TIME COALITION IN RANGE

August 24, 2023

Re: Time in Range Coalition Comments to Docket No. FDA-2023-D-0625
"Diabetes Mellitus: Efficacy Endpoints for Clinical Trials Investigating Antidiabetic Drugs and Biological Products; Guidance for Industry"

Dear Dockets Management Staff,

On behalf of the Time in Range Coalition (TIRC), thank you for the opportunity to comment on the Food and Drug Administration's (FDA or Agency) draft guidance, "Diabetes Mellitus: Efficacy Endpoints for Clinical Trials Investigating Antidiabetic Drugs and Biological Products; Guidance for Industry" (Draft Guidance). We appreciate the Agency's recognition of the need to facilitate the use of Time in Range (TIR) and other metrics derived from continuous glucose monitors (CGMs) in the development of new therapies for individuals living with diabetes. CGMs are an essential tool in achieving the appropriate TIR as part of daily diabetes management. The incorporation of CGM-based TIR metrics, including time above range (TAR) and time below range (TBR), into drug development and regulatory decision-making is critical to maximizing the benefits of TIR in improving health outcomes and reducing health disparities and as such, is a priority for members of TIRC.

About the Time in Range Coalition

TIRC is a global effort convened by The diaTribe Foundation and comprised of 26 nonprofit associations, patient advocacy organizations, professional societies, and industry members committed to driving awareness and adoption of TIR, measured through the use of a CGM, as an actionable metric for daily diabetes management and a means to improve long-term health outcomes. TIRC works to achieve this by educating individuals with diabetes, health care professionals, and regulators about the science of TIR and by working to establish TIR as an essential part of diabetes management and to make TIR accessible to all people with diabetes.

The Critical Role of CGMs in Diabetes Management

Thirty-seven million Americans are impacted by diabetes, a chronic condition that requires proactive daily management of glucose levels. High blood glucose levels can lead to serious and life-threatening acute complications, such as ketoacidosis or death, and over time, to severe long-term complications including heart and kidney disease, strokes, amputations, and blindness. On the opposite end of the spectrum is hypoglycemia, or low blood glucose levels, which in severe cases can lead to severe adverse reactions including disorientation, seizures, difficulty speaking, loss of consciousness, coma or death. As such, ensuring that people with diabetes have access to the real-time information they need to manage this disease can help prevent and reduce the frequency of such negative health outcomes and facilitate better disease management.

TIR empowers clinical decisions through actionable information to improve people's daily diabetes management. People with type 1 or type 2 diabetes can use the data generated by a CGM, including alarms to avoid dangerous blood glucose levels, to help make real-time adjustments to anti-diabetic

treatments, doses, food intake, exercise and more to stay within a healthy range. In addition, the CGM data collected through daily CGM wear plays a key role in assisting clinicians in choosing the most appropriate treatment option for each individual patient. TIR and other CGM-based metrics improve diabetes care by enabling better transparency to daily glucose control. A CGM is an important tool for patient and physician engagement.

Importantly, CGM use has been shown to improve diabetes outcomes in numerous studies (noted below) including the "Validation of Time in Range as an Outcome Measure for Diabetes Clinical Trials" study led by Drs. Roy Beck and Rich Bergenstal, which demonstrated that as an individual's TIR increases, the risk of microvascular complications decreases. We have been pleased to see that among key stakeholders, including federal partners, there is growing recognition of the value of CGMs. To that end, for example, earlier this year, the Centers for Medicare and Medicaid Services (CMS), expanded Medicare coverage of CGMs to additional Medicare beneficiaries living with diabetes. As TIRC noted in our comment letter to CMS, this policy change is a critical step toward improving access to care, advancing equity, reducing disparities, and decreasing health care costs. We look forward to continued efforts to expand CGM coverage by private and other insurers, as well as to address important issues of CGM accessibility for individuals with vision loss.

TIRC's Efforts to Advance the Use of CGM-based Metrics in Clinical Trials

TIRC has recognized that as diabetes technology continues to advance, the collection, analysis, and reporting of CGM data in clinical trials needs to be standardized so clinicians, scientists, and regulators across the globe can incorporate it into their decision-making to the benefit of individuals living with diabetes. To that end, in 2022, TIRC, along with The diaTribe Foundation and Advanced Technologies & Treatments for Diabetes (ATTD), convened a group of international experts to discuss the role of TIR and CGMs in clinical trials for diabetes treatments. The result of this convening was a historic consensus, the Continuous glucose monitoring and metrics for clinical trials: an international consensus statement (Consensus Statement) that was published in The Lancet Diabetes & Endocrinology in the January 2023; 11: 42–57 edition, published online on December 6, 2022.

The Consensus Statement includes 22 recommendations for optimizing CGM-based glucose data in clinical studies, including the parameters and specific glucose metrics researchers should evaluate and report, collection of baseline data and timing, information on clinically relevant changes in key glucose metrics over time, and training for both trial staff and participants. We appreciate the essential contributions and expertise of FDA staff in the development and review of the Consensus Statement.

In addition to The diaTribe Foundation and members of TIRC, the Consensus Statement was endorsed by ATTD, the American Diabetes Association (ADA), JDRF, the American Association of Clinical Endocrinologists, Association of Diabetes Care and Education Specialists, DiabetesIndia, European Association for the Study of Diabetes, International Society for Pediatric and Adolescent Diabetes, and Japanese Diabetes Society. This Consensus Statement serves as a valuable resource for regulatory agencies, industry, and researchers and we encourage the Agency to include its recommendations, where relevant and appropriate, in the final guidance.

Overview of TIRC Comments on the Draft Guidance

Reflecting the importance of TIR to quality of life and health outcomes for individuals living with diabetes, a central goal of TIRC has been for CGM-based TIR data to be used in regulatory decision-making, specifically for TIR to serve as a surrogate endpoint to support diabetes drug approvals, as a complement to hemoglobin A1c (A1C), and for TIR and other CGM-based data to be incorporated into the product prescribing information to support clinicians' treatment decisions. As diabetes management is increasingly reliant on continuous glucose monitoring, greater regulatory clarity on the use of CGM-based metrics in clinical trials will make a profound impact on the ability to advance innovation in diabetes treatments. We welcome the Draft Guidance as an important step forward in providing additional clarity and predictability. In particular, we applaud the Agency's willingness to consider including CGM-based metrics (e.g., TIR, TBR, TAR) in Section 14 of the drug label. We also appreciate the recognition in the Draft Guidance of the advantages of CGM systems over self-monitoring of blood glucose (SMBG) test systems in clinical trials assessing hypoglycemia as an efficacy endpoint and welcome FDA's acceptance of Level 2 hypoglycemia as a valid surrogate endpoint for efficacy claims, in addition to existing recognition of Level 3 hypoglycemia. We also support the acknowledgement in the Draft Guidance of the ADA's Level 1, Level 2, and Level 3 hypoglycemia definitions.

Consistent with our view that TIR is clinically meaningful and should be recognized by FDA as a surrogate endpoint sufficient to support drug approval, we urge the Agency – in the final guidance or another forum – to clarify the evidence it believes is necessary to validate TIR as a surrogate endpoint. Moreover, while we appreciate the need for sufficient flexibility to accommodate the evolving use of continuous glucose monitoring, among other implementation issues, we recommend additional specificity in several key areas to provide the necessary clarity and predictability to encourage incorporation of CGM-based metrics into drug development programs.

Please see below for our specific recommendations for strengthening and clarifying the Draft Guidance as it is finalized.

- **TIR as an endpoint**
    - As written, the Draft Guidance appears to indicate a lack of consideration of the possibility of TIR serving as a surrogate endpoint at a future date.

      Recommendation: ***Add "currently" to line 343, i.e., "…TIR is not currently acceptable as the primary endpoint for a glycemic-control indication."***

    - Additionally, the Draft Guidance does not provide clarity on the level of evidence FDA would view as necessary for acceptance of TIR as a surrogate endpoint. As noted in the Draft Guidance, the Diabetes Control and Complications Trial (DCCT) provided evidence to support a causal relationship between a change in A1C in patients with type 1 diabetes and a reduced risk of microvascular complications, leading to FDA's recognition of a reduction in A1C as a

validated surrogate endpoint for diabetes drug approvals. However, a study modeled after the DCCT and requiring similar financial and temporal resources to validate TIR as an endpoint is simply not feasible and would only further widen the current gap between the clinical standard of care and regulatory decision-making with regard to TIR.

In our view, the following studies provide compelling evidence of the impact of TIR on health outcomes and TIRC urges their review and consideration to support TIR as surrogate endpoint for drug approval:

- Beck RW, Bergenstal RM, Cheng P, Kollman C, Carlson AL, Johnson ML, et al. The relationships between time in range, hyperglycemia metrics, and HbA1c. Journal of diabetes science and technology. 2019;13(4):614–26.

- Hirsch et al. Connecting the Dots: Validation of Time in Range Metrics With Microvascular Outcomes. Diabetes Care. 2019;42(3):345-348.

- Pinsker JE, Müller L, Constantin A, Leas S, Manning M, McElwee Malloy M, Singh H, Habif S. Real-world patient-reported outcomes and glycemic results with initiation of control-IQ technology. Diabetes technology & therapeutics. 2021; 23(2): 120-7.

- Polonsky WH, Fortmann AL. The influence of time in range on daily mood in adults with type 1 diabetes, Journal of Diabetes and Its Complications. 2020;34(12):107746.

- Rodbard D. Continuous glucose monitoring metrics (Mean glucose, time above range and time in range) are superior to HbA1c for assessment of therapeutic efficacy. Diabetes, Obesity, and Metabolism. 31 October 2022. 25(2): 596-601.

- Shah VN, Sakamoto C, Pyle L, Akturk HK, Polsky S, Forlenza GP, Snell-Bergeon JK. Time in Range Is Associated with Incident Diabetic Retinopathy in Adults with Type 1 Diabetes—A Seven-Year Longitudinal Study. Oral presentation at the 83rd Scientific Sessions of the American Diabetes Association. June 23 – 26, 2023.

- Vigersky RA, McMahon C. The Relationship of Hemoglobin A1C to Time-in-Range in Patients with Diabetes. Diabetes Technology Therapy. 2019 Feb; 21(2): 81-85.

- Yapanis et al. Complications of Diabetes and Metrics of Glycemic Management Derived From Continuous Glucose Monitoring. The Journal of Clinical Endocrinology & Metabolism. 2022 May; 107(6): e2221-e2236.

***Recommendation*: In the final guidance or another forum, FDA should detail the evidence the Agency believes is necessary to validate TIR as a surrogate endpoint.**

- **CGM Metrics**

- TIRC appreciates that the "high level" nature of the Draft Guidance with respect to CGM-based metrics allows sponsors to work with FDA on acceptable implementation of continuous glucose monitoring into clinical trials and labeling expectations as the use of CGMs continues to evolve. However, the Draft Guidance may not provide sufficient information regarding what is minimally acceptable for sponsors to effectively design clinical development plans on which to engage with the Agency.

  Recommendation: ***Reference and/or use the Consensus Statement, where applicable. For example, for the appropriate length of monitoring to characterize glycemic control, TIRC urges adoption of the recommendations of the Consensus Statement in the Draft Guidance, including 14 consecutive days of CGM data with at least 70% of data collected every three months throughout the study, including at baseline. Complete CGM data should be included in trials' final analysis.***

  Recommendation: ***Provide greater clarity on what constitutes "adequate" performance characteristics of CGM devices for the purpose of supporting the inclusion of CGM metrics in CLINICAL STUDIES labeling. Parameters for "acceptable" CGM performance characteristics should not exceed those currently used for approval by FDA for non-adjunctive insulin dosing.***

- The Draft Guidance provides the following examples of TIR: 70-180, TAR >180, and TBR <70.

  Recommendation: ***Clarify whether the Agency intends to consider including these three ranges in the CLINICAL STUDIES section of the label; we urge FDA to consider including all five TIR levels (see below) per the recommendations in Panel 2 of the Consensus Statement, if appropriate based on study design. Additionally, consider if and how the Ambulatory Glucose Profile (AGP) may be beneficial for inclusion in the label.***

Time in range	*70–180 mg/dL*
Time below range	*<70 mg/dL including readings of <54 mg/dL*
Time below range	*<54 mg/dL*
Time above range	*>180 mg/dL, including readings of >250 mg/dL*
Time above range	*>250 mg/dL*

  Recommendation: ***Include TBR in the CLINICAL STUDIES section rather than only in the Safety section. Again, TIRC urges FDA to consider the clinical value of providing the complete information of all five TIR levels together, per the recommendations in Panel 2 of the Consensus Statement, under Section 14.***

- **Hypoglycemia Reduction Claims**

    - TIRC appreciates the recognition in the Draft Guidance that people with diabetes using insulin are at greater risk of hypoglycemia (Line 94). We are also pleased to see the Agency acknowledge the advantages of CGMs over SMBG in clinical trials assessing hypoglycemia as an endpoint.

    - Additional benefits of CGMs over SMBG in clinical trials include a minimum of 24 times the number of glucose measurements per day to better understand glycemic control, nocturnal glucose levels (highlighting hypoglycemia and hyperglycemia episodes), and significantly more postprandial hyperglycemia data.

    - TIRC appreciates the Agency's recognition of Level 2 hypoglycemia as a validated surrogate endpoint acceptable for traditional approval.

Conclusion

TIRC is grateful for FDA's efforts to update its guidance to industry and other stakeholders to reflect the central role of continuous glucose monitoring in clinical care and to facilitate the use of CGM-based metrics in diabetes drug development. FDA's issuance of this Draft Guidance continues the Agency's ongoing commitment to improving the lives of individuals living with diabetes. We appreciate the opportunity to provide our views on ways in which the Draft Guidance can be strengthened as it is finalized and hope the final guidance will provide new pathways for the development of new therapies to improve health outcomes for individuals living with diabetes. For any questions regarding these comments, please julie.heverly@diaTribe.org.

Sincerely,

Jim Carroll
Chief Executive Officer
The diaTribe Foundation

Julie Heverly
Senior Director, Time in Range Coalition
The diaTribe Foundation