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Joseph Ross, M.D., MHS
Chair
Medicare Evidence Development & Coverage Advisory Committee (MEDCAC)
c/o Tara Hall, MEDCAC Coordinator
Centers for Medicare and Medicaid Services
7500 Security Boulevard
Baltimore, Maryland 21244

Submitted via MedCACpresentations@cms.hhs.gov

RE: **Virtual Meeting of the Medicare Evidence Development and Coverage Advisory Committee – May 21, 2024 [CMS-3458-N]**

Dear Dr. Ross:

On behalf of The diaTribe Foundation and the Time in Range Coalition (TIRC), thank you for the opportunity to provide written comments in advance of the virtual Medicare Evidence Development & Coverage Advisory Committee (MEDCAC) meeting on May 21. We appreciate MEDCAC's consideration of "which health outcomes in studies of devices for self-management of Type 1 and insulin-dependent Type 2 diabetes should be of interest to CMS." There is a strong body of evidence supporting the use of time in range (TIR) as an actionable metric for daily diabetes management that, if fully incorporated into clinical trials and regulatory decision-making, should address MEDCAC's concerns about "more frequent evidence gaps with respect to clinically meaningful health outcomes" in newer medical technologies.

About the Time in Range Coalition

TIRC is a global effort led by The diaTribe Foundation and comprised of 27 nonprofit associations, patient advocacy organizations, professional societies, and industry members committed to driving awareness and adoption of TIR (including times above and below target range) measured through the use of continuous glucose monitoring (CGM) as an actionable metric for daily diabetes management and a means to improve long-term health outcomes.[1] 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 a fundamental part of daily diabetes management, including to make TIR accessible to all people with diabetes.

Reflecting its importance to the quality of life and health outcomes for individuals living with diabetes, a central goal of TIRC has been for CGM-derived TIR data to be used in regulatory decision-making, specifically for TIR to serve as an endpoint to support diabetes drug approvals, as a complement to HbA1c (A1C), and for TIR data to be incorporated into the product prescribing information to support the clinician's treatment decision. TIR provides healthcare professionals and people with diabetes the opportunity for immediate intervention to improve their management by providing real-time, detailed information on day-to-day glycemic patterns not delineated by A1C alone. As diabetes management is

[1] For the purposes of this comment letter, CGM means "continuous glucose monitoring" - the activity and CGMs means "continuous glucose monitors" - the device.

increasingly reliant on digital health technologies (DHTs), such as CGMs[2], greater regulatory clarity on the utilization of DHTs in clinical trials will make a profound impact on the ability to advance TIR and innovation in diabetes treatments.

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 chronic small blood vessel (microvascular) complications like eye (retinopathy), kidney (nephropathy including microalbuminuria) and nerve (neuropathy) disease and large blood vessel (macrovascular) complications like cardiovascular disease. On the opposite end of the spectrum is hypoglycemia, or low blood glucose levels, which in severe cases can lead to serious 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.

The Endocrine Society explains TIR as "the amount of time those with diabetes spend with their blood glucose levels in a recommended target range." CGMs provide real-time data on blood glucose levels and are a vital tool for individuals seeking to achieve TIR goals. 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 and alarms powered by CGMs to avoid dangerous blood glucose levels and 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 the daily use of CGMs 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 visibility of daily glucose control. CGMs are an invaluable tool for people with diabetes and their physicians.

Importantly, use of CGMs has been shown to improve diabetes outcomes (Maiorino et al. 2020; Lee et al., 2022). Further, CGM-based TIR metrics have been shown to be associated with clinically meaningful outcomes in numerous studies 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. These associations are discussed in more detail below. We have been pleased to see that among key stakeholders, including federal partners, there is growing recognition of the value of CGM. Medicare Administrative Contractors (MACs) recognized the essential role that CGM plays in helping people living with diabetes manage their blood glucose levels by expanding coverage of CGMs to include more beneficiaries with diabetes. This policy change, as TIRC noted in our comment letter to CMS MACs in 2022, takes a critical step toward improving access to care, advancing equity, reducing disparities, and decreasing health care costs. Additionally, FDA recently acknowledged the value of CGM and CGM-based metrics in the development and regulatory assessment of new therapies. In its May 2023 draft guidance, FDA notes that it "recognizes that CGM systems have certain advantages over self-monitoring blood glucose (SMBG) test systems" and indicates willingness to consider TIR as a secondary endpoint. We will continue to see the health and fiscal benefits of the expanded Medicare coverage policy in the months and years to come.

Overview of the Evidence of Clinically Meaningfulness of TIR

A substantial and growing body of evidence continues to demonstrate that TIR and the related time below

[2] Ibid.

range (TBR) and time above range (TAR) have added value in clinical, research, and regulatory settings far beyond A1C.

CGM is shown to be superior to SMBG in helping people with diabetes monitor and improve their glycemic control, specifically in improving their TIR, reducing glucose variability, and lowering their risk of hypoglycemia (Bolinder et al. 2016; Petrie et al. 2017; Beck et al. 2017; Lind et al. 2017; Dunn et al. 2018; Hood et al. 2020; Thabit et al. 2020; Maiorino et al. 2020; Lee et al., 2022). Unlike SMBG, which generally requires people with diabetes to collect at least seven fingersticks per day to effectively calculate their TIR, CGM automatically measures glucose levels every one to five minutes. Additionally, people with diabetes using SMBG do not test as regularly as they should (Hansen et al. 2009). This increased data availability, superior patient experience, and support of improved outcomes make CGM the best available tool for glucose monitoring.

In addition, there is mounting evidence that increasing TIR lowers risk of microvascular and macrovascular complications. In a cross-sectional study of people with type 2 diabetes, increased TIR was significantly associated with lower prevalence and decreased severity of diabetic retinopathy (DR) even after adjusting for clinical risk factors, including A1C (Lu et al. 2018). Subsequent studies have reaffirmed the association between increased TIR and decreased risk of DR in type 2 diabetes (Raj et al., 2022; Sheng et al., 2023; Yoo et al., 2020; Lu, Home, & Zhou 2020). Analysis of the Diabetes Control and Complications Trial longitudinal data similarly showed TIR was strongly associated with the risk of DR and development of microalbuminuria in type 1 diabetes—in fact, for each 10-percentage point reduction in TIR, the risk of DR progression increased 64 percent and risk of an adverse microalbuminuria outcome increased 40 percent (Beck et al. 2019). Similarly, a new study found that every 5 percent decrease in TIR increased odds of incident DR by 18% (Shah et al., 2024).

Strong associations have also been identified between TIR and diabetic peripheral neuropathy (DPN) (Li et al. 2020; Mayeda et al. 2020; Yoo et al. 2020). In people with type 2 diabetes and moderate-to-severe chronic kidney disease, lower TIR and higher glucose management indicator (GMI) were associated with symptoms of DPN. In contrast, the study found no significant association between A1C and DPN symptoms (Mayeda et al. 2020). In a cross-sectional study of individuals with type 2 diabetes, there was an association between greater TIR and reduced cardiovascular autonomic neuropathy (CAN), independent of A1C and glucose variability (Guo et al. 2020). The study found no difference in A1C among different stages of CAN.

Further, increased TIR has been cross-sectionally associated with a lower risk of abnormal carotid intima-media thickness, a marker for cardiovascular disease (Lu, Home, & Zhou 2020; Lu et al. 2020). A longitudinal study showed that an increase in TIR was significantly associated with a decrease in albuminuria among individuals with type 1 and a history of albuminuria, over a year-long period (Ranjan et al. 2020). A strong correlation has also been found between lower TIR and increased risk of all-cause and cardiovascular disease-related mortality (Lu et al. 2020).

The use of CGM and TIR furthermore correlates to improved psychosocial outcomes. Individuals with type 1 using CGM report positive psychosocial outcomes including lower levels of stress and improved sleep (Burckhardt et al. 2018; Nana et al. 2019; Volčanšek Š et al. 2019; Pinsker et al. 2021). This is especially true for children with type 1 and their parents, in particular, who report reduced fear of hypoglycemia using remote monitoring (Burckhardt et al. 2018). In a survey of 3,461 people with diabetes conducted by dQ&A, a diabetes market research company, most people with type 1 ranked TIR, of all the outcomes used to assess diabetes therapies, as having the biggest impact on daily life (Runge et al. 2018). Spending more TIR and less time in severe hyperglycemia has also been shown to improve mood (Polonsky & Fortmann, 2020). These findings reveal the importance of using TIR when exploring

the psychosocial and behavioral impact of diabetes and assessing the safety and efficacy of therapies and devices used in diabetes management.

Finally, CGM and TIR have a role to play in advancing equity and reducing health disparities. Minority communities bear a disproportionate burden of diabetes. Black (17.4%), Asian (16.7%), and Hispanic (15.5%) adults have higher prevalence rates than whites (13.6%) and Indigenous Peoples are twice as likely as whites to have diabetes. Diabetes is also disproportionately found among Americans with lower education levels. More than 13% of adults with less than a high school education have diagnosed diabetes compared to 9.2% of those with a high school education and 7.1% of those with more than a high school education. Increased use of TIR and CGM would have a disproportionate, positive effect on minority communities and those with lower education levels. Perhaps most importantly, TIR does not vary across race and ethnicities, while A1C levels can be falsely elevated in Black people with diabetes (Karter et al., 2023; Bergenstal et al., 2017; Wolffenbuttel et al., 2013). Using a metric without these discrepancies is important to avoiding premature diagnoses, harmful overtreatment, and exacerbation of disparities.

A robust "State of the Evidence" collection compiled by TIRC and diaTribe contains further information on the studies mentioned above and more, and can be found attached to these comments.

International Consensus Regarding CGM Data

TIRC and diaTribe recognize 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, diaTribe, 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 edition, published online on December 6, 2022 (attached).

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. The Consensus Statement was endorsed by the American Diabetes Association (ADA), JDRF, the American Association of Clinical Endocrinologists (AACE), the Association of Diabetes Care and Education Specialists (ADCES), DiabetesIndia, the European Association for the Study of Diabetes (EASD), the International Society for Pediatric and Adolescent Diabetes (ISPAD), and the Japanese Diabetes Society. This Consensus Statement serves as a valuable resource for regulatory agencies, industry, and researchers, including MEDCAC, and will guide future studies. We are pleased that this consensus statement is referenced in Appendix C of the Clinical Endpoints Review (CER) of the literature produced for CMS on December 11, 2023, which was shared as background material for the May MEDCAC meeting.

TIR is the Ideal Health Outcome for Research Studies of Devices for Diabetes Self-Management

The evidence is substantial, growing, and clear on TIR and CGMs; future DHTs likely also will help individuals living with diabetes manage their disease and help maximize their time in their targeted blood glucose range. TIRC believes that TIR is a health outcome that should be used in "studies of devices for self-management of Type 1 and insulin-dependent Type 2 diabetes." Further, TIR should be a health outcome of interest to CMS given the preponderance of evidence that TIR reduces adverse outcomes

associated with diabetes.

We are pleased that percentage of TIR, percentage of TBR, and percentage of TAR were included as surrogate markers in the *Appendix: Specific Outcome Measures by Endpoint Domain in the Panel Voting Questions* shared as part of the background information for the May MEDCAC meeting. We also appreciate the inclusion of TIR in the CER prepared for CMS and the CER reference to several publications that are included in our attached Statement of the Evidence. Given the recognition in the CER of TIR and the overwhelming evidence available, TIRC urges CMS to adopt TIR as a health outcome for assessment of new technologies for diabetes self-management.

Conclusion

Given the significant body of evidence demonstrating TIR is clinically meaningful, TIRC has long-standing policy advocating that TIR should be recognized by federal regulatory bodies as an endpoint for assessment of new drugs and devices and a factor considered for payment and coverage policies. To that end, we urge MEDCAC to recognize the importance and usefulness of TIR and to incorporate its use into any recommendations MEDCAC provides to CMS going forward.

Thank you for considering our comments. If we can be of any assistance to you as you consider which health outcomes in studies of devices for self-management of diabetes should be of interest to CMS, please do not hesitate to contact me at julie.heverly@diaTribe.org.

Sincerely,

Jim Carroll
Chief Executive Officer
The diaTribe Foundation

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