Medtronic

950 F Street NW
Washington, DC 20004
USA

Tel: 202.393.0444
www.medtronic.com

Medtronic Comments to the Medicare Evidence Development and Coverage Advisory Committee (MEDCAC) on Health Outcomes in Studies of Devices for Self-Management of Diabetes in Type 1 and Insulin-Dependent Type 2 Diabetes [CMS-3458-N]

Medtronic is the world's leading medical technology company, specializing in implantable and interventional therapies that alleviate pain, restore health, and extend life. We are committed to the continual research and development necessary to produce high-quality products and to support innovative therapies that improve patients' health outcomes, including a diverse and long-standing portfolio of medical devices and supplies to support individuals with type 1 and insulin-dependent type 2 diabetes. Medtronic's portfolio includes a range of technology from insulin management tools to automated insulin delivery systems, most notably the MiniMed™ 780G System with Meal Detection™ technology.

Thank you for the opportunity to comment on the questions and discussion points posed to the CMS Medicare Evidence Development & Coverage Advisory Committee (MEDCAC) relative to the types of endpoints that should be addressed in the body of evidence on devices for self-management of type 1 (T1D) or insulin-dependent type 2 diabetes (T2D) in older adults. In the meeting announcement, CMS expressed that this need has arisen "because the available devices for monitoring and controlling glucose levels have been studied and used primarily in individuals with type 1 diabetes, who historically have not been Medicare-age adults" and that "relevant clinical endpoints for assessing the effectiveness and safety of diabetes management devices may be unique for older adults." Medtronic appreciates CMS' interest in identifying meaningful endpoints for technologies that support ongoing diabetes treatment and management in these populations and providing recommendations under the Clinical Endpoints Guidance program for study developers.

We also appreciate that many Medicare beneficiaries can access advanced diabetes technologies, including continuous glucose monitors (CGM), insulin pumps, and closed loop systems under CMS' current coverage guidelines. We are hopeful that this MEDCAC and surrounding activities will lead to additional action on CMS' part to expand access further for patients with insulin-dependent T2D – in particular, through reconsideration of the continuous subcutaneous insulin infusion pump (CSII) National Coverage Determination (NCD 280.14(B)(1)(e)). As reflected in the Clinical Endpoints Review (CER) commissioned for this MEDCAC, the evidence base has grown tremendously since the NCD was last updated in 2004, leading to significant updates to consensus statements and clinical practice guidelines from the clinical community, and expanded access among commercial payers in the US. We urge CMS to similarly modernize national coverage standards to ensure continuity of care for individuals with T1D aging into the Medicare program, and to allow for the best possible care for the growing population of Medicare-aged individuals with insulin-dependent T2D. We are eager to partner with CMS in this process.

As outlined in more detail below, Medtronic recommends CMS consider the following as critical determinations on the evidence for devices for self-management of T1D and insulin-dependent T2D are made, through this MEDCAC and through any future national coverage activity:

- Recognize the breadth of clinical evidence available for these technologies and how that has shaped clinical practice and standards of care for patients with T1D and insulin-dependent T2D.
- Medtronic believes that the effectiveness of device-based therapies in the diabetes management space is best captured using a composite endpoint comprised of TIR without exceeding the goals for TBR as the gold standard surrogate now and into the future.
- As advances in critical algorithm technology enable the sophistication of insulin infusion from CSII to hybrid, advanced hybrid, and eventually closed loop systems, there is real a promise of alleviating significant burden and perceived barriers to technology use, especially in older populations that may experience cognitive and physical difficulty.

- Ensure minimally burdensome and flexible study designs, data sources and methods for collecting additional data relative to the identified endpoints of importance in the Medicare population.
- Strike an appropriate balance between continued, broad patient access to well-proven and widely accepted technologies with the further evidence that CMS believes is needed to assess coverage in the Medicare population.

Evidence Landscape and Impact on Clinical Practice

The clinical literature surrounding devices for self-management of T1D and insulin-dependent T2D dates back decades, yet is continuing to expand rapidly as the technologies become more advanced. Ongoing study has led to evolution in both language and strength of evidence-based guideline recommendations associated with use of technology in the treatment of diabetes in these populations, as well as strong support and acceptance within the clinical community.

We offer the following landmark studies, including clinical and real-world data, as a sample of the well-established clinical evidence that should serve as the backdrop as CMS considers the voting results of the MEDCAC on the specific outcome measures by endpoint domain.

- *DCCT*

  Findings from the 9-year NIH-sponsored prospective, randomized multi-center Diabetes Control and Complications Trial (DCCT) of 1,441 subjects have been well-accepted. The DCCT was designed—in part—to determine whether microvascular complications (retinopathy, nephropathy and neuropathy) of T1D could be prevented or delayed. The DCCT compared intensive therapy, defined as having a goal of achieving glycemia levels as close to the range as possible of individuals without diabetes, with conventional therapy, defined as maintaining safe, asymptomatic glucose levels. The results clearly favored intensive therapy in reducing the long-term complications of T1D in this population, and DCCT was discontinued 1 year early (Nathan et al., 1993).

- *EDIC*

  The Epidemiology of Diabetes Interventions and Complications (EDIC) study is the observational follow-up study of the DCCT. It includes 97.5% of the original DCCT cohort

with a mean of 27 years follow-up. This study has demonstrated that those in the intensive therapy group have had decreases in cardiovascular events compared to those in the conventional therapy group and that the usual care group had increased mortality compared to the US population even though the HbA1C's in the two groups converged after the completion of the DCCT portion of the trial (Nathan, 2014; DCCT/EDIC Study Research Group, 2016).

- *ORACL*

An open label randomized (1:1) crossover trial of 30 patients over age 60 with a mean age of 67 years and median T1D duration of 38 years showed closed-loop therapy is an effective treatment option for older adults with long-duration T1D (McAuley et al., 2022). Study participants had higher TIR accompanied by less TBR during closed loop than during sensor-augmented pump therapy and, importantly, closed loop reduced the time spent in hypoglycemic range overnight.

- *UKPDS*

The United Kingdom Prospective Diabetes Study (UKPDS) trial sought to explore and assess the extent to which findings from DCCT apply in the insulin-dependent T2D population. In the largest and longest study ever undertaken in diabetes at the time, it spanned 23 centers across the UK and the median follow-up was 10 years. Tighter glucose control led, predominately, to a reduction in microvascular disease and there was a strong trend (though not statistically significant) towards a reduction in macrovascular disease. Importantly, no threshold of improvement was seen: any improvement in glycemic control and blood reduces diabetes-related complications in this population (King et al., 1999).

- *OpT2mise (2022)*

Medtronic and others have sought to assess the benefits of insulin pump therapy for the treatment of poorly controlled patients with insulin-dependent T2D. The Medtronic OpT2mise randomized controlled trial (RCT) has been categorized by the American Diabetes Association's (ADA) Professional Practice Committee as constituting "Level A" evidence, defined as clear and supportive evidence from well-conducted, generalizable RCTs that are adequately powered (Draznin et al., 2022).

OpT2mise was a 6-month, multicenter, international, Medtronic-sponsored RCT including 331 patients with advanced T2D, with a subset of patients aged ⩾65 years. OpT2mize represents the strongest available evidence to date supporting CSII use for the treatment of T2D. At the 6-month follow-up point, the mean HbA1c decreased by 1.1±1.2%, from 9.0% to 7.9%, in the pump treatment group and by 0.4±1.1, from 9.0% to 8.6%, in the MDI group, resulting in a between-group treatment difference of -0.7% ($p<0.0001$). At the end of the continuation phase, during which the MDI group was switched to pump therapy for an additional 6 months, the pump-to-pump group maintained the previously achieved improvement (from 9.0% at baseline to 7.8% at 12-month follow-up, with an overall −1.2±1.14% HbA1c reduction; $p<0.0001$), while the MDI-to-pump group showed a further decrease in HbA1c from 8.6% to 7.8%, with an overall reduction by −0.8±1.2% ($p < 0.0001$) (Aronson et al., 2016; Reznik et al., 2014). There was no difference in glycemic improvement irrespective of baseline c-peptide. The improvement in glycemic response and in the Diabetes Treatment Satisfaction Questionnaire results in those aged ⩾65 years were indistinguishable from the entire group, regardless of treatment arm (Vigersky et al., 2018).

- *Breton and Kovatchev (2021)*

Breton and Kovatchev (2021) evaluated the real-world effectiveness of Tandem's t:slim X2 insulin pump with Control-IQ® technology, an AID system. The study included a substantial number of users (9451) with the majority having T1D (83%). Median percent time in the target range (70-180 mg/dL) increased from 63.6% at baseline to 73.6% over the 12 months with the use of Control-IQ technology while median percent time below target range remained low and consistent at around 1%. This study supports the effectiveness and reliability of AID systems managing diabetes and improving glycemic outcomes over time. Moreover, these findings are promising as they demonstrate the effectiveness of the system in a real-world patient population outside of controlled clinical trials.

- *Choudhary et al. (2022)*

Choudhary et al. (2022) study evaluated CGM-based endpoints using Medtronic's Carelink™ Personal data from 101,629 MiniMed 780G AID system users across Europe,

the Middle East, and Africa. CGM-based endpoints were examined for both the entire cohort and a 12-month longitudinal cohort. Mean time in range (TIR) was 72.3%, with a glucose management indicator (GMI) of 7%. Time below 70 mg/dL (TBR70) was 2.0%, and time below 54 mg/dL (TBR54) was 0.4%. For the longitudinal cohort, TIR reached 75.5% in the first month and remained at 73.3% or higher over the 12-month period. The AID system has shown consistent and effective control of glycemia among a large and diverse user base.

- *Forlenza et al. (2024)*

Forlenza et al. (2024) evaluated the real-world effectiveness of the Omnipod 5 system for 69,902 users aged two years and older with T1D. Mean TIR was 68.8%, 61.3%, and 53.6% for users with average glucose targets of 110, 120, and 130-150 mg/dL, respectively, with minimal time spent below 70 mg/dL (<1.13% for all groups). The system demonstrated favorable glycemic outcomes, with consistent effectiveness observed across different age groups and subgroups, including those transitioning from other insulin delivery methods and individuals with Medicaid/Medicare coverage.

- *ADAPT (2022)*

The Advanced Hybrid Closed Look Study in Adult Population with Tye 1 Diabetes (ADAPT) study, a randomized controlled trial, investigated the change in outcomes in an adult population with T1D using MDI and intermittently scanned CGM (isCGM) compared to the MiniMed 780G™ system (Choudhary et al., 2022). The MiniMed 780G system showed an increase in TIR of 27.6% without an increase in hypoglycemia; this corresponds to +6.6 hours of additional time in range vs. MDI+isCGM. The difference in HbA1c was 1.4% at the end of the study.

- *Real-world data MiniMed™ 780G System*

In an analysis of real-world data of Medtronic's MiniMed™ 780G System, 84% of 5,394 users aged ⩾65 years experienced TIR > 70% in line with the ADA standards. Notably, the average TIR for this cohort was an impressive 80%. Further, 97% experienced <1% TBR (54 mg/dL) while using the system, also in line with ADA standards. While these data are unpublished, it underscores the effectiveness and usability of the automated insulin

delivery (AID) system in achieving and maintaining target glycemic control in real-world datasets.

We urge CMS to consider how these studies and the broader evidence base have continued to impact clinical practice and standards of care, as reflected in updates to consensus statements and clinical practice guidelines as well as expanded access among commercial payers.

Endpoint Domains Identified in the CER

With the robust evidentiary history and evolution of clinical guidelines and general acceptance of these technologies in mind, Medtronic recognizes the importance of identifying the most appropriate endpoints for the purposes of evaluating coverage of these technologies specifically for beneficiaries with T1D and insulin-dependent T2D in the Medicare population. We support the categorization and endpoint domains identified during the CER process and MEDCAC subcommittee discussion.

Our specific commentary on each endpoint domain is as follows.

Endpoint Domain 1: Surrogate Markers

Medtronic believes that the most important, impactful, and measurable endpoints utilized in studies of diabetes management technologies and identified during the CER are those categorized in the surrogate marker domain, including but (importantly) not limited to A1c. This is based on technology advances in the CGM space, increased CGM utilization, and availability of ongoing, frequent collection of information via CGM-derived data. We encourage CMS to strongly consider evidence associated with these measures in future coverage decisions for diabetes technologies and we fully support each CGM-derived data endpoint as identified in the CER. We offer the following more in-depth observations related to impact on A1c, percentage of time in acceptable glucose range, and number of hypoglycemic episodes, in particular.

Impact on A1c

The importance of improving HbA1c (A1c) and keeping it as low as possible without increasing hypoglycemia is well established in the clinical literature associated with diabetes disease management. While HbA1c has historically been seen as the gold standard metric for diabetes, recognition of the limitations of A1c in describing both short- and long-term glycemic control has emerged. Indeed, the ADA and EASD issued a joint statement in which they said "As with any laboratory test, HbA1c has limitations. Because there is variability in the measurement of HbA1c, clinicians should exercise judgment, particularly when the result is close to the threshold that might prompt a change in therapy. HbA1c results may be discrepant from the patient's true mean glycemia in certain racial and ethnic groups, and in conditions that alter red blood cell turnover, such as anemia, end-stage renal disease (ESRD) (especially with erythropoietin therapy), and pregnancy, or if an HbA1c assay sensitive to hemoglobin variants is used in someone with sickle cell trait or other hemoglobinopathy. Discrepancies between measured HbA1c and measured or reported glucose levels should prompt consideration that one of these may not be reliable" (Davies et al., 2018).

For these reasons, while HbA1c is an important metric, Medtronic does not support the use of this measure by itself. Rather, we believe it should be evaluated in combination with other surrogate endpoints identified in the CER when considering technologies for self-management of T1 and insulin dependent T2 diabetes (for example, time in range as discussed below).

Professional societies have addressed the limitations on A1c. The ADA released the *Standards of Care in Diabetes – 2024*, stating that:

> *"The A1C test is an indirect measure of average glycemia. Factors that affect hemoglobin or red blood cell characteristics or turnover may affect A1C."*
>
> *"A1C does not provide a measure of glycemic variability or hypoglycemia. For individuals prone to glycemic variability, especially people with type 1 diabetes or type 2 diabetes with severe insulin deficiency, glycemic status is best evaluated by the combination of results from BGM or CGM and A1C."*

The American Association of Clinical Endocrinology (AACE), in its 2023 consensus statement for T2 management algorithm, stated that:

> *"A1C also has limitations and can be imprecise in some populations, including people with altered red blood cell lifespan, hemoglobinopathies, CKD, and some racial backgrounds. In addition, other glucose parameters have been shown to correlate with outcomes, such as TIR, as generated by continuous glucose monitoring (CGM). It is recommended that TIR (glucose range 70-180 mg/dL) be >70%, combined with minimal time below range (4% for <70 mg/dL and <1% for <54 mg/dL)."*

The Endocrine Society 2019 Clinical Practice Guideline recommends that when assessing glycemia in older adults with either T1D or T2D:

> *4.2 "In patients aged 65 years and older with diabetes who are treated with insulin, we recommend frequent fingerstick glucose monitoring and/or continuous glucose monitoring (to assess glycemia) in addition to HbA1c."*

Based on the recognized limitations of HbA1c as a metric coupled with advancements and utilization of newer technologies, time in range (TIR) in particular has been validated as an equally important and more precise outcome measure for diabetes clinical trials, as described in the next section.

CGM-Derived Endpoints: Time in Range (TIR)

Advances in diabetes management technologies coupled with high levels of adoption of continuous glucose monitoring (CGM) across both T1D and insulin-dependent T2D populations is enabling evaluation and use of ongoing CGM-derived data – primarily TIR, which is a measure of the percentage of time a person spends in the internationally accepted consensus and ADA standard target glucose range between 70-180 mg/dL while reducing time spent in hypoglycemia. The advantage of using CGM to derive TIR is that it provides a sensor glucose value every 5 minutes compared with the usual (e.g., 3-4 times a day) for fingerstick blood glucose measurements, which provides a more complete picture of glycemia.

An abundance of clinical and real-world evidence has demonstrated that TIR is a clinically meaningful and validated outcome. As CGM use has become more widespread, CGM-derived TIR has become a clinically relevant metric for patient care and a clinically meaningful endpoint for clinical trials (Beck 2023). Further, a systematic review of real-world evidence of AID system use found that real-world retrospective analyses confirm pivotal trial findings with larger and more diverse populations and follow-up periods of longer duration (Considine et al., 2024).

Vigersky & McMahon (2019) reviewed 18 articles (N=1179) that reported contemporaneously obtained HbA1c and TIR metrics across technologies. They concluded that there is good correlation between the two metrics and that a 10% change in TIR was approximately equal to a change in HbA1c of 0.8%. They opined that this relationship may permit the transition to TIR as the preferred metric for determining the outcome of clinical studies, predicting the risk of diabetes complications, and assessing an individual patient's glycemic control. These observations were confirmed by Beck et al. who found a similar relationship of HbA1c to TIR based on four RCT's (N=545) with a 10% change in TIR equal to a change in HbA1c of 0.6% on average (Beck et al, 2019b). Finally, a recently published study confirmed that the degree of association between HbA1c and new and readily available CGM-derived metrics, i.e., TIR, time above range (TAR), and CGM mean glucose, is robust in assessing the management of individuals with T1D in clinical settings (Eliasson et al., 2024).

In addition to the validated correlation between TIR and HbA1c, there is existing and emerging evidence that TIR is highly correlated with specific diabetes-related complications. CMS should consider the evolving relationships between CGM-derived metrics and complications in evaluating strength of these data as an endpoint.

For example, both TIR and HbA1c are reflective of hyperglycemia and are highly correlated. Therefore, it is not surprising that numerous published studies have demonstrated a strong association between CGM-derived TIR and chronic diabetic vascular complications. Beck et al. (2019) utilized proportional hazards models to assess the association of TIR and other glycemic metrics computed from the fingerstick data collected during DCCT with the rate of development of microvascular complications (i.e. progression of retinopathy and development of microalbuminuria) and concluded that a compelling case can be made the

TIR is strongly associated with the risk of microvascular complications and should be an acceptable endpoint for clinical trials in diabetes.

Additionally, there is robust evidence in people with T2D demonstrating the correlation of TIR to retinopathy (Lu J et al., 2018), peripheral neuropathy (Li et al., 2020), cardiac autonomic neuropathy (Guo et al., 2020), carotid intima media thickness (Lu et al., 2020). El Malahi et al. (2022) found that lower TIR was associated with the presence of composite microvascular complications and with hospitalization for hypoglycemia or ketoacidosis. Ranjan et al. (2020) found in a 1-year RCT in which they randomized subjects with T1D to a sensor-augmented insulin pump or multiple daily injections that improvement in albuminuria was significantly associated with an increase in TIR but not with a decrease in HbA1C. Finally, Shah et al. (2024) demonstrated that similar to HbA1C, TIR, time-in-tight range (TITR), and TAR, and mean glucose were all associated with increased risk for incident DR in adults with T1D. TITR (70-140 mg/dL) had the highest predictive value of all the glycemic metrics. It is also worth noting other CGM-derived measures beyond TIR, such as glycemia risk index (GRI), may also have strong correlations with diabetes-related complications (Wang et al, 2023).

Finally, in addition to CGM-derived TIR, it's important to consider the percentage of time spent below target glucose range (TBR) defined as <70mg/dL offer a more comprehensive picture of glycemic control. It's important to note that the goals for those who are elderly or high risk differ from the general population of people with T1D and T2D yet the CGM-derived metrics are the same (Battelino et al., 2019). For all these reasons, Medtronic believes that the effectiveness of device-based therapies in the diabetes management space is best captured using a composite endpoint comprised of TIR without exceeding the goals for TBR as the gold standard surrogate now and into the future.

Number of Hypoglycemia Episodes (<70mg/dL), Especially Episodes of Level 2 Hypoglycemia (<54 mg/dL)

As discussed above, we believe that capturing the percent TBR along with the percent TIR is sufficient to assess glycemic control. However, it is also possible to capture CGM-derived severe hypoglycemic events using the following CGM-derived definition: more than 3

consecutive glucose readings below 54 mg/dL that are greater than 10 minutes long, with events that occur less than 30 minutes apart combined as one event.

Endpoint Domain 2: Health Outcomes

We recognize the importance of health outcomes in coverage decision making and broadly support their use in evaluating devices for self-management of diabetes. As discussed above, we feel it is equally important to recognize the compelling surrogates that exist in the diabetes space and to approach evaluation of these technologies in a manner that balances both surrogate measures and health outcome measures.

Diabetes-Related ED Visits and Hospitalizations

Medtronic supports diabetes-related ED visits as an impactful endpoint in this domain. The broader diabetes-related hospitalizations endpoint is more difficult to define and would require further engagement with the stakeholder community to establish additional collection rigor around a diabetes-related hospitalizations measure as an endpoint, if desired.

Complications of Diabetes

As mentioned above, direct health outcomes are important to patients, and we do not argue the importance of these outcomes. However, as CMS considers potential endpoints around complications of diabetes, we underscore the difficulty and challenges with attribution associated with collecting these longer-term metrics—particularly in the Medicare-aged population with its recognized high rate of co-morbidities. We urge that CMS should be most interested in disease complication endpoints that are consistently documented and attributable to progression of diabetes and uncontrolled diabetes, for example:

- Diabetic retinopathy
- Diabetic foot ulcers
- Amputation

Medtronic does not support any endpoint associated with major adverse cardiovascular events (MACE). Adverse cardiac events have multiple risk factors, of which diabetes is merely one. Accurately discerning the impact of diabetes on MACE in a complex patient population would be challenging.

Restoration of Hypoglycemia Awareness

Though restoration of hypoglycemia awareness is an important endpoint, it is difficult to measure for the purpose of evaluating coverage and it remains unclear whether tight glycemic control and avoidance of hypoglycemia can restore hypoglycemia awareness. While we appreciate the commentary during the subcommittee discussion around the potential for AID systems to uniquely contribute to this potential measure, we note that doing so would require the administration and collection of an additional self-report questionnaire tool beyond important quality-of-life metrics.

Instead, we believe that the impact of restoration of hypoglycemia awareness is apparent in other endpoints that could be collected. Prior to the emergence of CGM, individuals relied upon their symptoms for awareness. Now, CGM values—with their accompanying alarms and alerts—are used as a surrogate to objectively collect and inform a patient of this information rather than the patient relying upon symptoms alone. TIR coupled with diabetes-related ED visits can provide relevant information without the need to increase burden by adding additional self-report metrics.

For these reasons, we urge that restoration of hypoglycemia awareness should not be considered by CMS as an endpoint informing future coverage of these technologies.

Endpoint Domain 3: Quality of Life

Patients with T1D or insulin-dependent T2D experience sustained significant physical, emotional, social, and mental disease burden that affects their quality of life, productivity, and life expectancy. In fact, current and future diabetes management technology development primarily centers on reducing—and even eliminating—such burdens. Therefore, Medtronic strongly supports the inclusion of quality-of-life metrics when considering coverage for these technologies.

However, the challenges with patient self-reported measurement are well known. Due to the number of tools and questionnaires currently available, we urge the agency to narrow its scope of interest for purposes of determining coverage by prioritizing quality of life metrics that either directly or indirectly measure burden reduction associated with technology use.

Thus, of all the tools identified as part of the CER and included in the discussion under this domain, we recommend reliance on only the following three as they each indirectly contribute to better understanding of burden reduction:

- Diabetes Treatment Satisfaction Questionnaire
- Problem Areas in Diabetes
- Hypoglycemia Fear Survey

As advances in critical algorithm technology enable the sophistication of insulin infusion from CSII to hybrid, advanced hybrid, and eventually closed loop systems, there is real a promise of alleviating significant burden and perceived barriers to technology use, especially in older populations that may experience cognitive and physical difficulty.

Under Medtronic's most advanced hybrid closed loop system to date, we have attempted to characterize burden reduction via device-derived, quantifiable metrics. Forlenza et al. compared burden of the MiniMed™ 780G advanced hybrid closed-loop system with the MM670G with Guardian™ Sensor 3 (GS3) via an unvalidated metric for diabetes management burden (i.e. pentagon composite metric), glycemic outcomes, and physical system burden (e.g. closed loop exits and fingersticks/day) (Forlenza et al., 2024). The MiniMed™ 780G with G4S use was associated with significant reduction in diabetes management burden with fewer closed loop exits, fingersticks and other interactions, and improvements in glycemic control when compared to the MiniMed™ 670G with GS3. Medtronic urges CMS and others to carefully consider additional ways to measure quality of life and burden reduction in patients using these technologies via stronger and more objective future tools that can be collected through device data alone and thus do not rely upon the use of patient-facing surveys and questionnaires.

Endpoint Domain 4: Device-Related Safety

The safety of devices and technology used to manage the highly complex disease of diabetes is of critical importance. We support the identified endpoint on hypoglycemia-related ED visits. CMS should also consider an endpoint in this domain for hospitalizations related to DKA or other hyperglycemic emergencies.

Endpoint Evidence Collection Principles

As CMS continues to evaluate what further evidence is needed relative to the endpoints discussed in the CER to assess coverage of these technologies in the Medicare population, we emphasize the need to balance appropriate access to well-proven technologies while generating any further evidence CMS believes is necessary for coverage. CGM-derived data is consistent, objective, passively collected, and easy to analyze. Evidence is emerging that real-world studies confirm clinical trial findings in the AID space (Considine & Sherr, 2024). Therefore, we urge that CMS ensure minimally burdensome and flexible study designs, data sources and methods for collecting additional data relative to the identified endpoints of importance in the Medicare population.

***

References

Aronson R, Reznik Y, Conget I, et al. Sustained efficacy of insulin pump therapy compared with multiple daily injections in type 2 diabetes: 12-month data from the OpT2mise randomized trial. *Diabetes, Obesity and Metabolism*. 2016;18(5):500-507. doi:10.1111/dom.12642

Battelino T, Danne T, Bergenstal RM, et al. Clinical Targets for Continuous Glucose Monitoring Data Interpretation: Recommendations From the International Consensus on Time in Range. *Diabetes Care*. 2019;42(8):1593-1603. doi:10.2337/dci19-0028

Beck RW, Bergenstal RM, Riddlesworth TD, et al. Validation of Time in Range as an Outcome Measure for Diabetes Clinical Trials. *Diabetes Care*. 2019;42(3):400-405. doi:10.2337/dc18-1444

Beck RW, Bergenstal RM, Cheng P, et al. The Relationships Between Time in Range, Hyperglycemia Metrics, and HbA1c. *Journal of Diabetes Science and Technology*. 2019b;13(4):614-626. doi:10.1177/1932296818822496

Breton MD, Kovatchev BP. One Year Real-World Use of the Control-IQ Advanced Hybrid Closed-Loop Technology. *Diabetes Technology & Therapeutics*. 2021;23(9):601-608. doi:10.1089/dia.2021.0097

Considine EG, Sherr JL. Real-World Evidence of Automated Insulin Delivery System Use. *Diabetes Technology & Therapeutics*. 2024;26(S3):53-65. doi:10.1089/dia.2023.0442
Choudhary P, Arrieta A, van den Heuvel T, et al. Celebrating the Data from 100,000 Real-World Users of the MiniMed™ 780G System in Europe, Middle East, and Africa Collected Over 3 Years: From Data to Clinical Evidence. *Diabetes Technology & Therapeutics*. 2024;26:32-37. doi:10.1089/dia.2023.0433

Choudhary P, Kolassa R, Keuthage W, et al. Advanced hybrid closed loop therapy versus conventional treatment in adults with type 1 diabetes (ADAPT): a randomised controlled study. *Lancet Diabetes Endocrinol*. 2022;10(10):720-731.

Davies MJ, D'Alessio DA, Fradkin J, et al. Management of Hyperglycemia in Type 2 Diabetes, 2018. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care*. 2018;41(12):2669-2701. doi:10.2337/dci18-0033

Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications (EDIC) Study Research Group. Mortality in Type 1 Diabetes in the DCCT/EDIC Versus the General Population. *Diabetes Care*. 2016;39(8):1378-1383. doi:10.2337/dc15-2399

Draznin, B, Aroda, VR, Bakris, G, et al. Diabetes Technology: Standards of Medical Care in Diabetes-2022. *Diabetes Care*. 2022;45(Suppl 1):S97-S112. doi:10.2337/dc22-S007
El Malahi A, Van Elsen M, Charleer S, et al. Relationship Between Time in Range, Glycemic Variability, HbA1c, and Complications in Adults With Type 1 Diabetes Mellitus. *Journal of Clinical Endocrinology & Metabolism*. 2022;107(2):e570-e581. doi:10.1210/clinem/dgab688

Forlenza GP, DeSalvo DJ, Aleppo G, et al. Real-World Evidence of Omnipod® 5 Automated Insulin Delivery System Use in 69,902 People with Type 1 Diabetes. *Diabetes Technology & Therapeutics*. February 2024. doi:10.1089/dia.2023.0578

Forlenza GP, Dai Z, Niu F, Shin JJ. Reducing Diabetes Burden in Medtronic's Automated Insulin Delivery Systems. *Diabetes Technology & Therapeutics*. 2024 Mar;26(S3):7-16. doi: 10.1089/dia.2023.0459

Guo Q, Zang P, Xu S, et al. Time in Range, as a Novel Metric of Glycemic Control, Is Reversely Associated with Presence of Diabetic Cardiovascular Autonomic Neuropathy Independent of HbA1c in Chinese Type 2 Diabetes. *Journal of Diabetes Research*. 2020;2020:5817074. doi:10.1155/2020/5817074

King P, Peacock I, Donnelly R. The UK Prospective Diabetes Study (UKPDS): clinical and therapeutic implications for type 2 diabetes. *British Journal of Clinical Pharmacology*. 1999;48(5):643-648. doi: 10.1046/j.1365-2125.1999.00092.x.

Li F, Zhang Y, Li H, et al. TIR generated by continuous glucose monitoring is associated with peripheral nerve function in type 2 diabetes. *Diabetes Research and Clinical Practice*. 2020;166. doi:10.1016/j.diabres.2020.108289
Lu J, Ma X, Zhou J, et al. Association of Time in Range, as Assessed by Continuous Glucose Monitoring, With Diabetic Retinopathy in Type 2 Diabetes. *Diabetes Care*. 2018;41(11):2370-2376. doi:10.2337/dc18-1131

Lu J, Ma X, Shen Y, et al. Time in Range Is Associated with Carotid Intima-Media Thickness in Type 2 Diabetes. *Diabetes Technology & Therapeutics*. 2020;22(2):72-78. doi:10.1089/dia.2019.0251

McAuley SA, Trawley S, Vogrin S, et al. Closed-Loop Insulin Delivery Versus Sensor-Augmented Pump Therapy in Older Adults With Type 1 Diabetes (ORACL): A Randomized, Crossover Trial. *Diabetes Care*. 2022;45(2):381–390. doi:10.2337/dc21-1667

Nathan DM, Genuth S, Lachin J, et al. Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *New England Journal of Medicine*. 1993;329(14):977-986

Nathan DM. The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Study at 30 Years: Overview. *Diabetes Care*. 2014;37(1):9-16. doi:10.2337/dc13-2112

Ranjan AG, Rosenlund SV, Hansen TW, et al. Improved Time in Range Over 1 Year Is Associated With Reduced Albuminuria in Individuals With Sensor-Augmented Insulin Pump-Treated Type 1 Diabetes. *Diabetes Care*. 2020;43(11):2882-2885. doi:10.2337/dc20-0909

Reznik Y, Cohen O, Aronson R, et al. Insulin pump treatment compared with multiple daily injections for treatment of type 2 diabetes (OpT2mise): a randomised open-label controlled trial. *The Lancet*. 2014;384(9950):1265-1272. doi:10.1016/S0140-6736(14)61037-0

Shah VN, Kanapka LG, Akturk HK, et al. Time in Range Is Associated with Incident Diabetic Retinopathy in Adults with Type 1 Diabetes: A Longitudinal Study. *Diabetes Technology & Therapeutics*. 2024;26(4):246-251. doi:10.1089/dia.2023.0486

Vigersky RA, Huang S, Cordero TL, et al. Improved Hba1c, Total Daily Insulin Dose, and Treatment Satisfaction with Insulin Pump Therapy Compared to Multiple Daily Insulin Injections in Patients with Type 2 Diabetes Irrespective of Baseline C-Peptide Levels. *Endocrine Practice*. 2018;24(5):446-452. doi:10.4158/EP-2017-0234

Vigersky RA, McMahon C. The Relationship of Hemoglobin A1C to Time-in-Range in Patients with Diabetes. *Diabetes Technology & Therapeutics*. 2019;21(2):81-85. doi:10.1089/dia.2018.0310

Wang Y, Lu J, Ni J, et al. Association between glycaemia risk index (GRI) and diabetic retinopathy in type 2 diabetes: A cohort study. *Diabetes, Obesity & Metabolism*. 2023;25(9):2457-2463. doi:10.1111/dom.15068