therapeutic inertia and its impact on the health of people with diabetes (i.e., creating a sense of urgency with regard to achieving glycemic targets and other important clinical outcomes), particularly among primary care clinicians.
2. Helping clinicians recognize likely therapeutic inertia using existing systems and tools at their disposal.
3. Conducting research to identify and promote activities, skills, and methodologies that are associated with achieving clinical targets throughout the journey of a person living with diabetes.
4. Improving clinicians’ understanding of and adherence to ADA’s Standards of Medical Care in Diabetes, with a focus on appropriate and timely treatment intensification.
5. Developing and disseminating user-friendly decision-support tools for use by clinicians and people with diabetes.
6. Promoting the adoption and expansion of person-centered diabetes care and the development of individualized diabetes management plans; and
7. Identifying crucial systems-level barriers contributing to therapeutic inertia and facilitating long-term strategies to promote change through consensus-building and engagement with key stakeholders.

Learn more about the ADA’s Overcoming Therapeutic Inertia initiative: https://therapeuticinertia.diabetes.org

Sponsors:
This research grant is sponsored by ADA’s Overcoming Therapeutic Inertia initiative with Strategic Sponsors AstraZeneca and Sanofi, plus Supporting Sponsors Merck and Novo Nordisk.
II. Overview

The ADA’s Overcoming Therapeutic Inertia (OTI) initiative is seeking proposals to conduct a pragmatic clinical trial leveraging findings and insights from an overcoming therapeutic inertia systematic review and meta-analysis. Ideally this will be a randomized, cluster trial that will leverage an EHR-based automated opt-out referral, driving patients to diabetes education, medication management support or coaching support services within the institution’s system. The ADA has developed a detailed pragmatic trial approach; however we understand that each researcher, institution, or organization brings its own strengths, experience, capacity, and perspectives. While the ADA does expect any final proposal to consider the recommended trial design when developing the proposal, we are also open to modifications and suggestions that could help refine and improve this pragmatic trial’s impact on addressing therapeutic inertia in diverse primary care settings or make it more cost effective and doable. As you consider submitting a proposal, keep in mind that we are seeking approaches that can help address delays in timely therapy intensification impacted by social determinants of health, COVID 19 and health equity challenges.

Key steps for you:

- **Step 1:** Complete the [Eligibility Quiz](#) (3 minutes) – If you pass this, then you will be asked to complete step 2 below.
- **Step 2:** Complete the Interest Survey (estimated 60 minutes). This will require in-depth knowledge of your institution’s diabetes patient population, including demographics. You will have access to this survey once you complete the Eligibility Quiz.
- **Step 3:** An independent peer panel will review the Interest Survey submissions and choose 5 for full proposal submission.
- **Step 4:** Submit a full proposal based on the details provided in this RFP. ADA is providing parameters for the pragmatic trial but welcomes creative and innovative approaches to test this approach.

The selected research organization will be expected to:

- Develop a final clinical trial plan, protocol, and analysis plan.
- Engage at least 600 people with diabetes who have an A1C of $\geq 8\%$. *We have engaged a statistician to who has determined that one optimal option is for each of 3 arms to have 10 clusters with at least 20 patients per cluster with diabetes with an A1C of $\geq 8\%$. This equates to 30 total clusters. Of course, total number of clusters will decrease as the number of patients in each cluster increases.* See Background below for more detail. ADA will be able to provide guidance to the awardee in this area.
- ID therapeutic inertia within the EHR leveraging a predetermined algorithm. ADA can assist with determining this algorithm. See one suggested operational definition below.
- Automate a referral in the EHR to non-physician clinicians for diabetes education, medication management or coaching support. This referral should trigger during all primary care visits.
- Track what each patient does.
- Track what the providers do.
- Track the outcomes (i.e. change in A1C; time to control, etc.)
- Include a diverse population to assess impact on underserved communities. This might include race, ethnicity, disability, rural/frontier, socio-economic, language, insurance status, LGBTQ+.
- Provide statistical analysis.
- Attempt to assess cost effectiveness of the intervention.
- Provide a final report of outcomes, findings, and insights.
- Share data with the American Diabetes Association in the future (negotiable).
- Draft a professional journal article (in collaborating with the ADA’s Overcoming Therapeutic Inertia leadership volunteers)
The American Diabetes Association will provide:

- A proposed pragmatic trial approach to be tested, based on results of a current systematic review and meta-analysis. This can absolutely be modified based on each individual organization’s strengths, capabilities, and experience.
- Technical assistance and support with pragmatic trial and protocol design, data evaluation design and journal article development.
- Free access to an accredited (3-4 hour) Overcoming Therapeutic Inertia program for all relevant clinical staff.
- An award of at least $400,000 to complete the trial within a 24-month period. This award may be supplemented with additional solicited funds.

III. Overcoming Therapeutic Inertia Pragmatic Trial Background

Early glycemic control leads to better outcomes, including a reduction in long-term macrovascular and microvascular complications. Therapeutic inertia, a delay in the initiation, intensification, or de-intensification of therapy when appropriate to do so, has been shown to be present throughout the diabetes treatment journey, from the first oral antihyperglycemic drug (OAD) to initiation of insulin. Therapeutic inertia is responsible for substantial, preventable complications in type 2 diabetes with associated excess in direct and indirect health care costs.

The ADA recently completed a first-ever systematic review and meta-analysis looking at interventions aimed at addressing therapeutic inertia in clinical practice. This study found that approaches leveraging non-physician clinicians to provide diabetes education or medication management support were most effective at reducing A1C in patient populations. In addition, complex interventions that utilized, as part of their approach, technology to improve the quantity and quality of patient engagement were also associated with more effective approaches.

STUDY AIM: The overall aim of this pragmatic trial will be to rapidly improve glycemic levels in non-pregnant adults with type 2 diabetes who are experiencing therapeutic inertia by optimizing the disease management through targeted pragmatic interventions aimed at facilitating the use of evidence-based treatments – such as initiation of appropriate therapy or escalating treatment modality. The study will address patient-level barriers to therapeutic inertia, including social determinants of health, emotional challenges, and delays in therapy intensification that have occurred as a direct or indirect result of the COVID-19 pandemic.

We would ideally like least 600 patients with diabetes and an A1C of ≥8% included within the entire of the study.

PRIMARY OUTCOME: The primary outcomes will be the proportion of patients with an A1C < 8% at 6, 12 and 18 months of “enrollment” in the trial.

Secondary Outcomes Include: (as much as is feasible)

- Time to control defined as an A1C of < 8%
- Time to intensification. We are interested in seeing if the referral to diabetes education (and actually going to the appt) had any impact on whether an intensification of therapy occurred.
- Absolute mean reduction in A1C from baseline to 6, 12 and 18 months.
- Pre-post comparison of proportion (%) of patients with an HbA1c of > 9% in 6 months before and 6, 12 and 18 months after the study.
- Pre-post comparison of proportion (%) of patients with an HbA1c of < 7.0% in the 6 months before and 6, 12 and 18 months after the study.
- Pre-post comparison of (%/#) of patients with emergency room visit or hospitalization during the last 6 months before and after of the study.
Pre-post comparison of number of reported severe hypoglycemia events (ED visits or hospitalizations with a primary diagnosis of hypoglycemia) during the last 6 corresponding 12 months of the previous year

**PROPOSED METHODOLOGY:** The proposed trial will be a 6-month, cluster randomized, prospective, open-treatment, active-controlled, three-arm, parallel-group, pragmatic trial conducted in multiple practices servicing a diverse population. The trial will employ a practice-level cluster randomization. Practices will be selected from an integrated health system comprising a primary care network and will be randomized 1:1 between intervention and control arms stratified by the size of the eligible patient register at recruited sites, as well as race and ethnic distribution. Data for analysis will be collected at baseline, 6 months, 12 months, and 18 months.

Potential arms of cluster randomization (if we go with 4):

<table>
<thead>
<tr>
<th>Arm A*: No intervention (control) – 200 to 250</th>
<th>Arm B*: OTI Education for Clinicians (3 hours) – 200 to 250</th>
</tr>
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<tbody>
<tr>
<td>N/A</td>
<td>Arm C*: Opt-out automated referral + OTI Education for Clinicians – 200 to 250</td>
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*NOTE: Assumes each arm has 10 clusters with at least 20 patients per cluster with diabetes with an A1C of ≥8% in each cluster. This equates to 30 total clusters. ADA has engaged a statistician to assist with defining the optimal number of clusters per arm and patients per cluster to achieve high quality result when comparing Arm A with either Arm B or Arm C.

**PROPOSED INCLUSION/EXCLUSION CRITERIA:** Adults age 18-75 y/o with a diagnosis of type 2 diabetes who have evidence of sustained suboptimal glycemic control as evidenced by an A1C ≥8.0% over a of the previous 6 months, with no therapy intensification [or other intervention, such as referral for DSMES] having occurred. Intensification of therapy is defined as medication and/or prescribing of new therapy. Exclusion criteria will include pregnancy (or possible pregnancy), shortened life expectancy, on insulin therapy, or severe psychiatric illness.

**PROPOSED INTERVENTIONS:** Patients will continue to visit their usual health care practitioner to receive network/provider specific standard-of-care for the management of their type 2 diabetes throughout the duration of the study. Additionally,

- **PRIMARY:** An automated opt-out referral within a practice’s electronic health record, to facilitate the identification and real-time referral of patients who qualify for this study (A1C >8% and evidence of therapeutic inertia). The referral will be automated and directed to an appropriate health care professional (diabetes educator, nurse, pharmacist, dietitian, health coach, etc.) within the health system or practice team, leveraging each institution’s existing strengths and capacities. These health care professionals will (1) facilitate implementation of standard-of-care medication management support, including the prescription of antidiabetic therapy, supported by appropriate guidelines, protocols, standing orders and collaborative agreements, OR (2) provide diabetes self-management education.

- **SECONDARY:** A three-hour training for primary care clinicians which will encompass information on therapeutic inertia and its impact on diabetes care, approaches for addressing therapeutic inertia in practice, and guidance on appropriate use of antidiabetic therapy to reduce A1C. This will be an accredited online course that primary care clinicians can access from ADA at no charge. Health care
professionals will also receive a toolkit to use with patients, including a patient self-assessment, to help identify potential barriers to care plan adherence, along with a conversation guide with talking point to help health care providers address known and newly identified barriers.

**EXPECTED DATA COLLECTION:** Data for primary and secondary outcomes will be collected at baseline (up to 6 months prior to study), during the 6-month study intervention period and at 6 months, 12 months, and 18 months.

**EVALUATION PLAN AND PUBLICATION PLAN:** The organization submitting a proposal will be expected to propose an evaluation strategy, including a plan and resources for statistical analysis, and publication plan at time of submission.

**IMPORTANT DEFINITIONS:**

**Therapeutic inertia:** Therapeutic inertia is a lack of timely adjustment to therapy when a patient’s treatment goals are not met. In diabetes care, it means being slow to add or change the care plan if a patient’s A1C is too high. Research has shown that managing glucose levels early on leads to better long-term outcomes and reduces a person’s chances of having a heart attack or stroke or of developing other complications such as eye disease, kidney disease, and nerve damage. People who reach their A1C targets soon after finding out they have diabetes are more likely to keep their glucose in their target ranges in the future. The ADA has agreed to use the following definition within its Overcoming Therapeutic Inertia Initiative: The failure to initiate, intensify or de-intensify therapy when appropriate to do so. Learn more about therapeutic inertia and why it is so urgent to address it now.

Operationally, we you might consider using this definition as a starting point:

- Includes non-pregnant adults with Type 2 diabetes age ≥ 18 years and an A1C ≥ 8% within the previous 6 months. If possible, it would also include no change in therapy in the previous 6 months.
- Must be logged into Endo / Primary Care Departments (Internal Medicine or Family Medicine.)
- Excludes patients with Type-1 Diabetes [ICD-10 code (E10.XX) in active problem list or in an encounter diagnosis within the past 12 months.

**Pragmatic Trial:** Pragmatic trials are designed to evaluate the effectiveness of interventions in real-life routine practice conditions, whereas explanatory trials aim to test whether an intervention works under optimal situations. Pragmatic trials produce results that can be generalized and applied in routine practice settings. Pragmatic trials were first proposed by Schwartz and Leblouh in 1967 as trials performed under normal conditions with the intention of providing results that are more applicable to clinical practice and decision making. The alternative, taking a more explanatory approach, leads to tightly controlled trials under ideal conditions that aim to provide understanding of how treatments work. Explanatory trials have an important role, but healthcare interventions are seldom given under circumstances similar to those used in such trials.

- An explanatory approach aims to answer the question 'Can this intervention work under ideal conditions?'
- A pragmatic approach and answer the question 'Does this intervention work under usual conditions?'

References on pragmatic trials:

- Pragmatic Clinical Trials: Testing Treatments in the real world (NIH National Inst. on Aging, 2017)
- The PRECIS-2 tool: Designing trials that are fit for purpose. (BMJ 2015;350:h2147)

Please direct any questions to grantquestions@diabetes.org.